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Melatonin, programmed death ligand-1, programmed death ligand-1, and cancer: imagine beyond the future?

José Maria Soares Junior[1], Ilker Sengul[2,3], Demet Sengul[4]*

Melatonin (N-acetyl-5-methoxytryptamine) (MT) is an indolamine and a neurohormone that is primarily synthesized and secreted mainly by the pinecone-shaped gland of the cerebrum, called the conarium or epiphysis cerebri, from amino acid tryptophan. MT, which has various biologic effects, like regulation of circadian rhythm, as well as antioxidant, anti-aging, and antitumor activities, was first isolated in 1958 from the bovine pineal gland by Maliki et al.[1] Furthermore, the 17th-century philosopher René Descartes hypothesized the pineal gland of the brain, representing the location of the *Homo sapiens* soul, which paleontologists described it as an ancestral "third eye." The third eye, per se, remains poorly understood, and modern psychology declares perception beyond physical visual function[2,3].

This "eye-associated" chemical messenger, per se, ensures high precision in recognizing the night period. It is an endocrine marker for darkness and regulates circadian rhythm and the sleep–wake cycle. Moreover, it can be reproduced by other vital organs, such as the brain, thyroid, lungs, gastrointestinal tract, liver, and reproductive and immune systems. Notably, it is present in mucus, saliva, breast milk, amniotic fluid, Graff follicle, sperm, urine, etc[1,4]. MT has been reported to possess significant antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, anti-angiogenic, and antimetastatic immunomodulatory properties[5,6]. Based on the immunoregulatory properties of MT, it has been researched as a therapeutic option for many autoimmune diseases, which attains its impact through the MT receptors type 1 and type 2 (MT1 [Mel_{1a}] and MT2 [Mel_{1b}]) of the membrane-bound receptors. Additionally, the presence of the MT1 receptor in the papillon gland has been proven to resemble the contingency of MT's impact on the thyroid activity and reproduction of hormonal processes. However, the MT3 receptor, the third membrane-bound MT binding site, was theorized as a biological and was detected to, in fact, be the cytosolic enzyme, quinone reductase II (NQO2)[7]. A single-nucleotide polymorphism of MTNR1A, coding the MT1 protein, gave liaison to a susceptibility of Graves' disease and thyroid autoantibody formation, which led to the contingency of the development of autoimmune thyroid disease in thyroidology[8-10].

Programmed cell death-1 (PCD-1) is a crucial immunological checkpoint receptor. It is preferably expressed in activated cells involving T, B, dendritic (DC), natural killer (NK), and T reg. In addition to this, PCD-1 is linked to augmented Treg-cell proliferation and enhanced immunosuppressive function. As such, the epithelial, endothelial, hematopoietic, and tumor cells can produce programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2) ligands. They are regulated by a couple of inflammatory cytokines involving interferon-gamma (IFN-γ), released by activated T and NK cells. Of note, oncogenes might be vital in promoting PD-L1 expression, unlike PD-L2[11-13]. PD-L1 messenger RNA (mRNA) transcription augments with the activation of the MEK/ERK[14-17] kinase through nuclear factor-kappa B, essential for its toll-like receptor (TLR)-mediated regulation. Furthermore, IFN receptors 1 and 2 are connected to regulating the PD-L1 expression of interferon regulatory factor-(IRF-1), which is another way through the Janus kinase (Jak)/signal transducer(s) and activator(s) of the transcription (STAT) pathway. The phosphatidylinositol 3 kinase (PI3K)/serine/threonine protein kinase B (PKB, also known as AKT) pathway[14-17] plays a permissive role in PD-L1 transcription through the phosphorylation of rapamycin's mammalian target. Notably, it might also up-regulate PD-L1 expression in response to the IFN-mediated activation of Jak/STAT[18]. To date, PD-L1 is weakly expressed in normal tissues, though it is overexpressed in many tumor cells. It was indicated that this leads

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to PD-L1 being an immunotherapeutic target[19]. The PD-L1-positive tumors were reported to respond to the treatment noticeably better than those PD-L1 negative. PD-L1 with a high expression in tumor cells was emphasized with a better response to nivolumab in recurrent head-and-neck cancer or renal cell carcinoma, like pembrolizumab in advanced non-small cell lung cancer (NSCLC). The interplay of PD-L1 on the membrane of cancer cells with PCD-1 expression on T cells provokes T cell exhaustion and attenuation of the succeeding immune reaction, skipping immune surveillance. Up to now, the mechanism of PD-L1 and -L2 regulation in tumorigenesis immune escape remains largely inscrutable[20-22]. The PD1 receptor might be located on both CD8+ and CD4+ T cells. At the same time, PD-L1 is expressed by activated T cells, tumor-infiltrating macrophages or fibroblasts, and ovarian cancer cells, which may impose upon the immune response against the tumorigenesis[22,23]. A growing interest in the possibility of employing immunotherapy in cases with gynecological cancers has led to the advancement of a large number of clinical trials testing immunotherapy as monotherapy and in combination with other strategies, such as chemotherapy, targeted agents, or both. As such, cancer immunotherapy targeting PCD-1 or PD-L1 has proven effective in causing durable antitumor immune responses with less toxicity in many tumors, including gynecological cancer[22-26].

MT was reported in order to enhance the antitumor activity of macrophages, suppressed by exosomes from gastric cancer cells, which was achieved through the regulation of PD-L1 in macrophages via the modulation of the associated microRNAs in the cancer-derived exosomes[27]. Moreover, MT treatment announced significant attenuation of cell viability in companies that trigger cell apoptosis in KRAS-mutant NSCLC cell lines, embracing A549, H460, and LLC1 cells. The lung cancer cells possessing the KRAS mutation exhibited an excelsior level of PD-L1. Nevertheless, MT therapy downregulated PD-L1 expressions on a large scale in both the presence and absence of IFN-γ stimulation[28].

Finally, though MT has demonstrated a broad spectrum of anticancer impacts and PCD-1 might be a key immune checkpoint receptor that mainly acts on activated T, B, DC, NK, and T reg cells, and checkpoint blockades are registered for the treatment of various cancers, accurately modulating tumor immunity remains largely unknown today. This issue merits further investigation—*post tenebras lux*.

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AUTHORS' CONTRIBUTIONS

JMSJ: Conceptualization, Methodology, Project administration, Validation, Visualization, Writing – review & editing. **IS:** Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **DS:** Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Maliki OF, Alagbon AI, Ibitoye CM, Olayaki LA. Melatonin and vitamin C modulate cassava diet-induced alteration in reproductive and thyroid functions. Niger J Exp Clin Biosci. 2021;9:133-43
2. Lane R. Of sight, and insight. Lancet. 2023;401(10371):97. https://doi.org/10.1016/S0140-6736(22)02589-2
3. Soares Junior JM, Kesicioglu T, Sengul D, Sengul I. Of sight, and insight into melatonin's role in breast cancer? Rev Assoc Med Bras (1992). 2023;69(7):e697EDIT. https://doi.org/10.1590/1806-9282.697EDIT
4. Stanojlović O, Šutulović N. Cirkadijalni sistem - mreža neurona sa suprahijazmati nim jedrom na vrhu hijerarhijske organizacije. Med Podml. 2018;69:3-13. https://doi.org/10.5937/mp69-18063
5. Wang SW, Tai HC, Tang CH, Lin LW, Lin TH, Chang AC, et al. Melatonin impedes prostate cancer metastasis by suppressing MMP-13 expression. J Cell Physiol. 2021;236(5):3979-90. https://doi.org/10.1002/jcp.30150
6. Farhood B, Goradel NH, Mortezaee K, Khanlarkhani N, Najafi M, Sahebkar A. Melatonin and cancer: from the promotion of genomic stability to use in cancer treatment. J Cell Physiol. 2019;234(5):5613-27. https://doi.org/10.1002/jcp.27391
7. Slominski RM, Reiter RJ, Schlabritz-Loutsevitch N, Ostrom RS, Slominski AT. Melatonin membrane receptors in peripheral tissues: distribution and functions. Mol Cell Endocrinol. 2012;351(2):152-66. https://doi.org/10.1016/j.mce.2012.01.004
8. Lin JD, Fang WF, Tang KT, Cheng CW. Effects of exogenous melatonin on clinical and pathological features of a human thyroglobulin-induced experimental autoimmune thyroiditis mouse model. Sci Rep. 2019;9(1):5886. https://doi.org/10.1038/s41598-019-42442-0
9. Sengul I, Sengul D, Pelikán A. Iodine-induced hyperthyroidism: Do you mind? Sanamed. 2020;15:215-7.
10. Sengul D, Sengul I, Soares Junior JM. Repercussion of thyroid dysfunctions in thyroidology on the reproductive system: conditio sine qua non? Rev Assoc Med Bras (1992). 2022;68(6):721-2. https://doi.org/10.1590/1806-9282.20220255
11. Bardhan K, Anagnostou T, Boussiotis VA. The PD1:PD-L1/2 pathway from discovery to clinical implementation. Front Immunol. 2016;7:550. https://doi.org/10.3389/fimmu.2016.00550

12. Yearley JH, Gibson C, Yu N, Moon C, Murphy E, Juco J, et al. PD-L2 expression in human tumors: relevance to anti-PD-1 therapy in cancer. Clin Cancer Res. 2017;23(12):3158-67. https://doi.org/10.1158/1078-0432.CCR-16-1761
13. Shin SJ, Jeon YK, Kim PJ, Cho YM, Koh J, Chung DH, et al. Clinicopathologic analysis of PD-L1 and PD-L2 expression in renal cell carcinoma: association with oncogenic proteins status. Ann Surg Oncol. 2016;23(2):694-702. https://doi.org/10.1245/s10434-015-4903-7
14. Sengul I, Sengul D. Ischemic preconditioning and postconditioning in cardiovascular surgery. Cumhuriyet Med J. 2010;32:365-73.
15. Sengul D, Sengul I. Connection of reactive oxygen species as an essential actor for the mechanism of phenomena; ischemic preconditioning and postconditioning: come to age or ripening? North Clin Istanb. 2021;8(6):644-9. https://doi.org/10.14744/nci.2021.78466
16. Sengul I, Sengul D. Potasyum–ATP kanalları ve reperfüzyon hasarı azaltıcı ko□ullanmalar. Nobel Med. 2010;6:112.
17. Sengul I, Sengul D, Guler O, Hasanoglu A, Urhan MK, Taner AS, et al. Postconditioning attenuates acute intestinal ischemia-reperfusion injury. Kaohsiung J Med Sci. 2013;29(3):119-27. https://doi.org/10.1016/j.kjms.2012.08.021
18. Boussiotis VA, Chatterjee P, Li L. Biochemical signaling of PD-1 on T cells and its functional implications. Cancer J. 2014;20(4):265-71. https://doi.org/10.1097/PPO.0000000000000059
19. Tsushima F, Iwai H, Otsuki N, Abe M, Hirose S, Yamazaki T, et al. Preferential contribution of B7-H1 to programmed death-1-mediated regulation of hapten-specific allergic inflammatory responses. Eur J Immunol. 2003;33(10):2773-82. https://doi.org/10.1002/eji.200324084
20. Świderska J, Kozłowski M, Kwiatkowski S, Cymbaluk-Płoska A. Immunotherapy of ovarian cancer with particular emphasis on the PD-1/PDL-1 as target points. Cancers (Basel). 2021;13(23):6063. https://doi.org/10.3390/cancers13236063
21. Otoshi T, Nagano T, Tachihara M, Nishimura Y. Possible biomarkers for cancer immunotherapy. Cancers (Basel). 2019;11(7):935. https://doi.org/10.3390/cancers11070935
22. Gutic B, Bozanovic T, Mandic A, Dugalic S, Todorovic J, Stanisavljevic D, et al. Programmed cell death-1 and its ligands: current knowledge and possibilities in immunotherapy. Clinics (Sao Paulo). 2023;78:100177. https://doi.org/10.1016/j.clinsp.2023.100177
23. Leary A, Tan D, Ledermann J. Immune checkpoint inhibitors in ovarian cancer: where do we stand? Ther Adv Med Oncol. 2021;13:17588359211039899. https://doi.org/10.1177/17588359211039899
24. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492
25. Eymerit-Morin C, Ilenko A, Gaillard T, Varinot J, Compérat E, Bendifallah S, et al. PD-L1 expression with QR1 and E1L3N antibodies according to histological ovarian cancer subtype: a series of 232 cases. Eur J Histochem. 2021;65(1):3185. https://doi.org/10.4081/ejh.2021.3185
26. Michielin O, Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019;30(12):1884-901. https://doi.org/10.1093/annonc/mdz411
27. Wang K, Cai R, Fei S, Chen X, Feng S, Zhang L, et al. Melatonin enhances anti-tumor immunity by targeting macrophages PD-L1 via exosomes derived from gastric cancer cells. Mol Cell Endocrinol. 2023;568-69:111917. https://doi.org/10.1016/j.mce.2023.111917
28. Chao YC, Lee KY, Wu SM, Kuo DY, Shueng PW, Lin CW. Melatonin downregulates PD-L1 expression and modulates tumor immunity in KRAS-mutant non-small cell lung cancer. Int J Mol Sci. 2021;22(11):5649. https://doi.org/10.3390/ijms22115649

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Before respiratory muscle weakness is attributed to a stroke, alternative causes must be considered and thoroughly ruled out

Josef Finsterer[1*]

Dear Editor,

We were interested to read the article by Yildiz et al. on a prospective study of respiratory muscle strength in stroke patients, in which maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured in 171 patients with chronic stroke compared to 32 healthy controls matched for age and gender[1]. Stroke patients were found to have lower MIP and MEP than healthy controls[1]. It was concluded that patients with chronic stroke can suffer from significant respiratory muscle weakness, which requires adaptation of rehabilitation programs for stroke patients[1]. The study is impressive, but some points should be discussed.

The first point is that the spectrum of the causes of respiratory muscle weakness is broad and that these various causes must be ruled out before respiratory muscle weakness is attributed to chronic stroke. The causes of respiratory muscle weakness to be ruled out include electrolyte disturbances, neuromuscular disorders, transmission diseases, polyradiculitis, neuropathy (including critically ill neuropathy), psychiatric illness (depression, delirium), pain, and acidosis or alkalosis.

The second point is that the degree of respiratory muscle weakness after a stroke can depend strongly on the localization of the stroke. The weakness may be different in a stroke in the right or left middle cerebral artery area compared to the basilar artery. If the respiratory center in the brainstem is affected by the stroke, the respiratory drive may be severely impaired. Respiratory muscle strength may also depend on whether the patient has had previous lung or bronchial disease, asthma, pulmonary embolism, allergy, sleep apnea syndrome, or heart disease, including left or right heart failure.

The third point is that the latency between the onset of the stroke and the date of the respiratory muscle examination was only given as a mean value without a range or standard deviation. We should know the minimum and maximum latencies. Since a mean latency of 388 days, as shown in Table 1, is quite long, it cannot be excluded that causes other than the stroke developed in the post-stroke period and were actually responsible for the decreased MIP or MEP. Therefore, we should know how many of the included patients had an intermediate disease after the stroke that could explain the reduction in MIP or MEP.

The fourth point is that the methods state that the stroke cohort and the healthy control group were matched by age and gender. As the two groups were of different sizes (171 vs. 32), it should be explained how the matching was performed.

The fifth point is that despite the indication that the two groups were matched for gender, there was a significant difference in the ratio of male to female in the patient and control groups[1]. In the stroke cohort, the proportion of males was 39%, while in the control group, 56% of the participants were male. This discrepancy should be corrected.

The sixth point is that the recruitment period also included the pandemic[1]. Since severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection can strongly influence MIP and MEP[2], we should know how many of the included patients had SARS-CoV-2 infection, its severity, and whether any of them needed mechanical ventilation.

The seventh point is that it was not explained what is meant by chronic stroke. Do the authors mean a history of stroke or do they mean an incomplete stroke? Were only patients with ischemic stroke or also patients with cerebral hemorrhage included in the study?

In summary, it can be said that the index study has limitations that relativize the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the results of the study. Before respiratory muscle weakness in stroke patients after 1 year is attributed to the vascular event, alternative causes must be considered and thoroughly ruled out.

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REFERENCES

1. Yildiz A, Mustafaoglu R, Bardak AN. Respiratory muscle strength in stroke: a case-control study. Rev Assoc Med Bras (1992). 2024;70(8):e20240061. https://doi.org/10.1590/1806-9282.20240061

2. Soares MN, Eggelbusch M, Naddaf E, Gerrits KHL, Schaaf M, Borst B, et al. Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. J Cachexia Sarcopenia Muscle. 2022;13(1):11-22. https://doi.org/10.1002/jcsm.12896

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Response to "The Glasgow prognostic score is unsuitable for stroke prediction in infective endocarditis"

Cihan Aydın[1*], Aykut Demirkıran[1]

Dear Editor,

We thank Josef for his interest in our article. We want to respond to your criticism and contributions. After pneumonia, intra-abdominal abscess, and sepsis, infective endocarditis is the most common infectious condition that causes a life-threatening risk and is linked to higher rates of mortality and morbidity[1]. It was stated by Mr. Finsterer that there was no difference between Glasgow prognostic score (GPS) levels. However, in our study, GPS was found to be higher in Group 1 who had a stroke [Group 1=2(1–2) vs. Group 2=1(0–2), $p<0.001$][2]. As is known, many biomarkers such as C-reactive protein and albumin can increase for various reasons[3]. In addition, many variables that suppress inflammation may cause lower detection of these biomarkers. We mentioned these issues in the limitation section of our study. In our study, we tried to create two homogeneous groups in terms of diseases, such as diabetes, heart failure, kidney failure, and liver failure. As a second criticism, it was mentioned that complications of infective endocarditis may cause GPS elevation. However, the GPS values of the patients were calculated at the time of admission to the hospital before the complications developed.

Scores should not limit us, of course. However, they can be practical in making decisions on some issues and are widely recommended in many guidelines. Also, no score is perfect and has shortcomings. There are of course many conditions that can cause a stroke. In our study, patients with carotid artery stenosis were excluded. We could have added in the limitation section that the coagulopathy panel could not be examined.

As we mentioned in the article, stroke diagnosis of patients is made using physical examination, computed tomography, and cranial magnetic resonance imaging methods.

Although scoring systems such as GPS cannot replace physical examination, anamnesis, and other diagnostic methods, we believe that they can help us in diagnosis and treatment.

AUTHORS' CONTRIBUTIONS

CA: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AD:** Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Emlek N, Özyıldız AG, Şahin MA, Ergül E, Aydın C. Is Glasgow prognostic score a predictor of mortality in infective endocarditis? Eur Res J. 2022;8(5):702-9. https://doi.org/10.18621/eurj.1100926
2. Aydın C, Demirkıran A, Aykaç H, Uslu N, Alpsoy Ş. Can the Glasgow prognostic score predict ischemic stroke in patients with infective endocarditis? Rev Assoc Med Bras (1992). 2024;70(3):e20231299. https://doi.org/10.1590/1806-9282.20231299
3. Aydın C, Uyan U, Karadeniz M, Demirkıran A. Role of simple inflammatory parameters in predicting the severity of coronary artery disease. Rev Assoc Med Bras (1992). 2023;69(11):e20230518. https://doi.org/10.1590/1806-9282.20230518

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Ventrogluteal site as the preferred choice for pediatric intramuscular injections: impact on pain and fear

Hongmei Xuan[1], Lifeng Meng[2], Peiyu Chen[3*]

Dear Editor,

I read with great interest the study by Tiryaki et al., examining the effects of different intramuscular injection (IMI) sites—specifically, the ventrogluteal (VG) and vastus lateralis (VL) sites—on pain and anxiety in young children[1]. This research offers valuable insights into methods for reducing discomfort associated with IMIs, a routine yet often distressing experience for pediatric patients. The selection of injection site in clinical practice has long been a topic of considerable interest, especially in pediatrics, where children's reactions to pain and anxiety can complicate standard medical procedures and influence their overall healthcare experience.

The authors provide compelling evidence that the VG site markedly reduces pain, fear, and crying duration in children compared to the VL site. The study employs a robust methodology, utilizing a randomized controlled trial (RCT), to compare the two sites across metrics, such as pain—measured by the Wong-Baker Faces Pain Rating Scale—and fear, assessed through the Children's Fear Scale (CFS). This rigorous approach lends credibility to the study's conclusions, making a strong case for favoring the VG site as the preferred choice for pediatric IMIs.

The effectiveness of the VG site in reducing pain and distress likely stems from its distinct anatomical and physiological features[2]. Unlike other areas, the VG site is free of major blood vessels and nerves, lowering the risk of accidental injury. Additionally, its thinner subcutaneous layer allows for more efficient absorption of medications, reducing prolonged irritation. These characteristics jointly contribute to less immediate pain and a shorter duration of post-injection discomfort. In contrast, the VL site is situated near denser muscle tissues and bones, potentially contributing to higher pain scores and longer crying times in this group. Children receiving injections at the VL site showed a mean pain score of 7.60 compared to 5.49 in the VG group, a statistically significant difference that underscores the VG site's advantages for pain management.

The study's findings align with the existing literature on the benefits of the VG site for IMIs in adults, where it has been linked to lower pain levels and fewer complications compared to sites like the dorsogluteal (DG) region[3]. However, research specifically focused on pediatric populations remains limited, particularly studies addressing subjective outcomes such as fear and crying duration—key indicators of a child's comfort during procedures. This study therefore fills an important gap in pediatric nursing by providing empirical support for the VG site as a safer and more comfortable choice for children.

Interestingly, the study also examines the psychological aspect of IMIs by exploring fear, a common response in children facing medical procedures. Anticipatory anxiety, often heightened when children can see the needle approaching, exacerbates this fear[4]. The VG site, positioned on the lateral side of the hip, is typically outside the child's direct line of sight during the injection, potentially contributing to lower fear scores. Children in the VG group indeed reported significantly less fear both during and after the procedure compared to those in the VL group. By minimizing visible exposure to the needle, this site likely helps alleviate distress and reduce anticipatory anxiety, highlighting the VG site's advantages from both physical and psychological perspectives.

The findings of the study are not only meaningful but also offer practical benefits for clinical practice. Managing fear and anxiety in children during routine procedures is a common challenge in pediatric nursing. Utilizing the VG site could potentially reduce the time needed for IMIs by decreasing crying and recovery duration, thereby streamlining workflow in high-demand settings like emergency departments. Moreover, using the VG site can create a more positive experience for young patients, who are especially sensitive to pain and fear in medical

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contexts. Reducing distressing experiences in early childhood may positively shape a child's long-term perception of health care, helping alleviate anxiety about future medical visits.

However, as the authors note, there are limitations to this study. The sample size was restricted to 83 participants from a single center, limiting the generalizability of the findings until further validation in larger and more diverse pediatric populations. Additionally, the study focused on children aged 4–6 years, highlighting the need for further research to determine whether the benefits of the VG site extend to other pediatric age groups, such as infants or older children. Since muscle mass and fat distribution vary with age, examining whether the VG site remains optimal across developmental stages would be valuable. Furthermore, replicating this study in diverse clinical settings—including outpatient clinics and primary care facilities—could help establish the VG site's practicality and effectiveness beyond emergency care environments.

Future research could also explore the impact of parental involvement and distraction techniques in reducing procedural anxiety. Involving parents in comforting their child or incorporating distraction tools—such as toys or visual entertainment—may further alleviate pain and fear, complementing the choice of the injection site. Combining optimal site selection with these supportive strategies could create a more comprehensive approach to pain management in pediatric nursing, particularly for procedures like IMIs, which are often distressing for young patients.

In conclusion, Tiryaki et al. provide valuable insights into pain management for pediatric IMIs. By showing that the VG site is associated with reduced pain, fear, and crying duration, they present a compelling case for adopting the VG site as standard practice in pediatric IMIs. Their findings endorse the VG site as the preferred option, promoting atraumatic care practices in pediatric nursing and potentially influencing clinical protocols for IMIs in children. To expand on these findings, I encourage future research to examine the VG site's effectiveness across various pediatric age groups and in diverse healthcare settings. Such studies could further confirm the VG site's role in enhancing procedural comfort and fostering a positive healthcare experience for young patients.

AUTHORS' CONTRIBUTIONS

HX: Writing – original draft. **LM:** Data curation and Formal Analysis. **PC:** Conceptualization, Formal Analysis and Writing – review & editing.

REFERENCES

1. Tiryaki Ö, Menekşe D, Özdemir Ö, Çınar N, Elmas B. Comparison of the effect of intramuscular injection from two different sites on pain and fear in children: a randomized controlled study. Rev Assoc Med Bras (1992). 2024;70(11):e20240826. https://doi.org/10.1590/1806-9282.20240826
2. Balci S, Sivri BB. Comparison of pain levels developed during intramuscular injections to laterofemoral and ventrogluteal regions in children: a randomized controlled study. Rev Assoc Med Bras (1992). 2023;69(1):85-9. https://doi.org/10.1590/1806-9282.20220770
3. Ayinde O, Hayward RS, Ross JDC. The effect of intramuscular injection technique on injection associated pain; a systematic review and meta-analysis. PLoS One. 2021;16(5):e0250883. https://doi.org/10.1371/journal.pone.0250883
4. Davies C, Marshall HS, Zimet G, McCaffery K, Brotherton JML, Kang M, et al. Effect of a school-based educational intervention about the human papillomavirus vaccine on psychosocial outcomes among adolescents: analysis of secondary outcomes of a cluster randomized trial. JAMA Netw Open. 2021;4(11):e2129057. https://doi.org/10.1001/jamanetworkopen.2021.29057

ORIGINAL ARTICLE

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Can handgrip strength alone detect individuals living with frailty according to the Clinical Frailty Scale?

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SUMMARY

OBJECTIVE: Several studies have been conducted to determine handgrip strength cutoffs that can identify people living with frailty. However, the handgrip strength cutoff value, which can detect individuals living with frailty based on the Clinical Frailty Scale, has not been determined before. The aim of this study was to investigate the capacity of handgrip strength to detect individuals living with frailty by using Clinical Frailty Scale as a reference scale.

METHODS: This retrospective study was carried out by including patients who applied to the geriatric outpatient clinic of a university hospital. A comprehensive geriatric assessment was performed on all patients. Level 4 and above were considered as living with frailty according to Clinical Frailty Scale. Receiver operating characteristic curve analysis was performed to determine the handgrip strength cutoff values for predicting individuals living with frailty.

RESULTS: The median age of 742 patients included in this study was 72.0 years (25p-75p: 68.0-77.0), of which 59.3% (n=440) were female and 49.3% (n=366) were living with frailty. The median Clinical Frailty Scale level was 3.0 (25p-75p: 3.0-4.0). According to the results of binary logistic regression analysis, age, sex, and handgrip strength displayed a statistically significant relationship with frailty (p<0001, p=0.001, and p<0.001, respectively). As a result of the receiver operating characteristic analysis performed to determine the handgrip strength cutoff values that predict frailty, cutoff values of 16 kg for females and 26.7 kg for males were identified. The area under the curve values for females and males were 0.679 (p<0.001) and 0.790 (p<0.001), respectively.

CONCLUSION: Handgrip strength can be used alone as a predictor to identify individuals living with frailty.

KEYWORDS: Hand strength. Frailty. Sarcopenia. Older adults.

INTRODUCTION

Life expectancy has nearly doubled as a result of advances in modern medicine and public health. The increase in life expectancy has generated several issues. Chronic diseases, cognitive impairments, mental disorders, falls, and other issues have appeared more frequently[1]. These issues have paved the way for the emergence of many innovative markers. One of them is the concept of frailty, which is used to evaluate and manage older adult patients more accurately. Frailty arises from an interruption in the harmonious interaction of biological, genetic, functional, cognitive, psychological, and socioeconomic dimensions. Although there is no formal definition, the general consensus is that it is the accumulation of deficits or losses in physical functions[2]. Frailty is associated with many adverse health outcomes, including the need for care, falls, hospitalization, and mortality. It is consequently critical to detect the frailty status[3].

Many scales have been designed to assess frailty. There is, however, no gold standard scale[4]. The Clinical Frailty Scale (CFS) is one of the most frequently used scales in frailty screening. It was developed in the second phase of the Canadian Study of Health and Aging[5]. Grading is made from 1 to 9. Its usability in the aged population in Türkiye was examined in a study by Aşık et al., and it was identified as a fast, reliable, and valid frailty screening tool for older adults in the Turkish population[6]. The CFS is widely used by non-geriatrician health personnel due to its advantages of easy application, short-time performance, no need for devices, and success in predicting health outcomes in different patient groups[7].

Handgrip strength (HGS) describes a physical function used in the screening of sarcopenia, with different cutoff points for females and males and differences in the cutoff points according to the genetic characteristics of the populations, and it is measured with the help of an auxiliary device[8]. Although lower HGS values are associated with a risk of living with frailty (LWF)[9], it has been questioned whether HGS alone can be used to identify patients LWF[10]. Several researches have been

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conducted to determine the HGS cutoffs that can identify individuals LWF[11,12]. However, the HGS cutoff value, which can detect individuals LWF based on CFS, has not been determined before. Hence, the present study aims to investigate the capacity of HGS to detect individuals LWF by using CFS as a reference scale.

METHODS

Participants

This retrospective study was carried out by including patients who applied to the geriatric outpatient clinic of a university hospital. The inclusion criteria were defined as being 65 years of age or older and having CFS and HGS values recorded in the hospital automation system. Patient demographic information (age, sex, educational level, marital status, and with whom they lived) and other details including presence of chronic diseases, dosage of medications taken, and comprehensive geriatric assessment results were recorded. The usage of five or more medicines per day was considered as polypharmacy, and the presence of two or more chronic diseases together was considered as multimorbidity.

Clinical Frailty Scale

The CFS was developed in the second phase of the Canadian Study of Health and Aging. Individuals are evaluated by taking into account their activities of daily living (ADL), mobility, disease symptoms, cognitive status, and life expectancy. It is a 9-point scale. Level 4 and above are considered as LWF. Levels 1-9 are graded as very fit, fit, managing well, living with very mild frailty, living with mild frailty, living with moderate frailty, living with severe frailty, living with very severe frailty, and terminally ill. The scale's validity and reliability in the Turkish geriatric population have been proven by Aşık et al.[6].

Handgrip strength

The HGS was measured using a hand dynamometer (Grip Strength Takei dynamometer, Niigata City, Japan). The measurement was performed three times with the dominant hand, the elbow flexion at 90°, and a neutrally rotated forearm when the patient was in the sitting position. The highest value was recorded.

Ethical approval

The study was approved by the Non-interventional Research Ethics Board of the Faculty of Medicine, University (blinded for review) (decision number: [blinded for review]). The authors declared that the study was conducted in accordance with the Declaration of Helsinki and the ethical standards of Türkiye were followed.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 24. Categorical variables were expressed as numbers and percentages, and numerical variables were expressed as mean and standard deviation or median and percentiles (p) according to the normal distribution condition. According to the normal distribution, comparisons were made with Student's t-test or Mann-Whitney U test for numerical variables and chi-square test for categorical variables. Binary logistic regression analysis was performed to determine the variables that affect frailty independently. Receiver operating characteristic (ROC) curve analysis was carried out to determine the HGS cutoff values for predicting individuals LWF. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. A p-value of 0.05 was deemed statistically significant.

RESULTS

The median age of 742 patients included in the study was 72.0 years (25p–75p: 68.0–77.0), of which 59.3% (n=440) were female, 78.4% (n=582) were living with multimorbidity, 63.2% (n=469) had polypharmacy, and 49.3% (n=366) were LWF. The median CFS level was 3.0 (25p–75p: 3.0–4.0). There was a statistically significant difference among demographics, clinical characteristics, and geriatric assessment results such as age, educational level, multimorbidity, polypharmacy, Katz ADL, Lawton-Brody Instrumental ADL, Mini Nutritional Assessment-Short Form, Mini-Mental State Examination, Strength, Assistance with Walking, Rising from a Chair, Climbing Stairs, and Falls, HGS, and falls between patients LWF and those not LWF (p=0.004 for multimorbidity and p<0.001 for other variables) (Table 1). According to the results of the binary logistic regression analysis, age, sex, and HGS displayed a statistically significant relationship with frailty (p<0001, p=0.001, and p<0.001, respectively) (Table 2).

The ROC curve analysis performed to determine the HGS cutoff values that predict frailty revealed cutoff values of 16 kg for females and 26.7 kg for males. The area under the curve (AUC) values for females and males were 0.679 (p<0.001) and 0.790 (p<0.001), respectively (Figure 1). The sensitivity, specificity, PPV, and NPV values are summarized in Table 3.

DISCUSSION

The capacity of HGS, one of the indicators of physical performance in older adults, in predicting individuals LWF was evaluated using CFS as a reference scale. The HGS cutoff points for predicting frailty have been identified to be 16 kg for females and 26.7 kg for males. The HGS is capable of detecting individuals LWF according to CFS, which not only provides a physical assessment but also allows the patient to be evaluated from several aspects.

HGS is one of the measures used to assess an individual's physical performance. It is used in the screening of sarcopenia according to the European Working Group on Sarcopenia in Older People criteria and is defined as probable sarcopenia if HGS cutoff value is low[8]. While its main role is in sarcopenia,

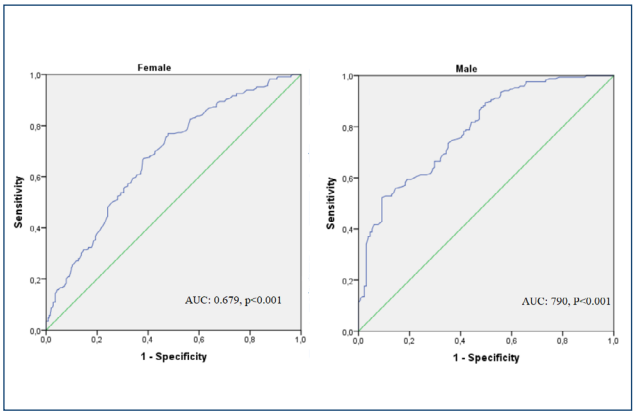

Figure 1. Receiver operating characteristic curve analysis according to sex. ROC: receiver operating characteristic, AUC: area under the curve.

Table 1. Patient demographics, clinical characteristics, and comprehensive geriatric assessment results.

	Total (n=742)	LWF (n=366, 49.3%)	Robust (n=376, 50.7%)	p
Age* (years)	72.0 (68.0-77.0)	74.5 (70.0-80.0)	70.0 (67.0-74.0)	<0.001
Sex (female)	440 (59.3)	224 (61.2)	216 (57.4)	0.30
Education (<8 years)	367 (49.5)	217 (59.3)	150 (39.9)	<0.001
Married	392 (52.8)	196 (53.6)	196 (52.1)	0.70
Living alone	109 (14.7)	55 (15.0)	54 (14.4)	0.80
Smoking	173 (23.3)	85 (23.2)	88 (23.4)	0.95
Multimorbidity	582 (78.4)	303 (82.8)	279 (74.2)	0.004
Polypharmacy	469 (63.2)	261 (71.3)	208 (55.3)	<0.001
Comprehensive geriatric assessment				
Katz ADL*	6.0 (5.0-6.0)	6.0 (5.0-6.0)	6.0 (6.0-6.0)	<0.001
Lawton-Brody Instrumental ADL*	8.0 (7.0-8.0)	8.0 (5.0-8.0)	8.0 (8.0-8.0)	<0.001
Mini Nutritional Assessment-Short Form*	14.0 (12.0-14.0)	13.0 (10.0-14.0)	14.0 (13.0-14.0)	<0.001
Mini-Mental State Examination*	28.0 (25.0-29.0)	26.0 (23.0-28.0)	29.0 (27.0-30.0)	<0.001
SARC-F*	1.0 (0.0-3.0)	3.0 (1.0-5.0)	0.0 (0.0-1.0)	<0.001
HGS# (kg)				
Female	17.6±5.1	16.1±4.7	19.2±5.0	<0.001
Male	26.2±7.4	21.4±6.9	29.5±6.2	<0.001
Falls	182 (24.5)	113 (30.9)	69 (18.4)	<0.001

*Median, 25-75 percentiles. #Mean±standard deviation. A CFS score ≥4 is considered LWF. LWF: living with frailty; ADL: activities of daily living; HGS: handgrip strength; CFS: Clinical Frailty Scale; SARC-F: Strength, Assistance with Walking, Rising from a Chair, Climbing Stairs, and Falls.

Table 2. Binary logistic regression analysis of variables affecting frailty.

	Total			Female			Male		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	P
Age (per year)	1.09	1.06-1.12	<0.001	1.11	1.07-1.16	<0.001	1.06	1.01-1.10	0.02
Sex (female)	2.11	1.38-3.23	0.001	–	–	–	–	–	–
Multimorbidity	1.30	0.88-1.93	0.19	0.96	0.57-1.60	0.86	2.01	1.06-3.78	0.03
HGS (per kg)	0.89	0.86-0.92	<0.001	0.91	0.87-0.95	<0.001	0.88	0.84-0.91	<0.001

CFS score ≥4 is accepted as LWF. LWF: living with frailty; OR: odds ratio; CI: confidence interval; CFS: Clinical Frailty Scale; HGS: handgrip strength.

Table 3. Receiver operating characteristic curve analysis results.

	AUC	HGS cutoff (kg)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total (95%CI)	–	–	57.1 (51.9-62.2)	73.9 (69.2-78.3)	68.1 (62.5-73.3)	63.9 (59.2-68.4)
Female (95%CI)	0.679	16.0	50.9 (44.2-57.6)	76.9 (70.7-82.3)	69.5 (61.9-76.5)	60.1 (54.1-66.0)
Male (95%CI)	0.790	26.7	66.9 (58.5-74.6)	70.0 (62.3-77.0)	66.4 (58.1-74.1)	70.4 (62.7-77.4)

AUC: area under the curve; HGS: handgrip strength; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval; ROC: receiver operating characteristic.

the association between a decrease in HGS and other adverse health outcomes has piqued researchers' interest. Its relationship with a variety of outcomes has been studied across a wide range of patient categories. The risks of cardiometabolic diseases, cognitive impairments, disabilities, hospitalizations, prolonged length of hospital stays, LWF, and mortalities increase with a decrease in HGS[13-15]. It is also part of the locomotory and vitality components of intrinsic capacity (IC)[16]. In addition, considering its relationship with cognition and mood, HGS is an indicator that can be used to monitor overall IC[17]. Therefore, HGS serves as a crucial guide for clinicians in patient follow-up.

Frailty is typically viewed as a complex entity comprising physical, cognitive, psychological, and social components. There is no fully agreed-upon definition[2]. Essentially, three models are used to define frailty: rule-based[18], summing the number of deficits (deficit accumulation)[19], and clinical judgment[5]. A typical example of the rule-based frailty definition is the Fried frailty phenotype (FFP). One of the characteristics of individuals LWF in FFP is low HGS[18]. One of the shortfalls in the deficit accumulation model could be a decrease in HGS[20]. In the clinical judgment model, frailty is specified according to the clinician's decision as a result of the medical history and clinical examination. The CFS is one of the most popular examples of clinical judgment models. The final decision is made by considering conditions, such as mobility, disease symptoms, ADL, cognition, and life expectancy[5]. Although HGS is not one of the elements covered in CFS, there is a significant association between CFS and HGS, particularly in females. The lower the HGS, the higher the CFS level and the risk of LWF[21]. In the present study, CFS and HGS were associated in both sexes independently of other variables.

Although HGS and CFS scores are closely related, HGS cutoff points that can predict LWF have not been determined according to CFS. However, some cutoff points are specified according to other frailty scales. For instance, the HGS cutoff point in the FFP is 20% lower than the values assigned by age and body mass index[18]. It has been stated that different cutoff values can be used in different races due to the difference in the muscle structure between races[22]. In addition, the capacity of HGS alone to detect individuals LWF has been tested in various studies. When FFP is used as a reference scale in older Chinese adults, the HGS cutoff values as a single predictor, which can detect individuals LWF, were 18 kg for females and 28 kg for males[11]. In a study conducted on female rheumatoid arthritis patients, the HGS cutoff value for predicting individuals LWF using the Kihon Checklist as a reference scale was 17 kg[23]. In a Turkish validation study of FFP, the HGS cutoff values were 13.6 kg for females and 27.7 kg for males[24]. In the present study, similar to previous studies, the HGS cutoff values were defined as 16 kg for females and 26.7 kg for males.

Limitations and strengths

This study has some limitations. The association of HGS with adverse health outcomes could not be assessed since the study was cross-sectional in nature. Different clinicians have applied CFS, and this may have caused an operator bias. The study's main strength is that the HGS, which is a physical measurement, has the capacity of detecting individuals LWF in a large sample size and it uses a reference scale that provides a multi-dimensional evaluation of individuals and also includes the clinician's opinion. Another strength is that all patients in the present study underwent a comprehensive geriatric assessment.

CONCLUSION

HGS can be used alone to identify individuals LWF. Prospective studies are needed to ascertain the capacity of determined HGS cutoff values in predicting adverse health outcomes.

AUTHORS' CONTRIBUTIONS

SC: Conceptualization, Data curation, Formal Analysis, Methodology, Resources, Writing – original draft. **YO:** Conceptualization, Data curation, Formal Analysis, Methodology. **MG:** Data curation, Formal Analysis. **AOB:** Data curation, Formal Analysis. **MK:** Data curation, Formal Analysis. **CB:** Supervision , Writing – review & editing. **BBD:** Supervision , Writing – review & editing. **MC:** Supervision , Writing – review & editing. **MGH:** Supervision , Writing – review & editing.

REFERENCES

1. Beard JR, Officer A, Carvalho IA, Sadana R, Pot AM, Michel JP, et al. The world report on ageing and health: a policy framework for healthy ageing. Lancet. 2016;387(10033):2145-54. https://doi.org/10.1016/S0140-6736(15)00516-4
2. Pilotto A, Custodero C, Maggi S, Polidori MC, Veronese N, Ferrucci L. A multidimensional approach to frailty in older people. Ageing Res Rev. 2020;60:101047. https://doi.org/10.1016/j.arr.2020.101047
3. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006;54(6):991-1001. https://doi.org/10.1111/j.1532-5415.2006.00745.x
4. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53-61. https://doi.org/10.1016/j.arr.2015.12.003
5. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-95. https://doi.org/10.1503/cmaj.050051
6. Aşık Z, Kılınç Ş, Kurşun Ö, Özen M. Validation of the Clinical Frailty Scale version 2.0 in Turkish older patients. Geriatr Gerontol Int. 2022;22(9):730-5. https://doi.org/10.1111/ggi.14445
7. Moreno-Ariño M, Torrente Jiménez I, Cartanyà Gutiérrez A, Oliva Morera JC, Comet R. Assessing the strengths and weaknesses of the Clinical Frailty Scale through correlation with a frailty index. Aging Clin Exp Res. 2020;32(11):2225-32. https://doi.org/10.1007/s40520-019-01450-w
8. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31. https://doi.org/10.1093/ageing/afy169
9. Marano L, Carbone L, Poto GE, Gambelli M, Nguefack Noudem LL, Grassi G, et al. Handgrip strength predicts length of hospital stay in an abdominal surgical setting: the role of frailty beyond age. Aging Clin Exp Res. 2022;34(4):811-7. https://doi.org/10.1007/s40520-022-02121-z
10. Syddall H, Cooper C, Martin F, Briggs R, Aihie Sayer A. Is grip strength a useful single marker of frailty? Age Ageing. 2003;32(6):650-6. https://doi.org/10.1093/ageing/afg111
11. Auyeung TW, Lee JS, Leung J, Kwok T, Woo J. The selection of a screening test for frailty identification in community-dwelling older adults. J Nutr Health Aging. 2014;18(2):199-203. https://doi.org/10.1007/s12603-013-0365-4
12. Velghe A, Buyser S, Noens L, Demuynck R, Petrovic M. Hand grip strength as a screening tool for frailty in older patients with haematological malignancies. Acta Clin Belg. 2016;71(4):227-30. https://doi.org/10.1080/17843286.2016.1162381
13. McGrath R, Johnson N, Klawitter L, Mahoney S, Trautman K, Carlson C, et al. What are the association patterns between handgrip strength and adverse health conditions? A topical review. SAGE Open Med. 2020;8:2050312120910358. https://doi.org/10.1177/2050312120910358
14. Kim J. Handgrip strength to predict the risk of all-cause and premature mortality in Korean adults: a 10-year cohort study. Int J Environ Res Public Health. 2021;19(1):39. https://doi.org/10.3390/ijerph19010039
15. Soysal P, Hurst C, Demurtas J, Firth J, Howden R, Yang L, et al. Handgrip strength and health outcomes: umbrella review of systematic reviews with meta-analyses of observational studies. J Sport Health Sci. 2021;10(3):290-5. https://doi.org/10.1016/j.jshs.2020.06.009
16. George PP, Lun P, Ong SP, Lim WS. A rapid review of the measurement of intrinsic capacity in older adults. J Nutr Health Aging. 2021;25(6):774-82. https://doi.org/10.1007/s12603-021-1622-6
17. Arokiasamy P, Selvamani Y, Jotheeswaran AT, Sadana R. Socioeconomic differences in handgrip strength and its association with measures of intrinsic capacity among older adults in six middle-income countries. Sci Rep. 2021;11(1):19494. https://doi.org/10.1038/s41598-021-99047-9
18. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56. https://doi.org/10.1093/gerona/56.3.m146
19. Rockwood K, Mitnitski AB, MacKnight C. Some mathematical models of frailty and their clinical implications. Rev Clin Gerontol. 2002;12:109-17. http://doi.org/10.1017/S0959259802012236
20. Brown JD, Alipour-Haris G, Pahor M, Manini TM. Association between a deficit accumulation frailty index and mobility outcomes in older adults: secondary analysis of the lifestyle interventions and independence for elders (LIFE) study. J Clin Med. 2020;9(11):3757. https://doi.org/10.3390/jcm9113757
21. Spiegowski D, Metzger L, Jain A, Inchiosa MA, Weber G, Abramowicz AE. The utility of grip strength as a simplified measure of frailty in the older adult in the preoperative clinic. Cureus. 2022;14(9):e28747. https://doi.org/10.7759/cureus.28747
22. Bahat G, Kilic C, Altinkaynak M, Akif Karan M. Comparison of standard versus population-specific handgrip strength cut-off points in the detection of probable sarcopenia after launch of EWGSOP2. Aging Male. 2020;23(5):1564-9. https://doi.org/10.1080/13685538.2020.1870038
23. Sobue Y, Suzuki M, Ohashi Y, Koshima H, Okui N, Funahashi K, et al. Validation of grip strength as a measure of frailty in rheumatoid arthritis. Sci Rep. 2022;12(1):21090. https://doi.org/10.1038/s41598-022-21533-5
24. Varan HD, Deniz O, Çöteli S, Doğrul RT, Kızılarslanoğlu MC, Göker B. Validity and reliability of Fried frailty phenotype in Turkish population. Turk J Med Sci. 2022;52(2):524-7. https://doi.org/10.55730/1300-0144.5318

ORIGINAL ARTICLE

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Human papillomavirus vaccination: if the vaccine is important and available, why not use it?

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SUMMARY

BACKGROUND: Human papillomavirus (HPV) is the most common virus of the reproductive tract, is linked to cervical cancer, and can be prevented by vaccination, which is most effective if the vaccine is administered before sexual activity begins.

METHODS: This descriptive, cross-sectional, and qualitative study was based on a survey containing 15 questions delivered to schools in three cities in the ABC region. Two schools from high-income neighborhoods and two from low-income neighborhoods were selected in each city based on real estate values. Data were expressed in absolute numbers and percentages and interpreted by descriptive analysis. The statistical tests of association were performed.

RESULTS: Twelve schools were invited and nine agreed to participate. Of the 4,503 questionnaires delivered, 1,921 were completed by parents and guardians. The vaccination rate was 56.05% in private schools and 66.58% in public schools. Private vs. public school was not an independent factor for vaccination, but residing in a low-income neighborhood and city was a determinant factor. Approximately 40% of the parents/guardians reported not having their children vaccinated, primarily due to concerns about adverse effects.

CONCLUSION: Despite being freely available and proven effective, the human papillomavirus vaccine remains underutilized. The reasons exposed in this paper may be useful in strategies to enhance vaccination coverage.

Trial registration: This study was approved by the research ethics committee under the number 2.143.196.

KEYWORDS: Immunization schedule. Papillomavirus vaccine. Papillomavirus infection. Public health. Brazil.

INTRODUCTION

Human papillomavirus (HPV) is the most common reproductive tract virus and can be acquired by sexually active women and men[1]. It is the main cause of almost all cervical cancers and is responsible for a significant fraction of other genital and oropharyngeal cancers[2]. With approximately 570,000 new cases per year worldwide, cervical cancer is the fourth most common type of cancer among women worldwide[3,4]. It accounts for 311,000 deaths per year and is among the most frequent causes of cancer deaths in women[5,6].

The most effective prevention strategy is the HPV vaccine. Currently, there are three vaccines available: quadrivalent (Gardasil®), bivalent (Cervarix®), and ninevalent vaccine, which is the only one not yet available in Brazil[7]. According to the World Health Organization (WHO), both the available vaccines are safe and may reach efficacy levels of 90–100% if administered before exposure to the virus[8-10].

In this sense, the Brazilian Ministry of Health initiated free Gardasil® vaccinations for girls aged 9-13 years through the Unified Health System in 2014. Subsequently, boys aged 11-15 years were included. However, despite being free, coverage with one dose decreased by 23% from 2014 to 2015, making it necessary to understand the social and structural barriers that caused such a decline[11,12].

Therefore, this study aimed to explore the reasons why children are not being vaccinated and to aid the development of new approaches that encourage better adherence to immunization campaigns.

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METHODS

This descriptive, cross-sectional, and qualitative study received prior approval from the Research Ethics Committee under the number 2.143.196. All participants were informed about the objectives of the study and the use of its data.

Sample selection

In this study, schools were chosen for two reasons: They serve as a gathering place for children of a specific age group and facilitate communication with parents and guardians and they allow for the evaluation of income's impact on public health knowledge.

For each city in the ABC Paulista (São Caetano do Sul, Santo André, and São Bernardo do Campo), two schools from a high-income neighborhood and two from a low-income neighborhood were selected based on the average value of the real estate in each region. Thus, the study involved a total of 12 schools (six public and six private) across six different neighborhoods (three high-income and three low-income).

Data collection

We utilized a survey containing 15 questions about HPV to analyze the knowledge of the parents and guardians of children in the age group targeted by the public vaccination policy. The study was conducted in three stages:

1. Visits to selected schools to issue invitations to the board of directors to participate in this study.
2. Delivery of questionnaires to students in the fourth through ninth grades (age range: 9-14 years). The questionnaires were sent home via school diaries for guardians to complete and then were returned to teachers.
3. Collection of the completed questionnaires.

Statistical analysis

Data collected from the questionnaires were tabulated, expressed in absolute numbers and percentages, and interpreted using a descriptive analysis. Differences between high- and low-income neighborhoods and between public and private schools were compared. A multivariate analysis was performed to evaluate the association between qualitative variables explored in the questionnaires.

RESULTS

Of the 12 pre-selected schools, nine agreed to participate in the study¾six in high-income neighborhoods and three in low-income neighborhoods. Five schools were private and four were public. Of 4,503 questionnaires delivered, only 1,921 were completed.

Profile of parents and/or guardians

The questionnaires were completed mainly by mothers. Regarding educational level, 50% of the respondents had completed higher education and 40% had high school diplomas. Approximately 64.7% had access to the private healthcare system (Table 1). The average age of the respondents was 41.9±7.3 years, and the families had up to four children, aged 6.2±5.3 to 12.2±4.2 years.

Knowledge about human papillomavirus

Almost everyone reported having some knowledge about HPV, with television as the most common source of information (74.1%). Majority of the respondents (68.5%) indicated that their information came from a doctor or other health professionals. When asked about which diseases HPV was related to, 87.7% of the participants said sexually transmitted diseases (STDs) and 62.6% said cancer.

Vaccine against human papillomavirus

The vaccine availability in public and private networks was known by most participants: They knew the ideal age range for vaccination, its appropriate timing, and the guidelines provided by the Ministry of Health (Table 3). However, approximately 40% of the respondents reported not having vaccinated their children, primarily due to concerns about perceived adverse events (Table 2).

Vaccination coverage

Most of the guardians were not afraid to vaccinate their children, but only 60.37% of children were vaccinated. Public schools had the highest percentage of vaccinated students at 66.58%, compared to 56.05% in private schools. A multivariate analysis by logistic regression indicated that the type of school (private vs. public) was not an independent factor for vaccination, but residing in a low-income neighborhood was a significant determinant (Table 3).

DISCUSSION

In the present study, we found that, contrary to what was expected, there was low adherence to a survey that could contribute to public health. There was also resistance from schools to deliver the questionnaires for logistical reasons, religious ties, and concerns about the potential reaction of parents.

Despite these challenges, it is noteworthy that almost all participants had some knowledge about HPV, and approximately 60% took their children for vaccination. In this context, Brabin et al. conducted a similar study in schools on parents and guardians to evaluate the acceptance of HPV vaccination.

Table 1. Profile of the families participating in the study and human papillomavirus transmission according to them | *the (%) that equals less than 100 is due to "not informed" answers.

Variable	Frequency	Percentage (%)
Who answers		
Mother	1.328	79.8
Father	264	15.8
Grandmother	51	3
Grandfather	3	0.18
Sister	3	0.18
Gender		
Female	1.436	86.2
Male	221	13.2
Education		
Elementary education	161	9.6
Secondary education	528	31.7
Higher education	841	50.5
Master's degree	93	5.5
Doctorate	14	0.84
Graduate degree	1	0.06
Medical care		
Agreement	883	53
Public health	428	27.3
Private	134	8
Agreement and public health	21	1.2
Agreement and private	49	2.9
Private and public health	7	0.4
Private, public health, and health insurance	8	0.4
HPV transmission according to participants		
	Frequency	**Percentage (%)**
Way of transmission		
Towel		
Yes	239	14.4
No	1,421	85.6
Sexual		
Yes	1,618	97.6
No	39	2.3
Saliva		
Yes	232	14
No	1,419	85.9
Insect		
Yes	24	1
No	1,626	99
Syringe		
Yes	336	20.3
No	1,315	79.6
Closed environments		
Yes	8	0.4
No	1,641	99.4

HPV: human papillomavirus.

Table 2. Knowledge about the availability and indication for the human papillomavirus vaccine.

Question	Frequency	Percentage (%)
Related to sexual activity		
Yes	1,511	92.6
No	64	3.9
I don't know	55	3.3
Is there a vaccine for women?		
Yes	1,565	94.9
No	15	0.9
I don't know	69	4.1
Is there a vaccine for men?		
Yes	1,246	76
No	102	6.2
I don't know	288	17.5
Availability		
Private	36	2.2
Public health	204	12.5
Both	1,381	84.9
Are children vaccinated?		
Yes	987	60
No	623	37.9
I don't know	33	2
Is there a fear of vaccination?		
Yes	194	11.9
No	1,436	88
Is there an ideal age range for vaccination?		
Yes	1,423	86.9
No	55	3.3
I don't know	158	9.6
What is the age recommended by the MS*?		
Newborns up to 1 year	13	0.8
2-7 years	8	0.5
9-13 years	1,587	97.1
After 18 years	25	1.5
Do vaccines have to be made before the first sexual intercourse?		
Yes	1,004	61.4
No	314	19.2
I don't know	313	19.1
Is there a benefit in receiving the vaccine after the recommended age?		
Yes	1,271	77.5
No	85	5.2
I don't know	278	17

*MS = Ministério da Saúde.

Table 3. Vaccination coverage descriptives and multivariate analysis by logistic regression.

Variable	No		Yes		
	n	%	n	%	
Fear of vaccination?	1,669	88.54%	216	11.46%	
	Vaccinated		Non-vaccinated		
	n	%	n	%	
Total	1,147	60.37%	753	39.63%	
School					
Public	518	66.58%	260	33.42%	p<0.001 (χ^2)
Private	629	56.05%	493	43.94%	
Neighborhood					
Low income	714	69.25%	317	30.75%	p<0.001 (χ^2)
High income	433	49.83%	436	50.17%	
City					
SCS	50	57.47%	37	42.53%	p<0.001 (χ^2)
SA	662	54.26%	558	45.74%	
SBC	435	73.36%	158	26.64%	
Multivariate analysis					
Vaccinated children	**Odds ratio**	**Std. error**	**z**	**p>[z]**	
School (public vs. private)	1.05	0.12	0.43	0.665	
Neighborhood (low vs. high income)	1.85	0.25	4.59	<0.001	
City (SCS, SA, and SBC)	1.36	0.15	2.81	0.005	

SCS: São Caetano do Sul, SA: Santo André, SBC: São Bernardo do Campo.

With a response rate of 22%, it was found that most respondents intended to vaccinate their children but feared its potential side effects[13]; interestingly, these data are still consistent with ours, despite a 10-year difference.

Besides, it is already well established that school-based HPV vaccination programs have improved vaccine uptake among adolescents worldwide, and school-based vaccination has proven to be an effective tool in increasing vaccination equity even during the most recent COVID-19 pandemic[14,15]. It has also been shown that after implementing a vaccination promotion program, the HPV vaccination uptake tends to rise, especially in schools where on-site vaccination events take place[16,17]. Thus, it would be reasonable to expect that both private and public schools would greet our effort to further expand the knowledge about HPV and the available vaccination programs. However, there were challenges in establishing contact with institutions from both sectors, and we found it easier to schedule a meeting and deliver questionnaires to private schools in high-income neighborhoods in Santo André. In public schools, the delivery was possible through a meeting with the State Department of Education, which was requested to help contact schools. Nevertheless, return rates were similar between public and private schools, which might be due to the questionnaires being delivered to children in the fourth and fifth grades only, an age group in which parents and guardians tend to accompany children to visits with doctors and the interest in vaccination may be greater.

Furthermore, most participants reported having heard about HPV, with the Internet being the most common source of information. This trend reflects findings from prior studies that were conducted before the implementation of vaccination as a public health policy[18,19]. Although convenient, this method of learning poses risks, as the media can disseminate incorrect information. It must be mentioned, however, that the role of healthcare providers in vaccine uptake cannot be overlooked. More specifically, a study conducted by the Cochrane group has found that positive interactions with frontline healthcare workers were positively associated with vaccination acceptance, thus reinforcing the positive influence that well-trained professionals might have in combating misinformation and providing parents with scientifically accurate guidance[20].

Still, healthcare providers are not the only influential source of information. In a study on vaccine knowledge among students, mothers, and teachers in public schools in Recife-PE, Silva et al. found that participants pointed to schools as the most effective medium to disseminate knowledge[21]. The discussion about sexuality and the fear of encouraging early sexual practice was one of the obstacles to vaccination education. The fear of adverse reactions to vaccination was also raised.

However, postponing vaccination implies reducing the chances of preventing HPV infections. The lack of knowledge of this information by parents or guardians and the association made between HPV and other STDs may prevent the immunization of children. Thus, the American Society of Clinical Oncology (ASCO) reinforced the need for more aggressive policies to increase the rate of HPV vaccination; the American Cancer Society (ACS), through the National HPV Vaccination Roundtable, created the Vaccinate Adolescents Against Cancer program to promote awareness and education, and in July 2016, the ACS instituted new guidelines, recommending that all men and women receive the vaccine, which shows the importance of vaccination to prevent cancers related to HPV infection[22].

Recently, the Commission for the Defense of Women's Rights in the Brazilian Chamber of Deputies held a public hearing to expand HPV vaccination, as coverage remains far from the target, especially among boys, whose vaccination rate is below 25%[23]. Our analysis found that living in a low-income neighborhood significantly impacted vaccination rates. Furthermore, currently, we are still facing the aftermath of the COVID-19 pandemic, so interest in the topic discussed in this study has decreased. It has been previously shown that the high HPV vaccination coverage in girls could practically lead to the eradication of cervical cancer in most low- and middle-income countries by the end of the century; however, given the present situation, the HPV infection rate may worsen in the future as the pandemic has caused a major setback in childhood vaccinations worldwide[24,25].

In summary, addressing HPV in elementary schools is challenging due to logistical and cultural factors, including the stigma associated with discussing sexual health. Reinforcing the relationship between HPV and cancer in public policies is essential, and incorporating scientific discussions on vaccinations in science classes could be a viable strategy not only to educate young people about the importance of the vaccine but also to separate the vaccination campaign from discussions about sexual activity while minimizing the impact of misinformation in the media and on social networks.

CONCLUSION

Despite being freely available and proven effective, the HPV vaccine remains underutilized. The present study provides insights into the reasons why parents and guardians choose not to vaccinate their children, along with the socioeconomic data for reference. This information may be useful in actions aimed at increasing vaccine coverage in the target population.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ABC Medical School board review (Research Ethics Committee) under the number 2.143.196.

AUTHORS' CONTRIBUTIONS

GSF: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **CLRA:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **JJR:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **CBA:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **CVMS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **JVBB:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **JHMS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **LVAS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **ADG:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **DIGC:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. Gearhart PA. Human papillomavirus. [cited on 2024 Jun 13]. 2024. Available from: http://emedicine.medscape.com/article/219110-overview#a2
2. Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141(4):664-70. https://doi.org/10.1002/ijc.30716
3. Arbyn M, Weiderpass E, Bruni L, Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020;8(2):e191-e203. https://doi.org/10.1016/S2214-109X(19)30482-6
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/

caac.21492. Erratum in: CA Cancer J Clin. 2020;70(4):313. PMID: 30207593

5. International Agency for Research on Cancer (IARC). [cited on 2024 June 13]. 2024. Available from: https://gco.iarc.fr/today/home
6. Instituto Nacional de Câncer (INCA, Brazil). Números de câncer. [cited on 2024 Jun 13]. 2023. Available from: https://www.inca.gov.br/numeros-de-cancer
7. Instituto Nacional de Câncer (INCA, Brazil). HPV e câncer - Perguntas mais frequentes. [cited on 2024 Jun 13]. Available from: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/colo_utero/hpv-cancer-perguntas-mais-frequentes
8. Mishra GA, Pimple SA, Shastri SS. Prevention of cervix cancer in India. Oncology. 2016;91(Suppl 1):1-7. https://doi.org/10.1159/000447575
9. Handler NS, Handler MZ, Majewski S, Schwartz RA. Human papillomavirus vaccine trials and tribulations: vaccine efficacy. J Am Acad Dermatol. 2015;73(5):759-67;quiz 767-8. https://doi.org/10.1016/j.jaad.2015.05.041
10. Herrero R, González P, Markowitz LE. Present status of human papillomavirus vaccine development and implementation. Lancet Oncol. 2015;16(5):e206-16. https://doi.org/10.1016/S1470-2045(14)70481-4
11. Instituto Nacional de Câncer (INCA, Brazil). Para saber mais: profissional de Saúde. [cited on 2024 Jun 13]. 2023. Available from: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/colo_utero/definicao
12. Nogueira-Rodrigues A, Bukowski A, Paulino E, Louis J, Barrichello A, Sternberg C, et al. An alert to Latin America: current human papillomavirus vaccination trends highlight key barriers to successful implementation. Cancer. 2017;123(12):2193-9. https://doi.org/10.1002/cncr.30647
13. Brabin L, Roberts SA, Farzaneh F, Kitchener HC. Future acceptance of adolescent human papillomavirus vaccination: a survey of parental attitudes. Vaccine. 2006;24(16):3087-94. https://doi.org/10.1016/j.vaccine.2006.01.048
14. Shin MB, Sloan K, Baezconde-Garbanati L, Dang E, Garcia S, Palinkas LA, et al. Multilevel perspectives on school-based opportunities to improve HPV vaccination among medically underserved adolescents: beyond school entry mandates. Hum Vaccin Immunother. 2023;19(2):2251815. https://doi.org/10.1080/21645515.2023.2251815
15. Morissette A, Lefebvre G, Bacque-Dion C, Bélanger R, Cazelais-Asselin F, Lalonde B, et al. Disparities in high schools' vaccination coverage (COVID-19). A natural experiment in the Province of Quebec. Prev Med. 2022;159:107056. https://doi.org/10.1016/j.ypmed.2022.107056
16. Kaul S, Do TQN, Hsu E, Schmeler KM, Montealegre JR, Rodriguez AM. School-based human papillomavirus vaccination program for increasing vaccine uptake in an underserved area in Texas. Papillomavirus Res. 2019;8:100189. https://doi.org/10.1016/j.pvr.2019.100189
17. Rane MS, Page LC, McVeigh E, Miller K, Baure D, Elizabeth Halloran M, et al. Improving adolescent human papillomavirus (HPV) immunization uptake in school-based health centers through awareness campaigns. Vaccine. 2021;39(12):1765-72. https://doi.org/10.1016/j.vaccine.2021.02.006
18. Silveira CF, Melo MMD, Rodrigues LR, Parreira BDM. Knowledge of 40-60 year old women about human papillomavirus. Northeast Netw Nurs J. 2011;12(2):309-15.
19. Pereira RGV, Machado JLM, Machado VM, Mutran TJ, Santos LS, Oliveira E, et al. A influência do conhecimento na atitude frente à vacina contra o papilomavírus humano: ensaio clínico randomizado. ABCS Health Sci. 2016;41(2):78-83.
20. Cooper S, Schmidt BM, Sambala EZ, Swartz A, Colvin CJ, Leon N, et al. Factors that influence parents' and informal caregivers' views and practices regarding routine childhood vaccination: a qualitative evidence synthesis. Cochrane Database Syst Rev. 2021;10(10):CD013265. https://doi.org/10.1002/14651858.CD013265.pub2
21. Silva PMC, Silva IMB, Interaminense INCS, Linhares FMP, Serrano SQ, Pontes CM. Conhecimento e atitudes sobre HPV e vacinação. Esc Anna Nery 2018;22(2):e20170390
22. Hackethal V. ACS recommends HPV vaccine for girls and boys ages 11 12. [cited on 2024 Jun 13]. 2016. Available from: http://www.medscape.com/viewarticle/866337
23. Camara Dos Deputados (Chamber of Members, Brazil). Debatedores pedem medidas para ampliar a vacinação contra o HPV. Brasília, 30/10/2019. [cited on 2024 Jun 13]. 2019. Available from: https://www.camara.leg.br/noticias/607184-debatedores-pedem-medidas-para-ampliar-a-vacinacao-contra-o-hpv/
24. WHO. COVID-19 pandemic leads to major backsliding on childhood vaccinations, new WHO, UNICEF data shows. [cited on 2024 Jun 13]. 2021. Available from: https://www.who.int/news/item/15-07-2021-covid-19-pandemic-leads-to-major-backsliding-on-childhood-vaccinations-new-who-unicef-data-shows
25. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet. 2020;395(10224):575-90. https://doi.org/10.1016/S0140-6736(20)30068-4

ORIGINAL ARTICLE

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Diagnostic accuracy of tru-cut biopsy and acid cytology from patients operated with suspicious for ovarian cancer**

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SUMMARY

OBJECTIVE: In women who are believed to have ovarian cancer but have a poor performance status or have advanced disease thought to be beyond the scope of primary cytoreductive surgery, neoadjuvant chemotherapy can be administered with acid cytology and/or tru-cut biopsy referral. The aim of this study was to determine the accuracy, adequacy, safety, and reliability of these minimally invasive interventional procedures.

METHODS: This is a retrospective analysis of 63 patients with a suspicion of ovarian cancer who reported to Bezmialem University Hospital between 2014 and 2021, underwent ultrasound-guided acid cytology and tru-cut biopsy, and also had postoperative final pathology results.

RESULTS: On comparing acid cytology and tru-cut biopsy at the same time with the postoperative final pathology results, it was seen that the positive predictive value was 100% in all groups. It was revealed that the sensitivity of acid cytology was 64%, the specificity was 100%, the negative predictive value was 12%, and the accuracy of the test was 65%. The sensitivity of the tru-cut biopsy was 91%, the specificity was 100%, the negative predictive value was 42%, and the accuracy of the test was 92%. In the case of both procedures, the sensitivity was calculated as 93% and the accuracy of the test was calculated as 93%. There were no false-positive cytology and biopsy results.

CONCLUSION: Due to its high reliability and accuracy, the combined application of these minimally invasive methods has the potential to routinely replace more invasive methods for adequate tumor sampling, such as diagnostic laparoscopy or exploratory laparotomy.

KEYWORDS: Ultrasound. Biopsy. Cytology.

INTRODUCTION

Ovarian cancer has the second highest mortality rate of all gynecological malignancies[1]. Patients do not apply to the hospital at an early stage due to their non-specific symptoms, so only 30% of cases can be diagnosed at stage I or II, and the majority of ovarian cancer cases are diagnosed at an advanced stage[2]. It is a disease with a poor prognosis since it can be diagnosed at an advanced stage, with high recurrence rates despite treatment and low disease-free and overall survival rates in the advanced stage.

The primary treatment for advanced-stage ovarian cancer is primary debulking surgery (PDS) or interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT), depending on whether surgical excision is possible or not and the comorbidities of the patients[3]. One of the most important factors affecting survival in ovarian cancer is the ability to achieve complete resection or at least optimal cytoreduction (the largest tumor diameter should be less than 1 cm) with surgery[4]. The PDS approach minimizes the tumor burden of patients and contributes effectively to the postoperative chemotherapy process. However, patients with diffuse deep involvement of the small intestinal mesentery, diffuse infiltration of the stomach or duodenum, multiple liver metastases (multisegmental), diffuse carcinomatosis of the small intestine, involvement of the head or the large part of the pancreas, unresectable lymph node disease (e.g., thoracic), multiple lung metastases, and brain metastases are not suitable for PDS[5]. Additionally, IDS is preferred in some patients because their poor preoperative performance and poor nutritional status are associated with postoperative morbidity and mortality[6].

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Today, image-guided biopsy/ascites cytology application using ultrasonography (USG), computed tomography (CT), or magnetic resonance (MR) guidance is precious in the presence of an advanced-stage ovarian cancer suspicion. However, ultrasound-guided methods, with the flexibility to use transvaginal, transabdominal, and transrectal approaches, offer benefits and have minimal risk of complications, high accessibility, and low costs compared to CT or MR guidance[7]. Usually, a histological diagnosis can be achieved without diagnostic laparoscopy or laparotomy by providing a site-specific primary tumor diagnosis. Tissue sampling by diagnostic laparoscopy or laparotomy requires general anesthesia and hospitalization, resulting in higher costs and potential surgical morbidity.

The present study was designed to compare the tru-cut biopsy/ascites cytology samples obtained under preoperative ultrasound guidance and the postoperative final pathology results of the patients operated on with a preliminary diagnosis of ovarian cancer. The primary aim was to compare the consistency of tru-cut biopsy and ascites cytology results with the final pathology results (accuracy). Our secondary aim was to determine these procedures' safety, reliability, and proficiency.

METHODS

This study was a retrospective analysis of the tru-cut biopsy, ascites cytology, and postoperative final pathology results of patients with suspicious ovarian cancer who reported to the Department of Obstetrics and Gynecology in Bezmialem University Hospital, Turkey, between January 2014 and December 2021. The Non-interventional Ethics Committee decision number of the study was 2022/31. Data were collected by reviewing electronic patient records, including USG/MR/CT/positron emission tomography reports, laboratory tests, and pathology/surgery reports. The radiologists obtained written informed consent from all patients before the tru-cut biopsy or ascites cytology procedure.

The study included patients who were initially evaluated for ovarian cancer based on imaging, laboratory tests and physical examination findings, but in whom optimal cytoreduction was not possible; patients with a history of previous malignancy and suspected recurrence; patients who were not suitable for PDS due to comorbidities and performance status; and patients who underwent tru-cut biopsy and/or ascitic cytology to make the differential diagnosis of benign (tuberculosis, chronic pelvic infections) and malignant (lymphoma, gastrointestinal system tumors) diseases that were clinicoradiologically similar to ovarian cancer. These patients were also patients with final pathology results who had been operated on with or without NACT. Patients for whom tru-cut/acid cytology results were not available, who died during the NACT treatment, who were lost to follow-up after tru-cut/acid cytology samples were taken or after receiving NACT, and who were under the age of 18 years were excluded from the study.

The patients' demographic characteristics, physical examination findings, laboratory test results, imaging findings, the site of the biopsy obtained, histopathological features in the tru-cut biopsy and ascites cytology, and final pathology reports were analyzed using the hospital database. The statistical evaluation was performed accordingly.

Ascites cytology technique

Following the determination of the localization where the procedure would be performed by abdominal USG, immediately after the application of local anesthesia to this area with Locanest Spray containing 10% lidocaine, paracentesis guided by abdominal USG was performed with a 20-Gauge Spinal Needle Quincke 6" to collect at least 60 cc of the ascites fluid.

Tru-cut biopsy technique

The biopsy was not performed if international normalized ratio (INR) >1.5 or platelet<50,000 cells/mL in the peripheral blood of the patients. In patients using anticoagulants, the drug was discontinued 5 days before the procedure and was restarted after the procedure. Following the determination of the localization where the procedure would be performed with abdominal USG, 5 min after the application of local anesthesia to this area with 3 cc subcutaneous injection of 2% prilocaine hydrochloride, a tru-cut biopsy guided by abdominal USG was performed with the help of 17-Gauge TruGuide Bard coaxial needle and 18-Gauge Max-Core gun to obtain at least two tissue cylinders of 20 mm long.

The Doppler imaging feature of USG was also utilized during the procedure. In this way, the inferior epigastric artery and vein were visualized and vascular injuries were avoided during the needle entry into the abdomen. In addition, attention was paid to the mesenteric vascular structures that may be close to the tissues to be biopsied in the abdomen. Since the vascularity in the tissues can also be evaluated with the help of Doppler imaging, instead of necrotic tissues, live tissues with vascularity were detected in the tumoral areas to be biopsied, and the adequacy of the material that can provide tissue diagnosis was ensured. Another advantage of USG is that it is mobile during the procedure, thus enabling simultaneous tissue acquisition from different localizations within the same mass by moving with the needle.

In this study, radiologists who performed USG-guided paracentesis and tru-cut biopsy procedures have 10, 20, and

25 years of experience, respectively. As indicated in previous studies, we know that performing these procedures with the help of experienced radiologists, especially under USG guidance, has a crucial role in tissue sufficiency[8].

Histopathological evaluation

All cytology and tissue samples obtained in our study were examined by two experienced pathologists. All tru-cut biopsy and acid cytology materials examined by the pathologist; reported detailing tumor origin and histological subtype.

Statistical evaluation

In this study, the descriptive statistics of the qualitative variables were presented as numbers and percentages, and the descriptive statistics of the quantitative variables were presented as mean, median, standard deviation, and minimum and maximum values. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated with confidence intervals for evaluating ascites cytology and tru-cut biopsy techniques in terms of final pathology results. The SPSS (version 28) package program was used in the analyses.

RESULTS

Between January 2014 and December 2021, a total of 76 patients were evaluated at our department. In the examinations, three patients who were known to have had IDS but whose tru-cut/acid cytology results were not available before NACT, three patients who died during NACT treatment and therefore debulking surgery could not be performed, two patients who were lost to follow-up after tru-cut/acid cytology procedures, four patients whose surgery was not performed in our hospital after NACT, and one patient under the age of 18 years were identified. Sixty-three patients were included in the study after exclusion (Figure 1). The patients were divided into three groups. In 12 of these patients, only acid cytology was obtained before the operation, and only tru-cut biopsy was taken in 22 of them. In 29 patients, both acid cytology and tru-cut biopsy were taken.

The mean age of the 63 female patients included in the study was 62 years, the mean body mass index was 28.5 kg/m², and the mean serum CA125 value was 1,546 U/mL. The complaints, comorbidities, presence of preoperative ascites, Eastern Cooperative Oncology Group scores, clinical stages, and biopsy sites of the patients are presented in Table 1. There were no major differences in the preoperative evaluation between the groups. Tru-cut biopsy

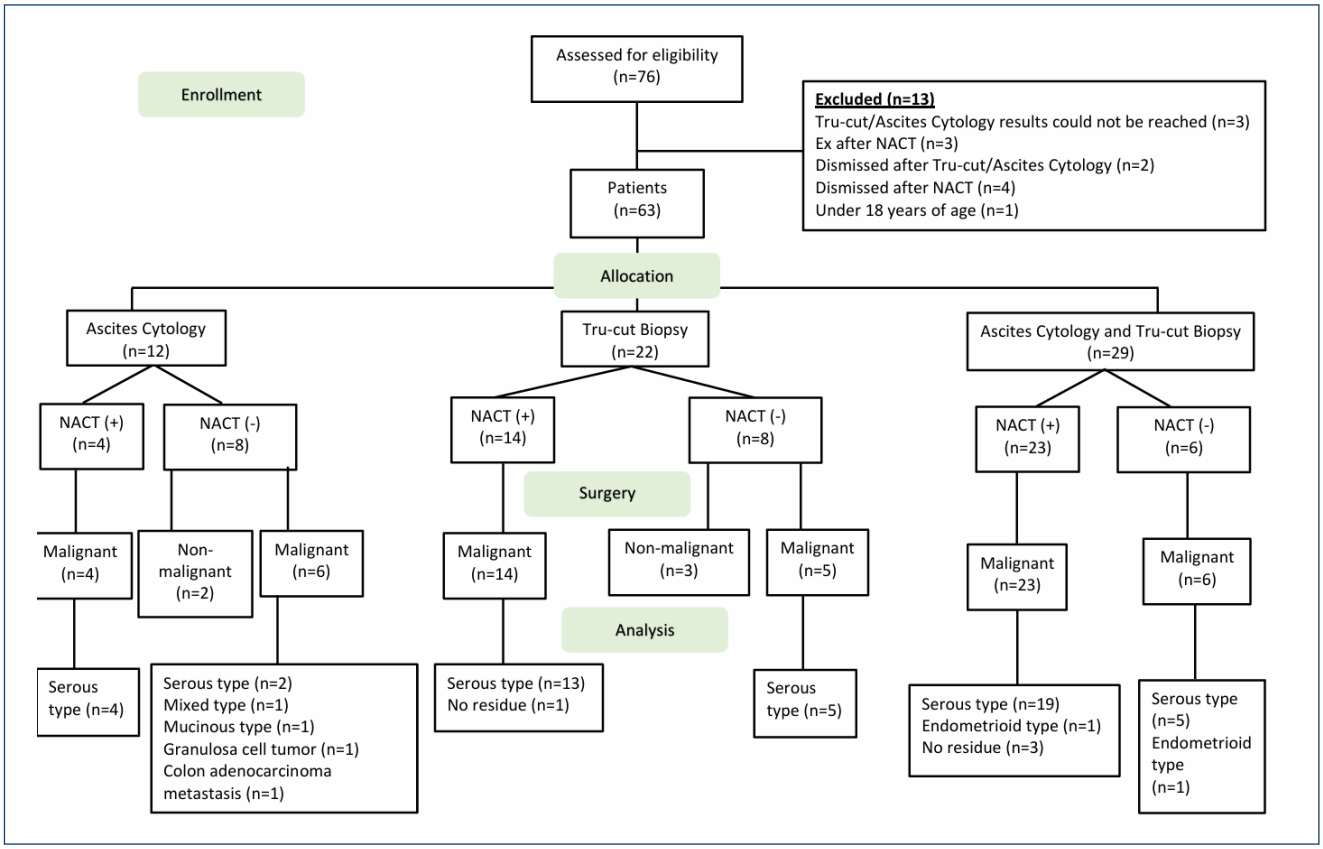

Figure 1. Flowchart of the study.

Table 1. Preoperative evaluation of patients and biopsied sites.

Parameters (n=63)	
Age (years); mean±SD** (range)	62.5 ± 11.2 (32–81)
BMI* (kg/m²); mean±SD (range)	28.6 ± 5.1 (16.2–44.1)
CA125 (U/ml); mean±SD (range)	1546.0 ± 2365.0 (7.2–2230.0)
Complaint; n%	
Pain, swelling, palpable mass	42 (66.7)
Constipation, diarrhea, weight loss	3 (4.8)
Urinary complaint, abnormal uterine bleeding	6 (9.5)
Loss of appetite	7 (11.1)
Shortness of breath	5 (7.9)
Presence of comorbidity***;n%	38 (60.3)
Presence of preoperative ascites; n%	56 (88.9)
ECOG**** score; n%	
0	10 (15.9)
1	27 (42.9)
2	21 (33.3)
3	5 (7.9)
Clinical stage; n%	
2	8 (12.7)
3	38 (60.3)
4	17 (27)
Biopsy location; n%	
Omentum	15 (23.9)
Peritoneum	24 (38.1)
Mass	8 (12.7)
Other	4 (6.3)

*Body mass index; ** standard deviation.
***Comorbidity defined as hypertension, diabetes mellitus, and cardiac, metabolic, and cerebrovascular disorders.
****Eastern Cooperative Oncology Group. SD: standard deviation; BMI: body mass index; Eastern Cooperative Oncology Group.

was obtained from the omentum in 15 patients, the peritoneum in 24, the pelvic mass in 8, the liver in 2, right cervical lymphadenopathy (LAP) in 1, and left inguinal LAP in 1 patient.

Ascites cytology was obtained in 41 of the 63 patients included in the study. In 25 of these patients, both the ascites cytology and final pathology results were reported as "malignant" (true-positive cytology). In two patients, both ascites cytology and final pathology results were reported as "benign" (true-negative cytology). Incompatibility was present in 14 patients. The final pathology results of these patients whose ascites cytology was "non-malignant" were reported as "malignant" (false-negative cytology). There was no patient whose ascites cytology result was "malignant" but whose final result was reported as "non-malignant" (false-positive cytology). Tru-cut biopsy was taken in 51 patients. The biopsy was true positive in 44 of the 51 patients and true negative in three patients. There was incompatibility in four patients (false-negative biopsy). There was no false-positive biopsy. Both ascites cytology and tru-cut biopsy were taken in 29 patients. If at least one of the two procedures was reported as "malignant," the result was evaluated as "malignant." There was a true-positive result in 27 patients and a false-negative result in two patients. In two of the true-positive patients, tru-cut biopsy was benign, while acid cytology was reported as malignant, and in eight of them, tru-cut biopsy was malignant, while acid cytology was reported as benign. True negativity could not be assessed since no patients in this group had a "non-malignant" final result. False positivity was not present. Among the patients included in the study, the final pathology results of five patients were reported as benign. These patients were thought to have ovarian cancer clinically and radiologically.

When the pathology results of patients with acid cytology and tru-cut biopsy were compared with the postoperative final pathology results, we found that the PPV was 100% in all groups. We found that the sensitivity of the acid cytology procedure was 64%, the specificity was 100%, the NPV was 12%, and the accuracy of the test was 65%. We found that the sensitivity of the tru-cut biopsy procedure was 91%, the specificity was 100%, the NPV was 42%, and the accuracy of the test was 92%. In the case of both procedures, we found that the sensitivity was 93% and the accuracy of the test was 93%. However, the specificity and NPV could not be calculated since there were no patients in the third group whose final pathology result was reported as benign (Table 2).

The present study performed 97 ultrasound-guided minimally invasive procedures. The tru-cut biopsy material was reported as insufficient in one patient and acid cytology material in four patients, but sufficient tissues and cells were obtained in the second attempt. Therefore, the results of 92 procedures were available, 51 tru-cut biopsy and 41 acid cytology. Adverse events occurred in two of them during the procedure. One was subcutaneous hemorrhage after tru-cut biopsy, and the other was drainage catheter-related closed perforation in the colon. The adverse event rate was 2%.

DISCUSSION

In recent years, IDS has become an option for advanced ovarian cancer. Randomized controlled studies on large populations

Table 2. Evaluation of the sensitivity, specificity, positive predictive value*, negative predictive value**, and accuracy of ascites cytology and tru-cut biopsy.

Procedures	Sensitivity (95%CI) (%)	Specificity (95%CI) (%)	PPV (95%CI) (%)	NPV (95%CI) (%)	Accuracy (%)
Ascites cytology (n=41)	64.1 (47.1–78.3)	100 (19.7–100)	100 (83.4–100)	12.5 (2.2–39.5)	65.9
Tru-cut biopsy (n=51)	91.7 (79.1–97.2)	100 (30.9–100)	100 (89.9–100)	42.8 (11.8–79.7)	92.2
Ascites cytology+tru-cut biopsy (n=29)	93.1 (75.7–98.7)	N/A	100 (84.4–100)	N/A	93.1

*Positive predictive value. **Negative predictive value. Patients who underwent both procedures were included in the first and second groups. CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

have revealed that IDS has the advantages of achieving optimal cytoreduction, providing palliative chemotherapy, and increasing the quality of life when evaluated together with emotional and cognitive functions. It also saves time in the preparation of the operation for patients who are not suitable for the operation because of the high risk of morbidity/mortality after cytoreductive surgery[9,10]. Tissue diagnosis should usually be obtained by image-guided paracentesis, biopsy, or surgery (laparoscopy, laparotomy) before NACT can be initiated. Ascites cytology and tru-cut biopsy techniques are less invasive methods for diagnosing malignancies. These techniques can be particularly useful in patients unsuitable for primary surgery and may obviate the need for open or closed surgical procedures.

The accuracy of ascites cytology and tru-cut biopsy was evaluated in the present study. In the study by Baransi et al., including 551 patients, the sensitivity, specificity, PPV, and NPV values of ascites cytology in the diagnosis of epithelial ovarian cancer were 80.6, 100, 100, and 16.7%, respectively[11]. However, we found that the sensitivity, specificity, PPV, NPV, and accuracy of acid cytology were 64, 100, 100, 12, and 65%, respectively. In our study, patients who underwent acid cytology also had non-epithelial ovarian cancer and metastases from another cancer in their final pathology results. Serous adenocarcinomas may show papillary configuration and psammoma bodies on cytological evaluation, whereas their absence in other acid-produced carcinomas may explain the low sensitivity.

In the study by Zikan et al., in which 195 tru-cut biopsies including 190 patients were performed, the diagnostic accuracy was 98.3%[12]. In our study, the diagnostic accuracy of tru-cut biopsy was found to be 92%. The only study similar to ours was the study published by Vlasak et al. in 2020, which compared the diagnostic reliability, accuracy, and safety of ultrasound-guided ascites cytology and tru-cut biopsy, covering 79 patients. The rates of the confirmation of malignancy and compliance with the final report were, respectively, 72.9 and 43.7% for the cytology and 95.8 and 95.4%, respectively, for the tru-cut biopsy. However, not all patients included in the study had final pathology results. There are also patients whose disease progresses and cannot be operated on despite NACT[13].

Mascilini et al. evaluated the diagnostic accuracy of transvaginal ultrasound-guided biopsy. The accuracy of biopsy over surgery was found to be 94% (96/102), which was similar to ours, while six false-negative cases (6%) were reported. Biopsy correctly identified 86 primary invasive tubo-ovarian carcinomas and 10 metastatic tumors. In addition, tumor location (prevesical peritoneum) and size (<8 mm) were cited as the major predictive factors for ultrasound-guided biopsy failure (false negativity)[14]. False-positive cytology and biopsy results, which could lead to unnecessary NACT, were not reported in any other study, including ours. These results show that NACT can be administered safely to patients determined to be "malignant" with ascites cytology and tru-cut biopsy to diagnose ovarian cancer. However, it is seen that the sensitivity for tru-cut biopsy is much higher than that for ascites cytology, so a tru-cut biopsy is more reliable than ascites cytology in detecting patients with ovarian cancer.

While the adverse event rate detected in our study was 2%, this rate was similarly found to be 1% in the study by Zikan et al.[12]. In another study evaluating the accuracy, adequacy, safety, and clinical use of tru-cut biopsy in gynecological cancers, infection-related complications occurred in four of 300 patients (1.3%), who underwent biopsy[15]. To achieve these rates, adverse events observed in previously published studies related to tru-cut biopsy were considered, and the procedure was performed by confirming that the patients' routine platelet and INR values were appropriate before the procedure and attention was paid to sterilization.

The fact that all patients had final pathology results and that we could compare ascites cytology and tru-cut biopsy simultaneously both with the final pathology results and among themselves reflects the study's strength. Being single-center in design and having two pathologists evaluating all pathology reports increase the study's objectivity. The 10 years or more experience of the radiologists who performed these minimally invasive procedures under USG guidance added strength to our research. However, because of the study's retrospective nature,

the choice of who would or would not perform the procedures and the decision about suitability for surgery after NACT were variables we could not control. In clinical practice, disagreements are not uncommon within the council that decides on the suitability of these patients for surgery. The relatively small number of patients included in the study also limits the results obtained regarding the safety, adequacy, reliability, and accuracy parameters we investigated in the study.

CONCLUSION

Ultrasound-guided tru-cut biopsy currently appears to be the single best minimally invasive method for collecting sufficient tissue samples for histopathological examination. It is also suitable for confirming recurrences, diagnosing non-gynecological malignancies infiltrating the pelvic organs, or distinguishing between malignant and benign tumors. When acid cytology can be added to this procedure, the probability of false-negative results appears to be much less. However, when tru-cut biopsy is not possible, considering ascites cytology alone as a diagnostic method does not seem appropriate, as it would not allow a significant proportion of patients suitable for IDS to benefit from NACT. Due to its high reliability and accuracy, the combined application of these minimally invasive methods has the potential to routinely replace more invasive methods for adequate tumor sampling, such as diagnostic laparoscopy or exploratory laparotomy.

AUTHORS' CONTRIBUTIONS

FBT: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **GK:** Conceptualization, Methodology, Writing – review & editing. **CC:** Investigation, Supervision. **BG:** Project administration. **OP:** Formal Analysis. **TFY:** Project administration.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. Nakamura K, Banno K, Yanokura M, Iida M, Adachi M, Masuda K, et al. Features of ovarian cancer in Lynch syndrome (Review). Mol Clin Oncol. 2014;2(6):909-16. https://doi.org/10.3892/mco.2014.397
3. Okunade KS, Adekanye TV, Osunwusi B, Harry AS, Okoro AC, Toks-Omage E, et al. Survival outcomes following interval versus primary debulking surgery in advanced epithelial ovarian cancer: a retrospective cohort study in Lagos, Southwest Nigeria. Res Sq [Preprint]. 2024;rs.3.rs-3834135. https://doi.org/10.21203/rs.3.rs-3834135/v1
4. Romero V, Angeles MA, Rodríguez González E, Cabarrou B, Gil-Moreno A, Pérez-Benavente A, et al. Outcomes of minimal residual disease at upfront debulking surgery compared with complete cytoreduction after neoadjuvant chemotherapy. Int J Gynecol Cancer. 2025;ijgc-2024-005692. https://doi.org/10.1136/ijgc-2024-005692
5. Pinelli C, Guerrisi R, Brusadelli C, Artuso V, Majd HS, Bogani G, et al. Interval debulking surgery for advanced ovarian cancer: when, how and why? Gynecol Pelvic Med. 2021;4:16.
6. Aletti GD, Eisenhauer EL, Santillan A, Axtell A, Aletti G, Holschneider C, et al. Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. Gynecol Oncol. 2011;120(1):23-8. https://doi.org/10.1016/j.ygyno.2010.09.010
7. Asp M, Mockute I, Måsbäck A, Liuba K, Kannisto P, Malander S. Tru-cut biopsy in gynecological cancer: adequacy, accuracy, safety and clinical applicability. J Multidiscip Healthc. 2023;16:1367-77. https://doi.org/10.2147/JMDH.S396788
8. Verschuere H, Froyman W, Bosch T, Hoefs M, Kaijser J, Schoubroeck D, et al. Safety and efficiency of performing transvaginal ultrasound-guided tru-cut biopsy for pelvic masses. Gynecol Oncol. 2021;161(3):845-51. https://doi.org/10.1016/j.ygyno.2021.03.026
9. Yang L, Zhang B, Xing G, Du J, Yang B, Yuan Q, et al. Neoadjuvant chemotherapy versus primary debulking surgery in advanced epithelial ovarian cancer: a meta-analysis of peri-operative outcome. PLoS One. 2017;12(10):e0186725. https://doi.org/10.1371/journal.pone.0186725
10. Narasimhulu DM, Fagotti A, Scambia G, Weaver AL, McGree M, Quagliozzi L, et al. Validation of a risk-based algorithm to reduce poor operative outcomes after complex surgery for ovarian cancer. Int J Gynecol Cancer. 2023;33(1):83-8. https://doi.org/10.1136/ijgc-2022-003799
11. Baransi S, Michaan N, Gortzak-Uzan L, Aizic A, Laskov I, Gamzu R, et al. The accuracy of ascites cytology in diagnosis of advanced ovarian cancer in postmenopausal women prior to neoadjuvant chemotherapy. Menopause. 2020;27(7):771-5. https://doi.org/10.1097/GME.0000000000001534
12. Zikan M, Fischerova D, Pinkavova I, Dundr P, Cibula D. Ultrasound-guided tru-cut biopsy of abdominal and pelvic tumors in gynecology. Ultrasound Obstet Gynecol. 2010;36(6):767-72. https://doi.org/10.1002/uog.8803
13. Vlasak P, Bouda J, Kostun J, Berezovskiy D, Zikan M, Weinberger V, et al. Diagnostic reliability, accuracy and safety of ultrasound-guided biopsy and ascites puncture in primarily inoperable ovarian tumours. Anticancer Res. 2020;40(6):3527-34. https://doi.org/10.21873/anticanres.14341
14. Mascilini F, Quagliozzi L, Mirandola M, Moro F, D'Alessandris N, Felice F, et al. Transvaginal ultrasound-guided biopsy in patients with suspicious primary advanced tubo-ovarian carcinoma. Int J Gynecol Cancer. 2023;33(2):236-42. https://doi.org/10.1136/ijgc-2022-003890
15. Asp M, Mockute I, Måsbäck A, Liuba K, Kannisto P, Malander S. Tru-cut biopsy in gynecological cancer: adequacy, accuracy, safety and clinical applicability. J Multidiscip Healthc. 2023;16:1367-77. https://doi.org/10.2147/JMDH.S396788

ORIGINAL ARTICLE

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Approach to external cephalic version through social media: experience from a tertiary center in Brazil

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SUMMARY

OBJECTIVE: The aim of this study was to develop a communication and health education page on external cephalic version through the social media Instagram and, second, to assess the degree of patients' prior understanding of the external cephalic version procedure.

METHODS: We conducted a prospective cohort study on 133 singleton pregnancies (until 41 weeks of gestation), for which an online questionnaire (Google Forms) was applied on the social media Instagram, with four sections. The questionnaire was applied between January 2022 and December 2023. Before the intervention (reading the content displayed on Instagram), sections 1, 2, and 3 were applied, and after reading, section 4. Pregnant women of any gestational age who received prenatal care at our service were included. Patients< 14 years of age and those who could not read were excluded.

RESULTS: A statistically significant difference was found after reading the content made available on Instagram, with a positive evolution after reading ($p<0.001$). Of this sample, 100% felt that knowledge about the external cephalic version should reach the major population of pregnant women, 131 (98.50%) opined that they would talk to other pregnant women about it, and 113 (84.96%) said that they would perform the procedure if they had indications for it.

CONCLUSION: This study provided a comprehensive overview of pregnant women's knowledge about external cephalic version. Through the results obtained, it is possible to observe the evolution of pregnant women's knowledge about external cephalic version after reading the content available on Instagram. In addition, the pregnant women expressed a strong desire to share information about the external cephalic version with other pregnant women.

KEYWORDS: External cephalic version. Social media. Questionnaire.

INTRODUCTION

The Internet is now the primary source of health information for people around the world, with social media increasingly serving as a channel for health education. In addition, the number of health-focused social media accounts has skyrocketed, with daily growth rates of up to 28% by 2020[1]. One of the great benefits of social media for health communication is the accessibility and reach of health information to diverse populations, regardless of age, education, race or ethnicity, and location, compared to traditional communication methods[2].

According to the Brazilian Internet Steering Committee, 83% of Brazilian households had access to the Internet in 2020, and in absolute terms, the country now has 61.8 million connected households[3]. The social media Instagram has surpassed more than 100 million users in Brazil and involves the publication of images and videos combined with texts, enabling interaction among users and the multiplication of knowledge[4].

Unfortunately, social media tools remain informal and unregulated mechanisms for collecting, sharing, and promoting information, so the information shared is of variable quality and consistency[2]. It is important that trained health professionals teach patients how to search and filter information on the Internet so that they do not consume low-quality content and that the information comes from reliable sources and is always confirmed in consultation with the doctor responsible for their care. One study found that the more specific a search term on the Internet, the more useful the information[5].

External cephalic version (ECV) is a procedure performed to change the non-cephalic fetal position to a cephalic presentation[6]. In this procedure, the fetus is manipulated by applying pressure through the mother's abdominal wall to change the breech presentation to a cephalic presentation. The aim of the ECV is to increase the number of cephalic presentations and thus reduce the incidence of breech deliveries and cesarean sections, which have a higher risk of complications compared to cephalic deliveries[7]. The ECV should be performed in pregnant women>37 weeks of gestation, as the spontaneous version is likely to have already occurred and there is less chance for reversal of the ECV[8].

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Pelvic presentation occurs in 3–4% of term pregnancies[9], and the cesarean section rate is nearly 100%[10]. This rate could be halved if ECV were performed on all eligible pregnant women, as the success rate of ECV varies between 40 and 50%[9]. However, due to a lack of public awareness of ECV and a certain reluctance on the part of physicians, this procedure is still rarely performed in Brazil.

Having in mind that social media has been commenting a lot about this procedure, especially nowadays with the increased demand for vaginal deliveries, but we have seen few healthcare physicians speaking out, it is important to share quality information with those who might benefit from it: pregnant women.

Therefore, the general objective of this study was to develop a communication and health education page on ECV through the social media Instagram, so pregnant women have knowledge of it as an option in the birth-planning process.

METHODS

A prospective cohort study was carried out on singleton pregnant women who underwent prenatal care at the Department of Obstetrics, Paulista School of Medicine – Federal University of São Paulo (EPM-UNIFESP). It was a convenience sample, with the sample size calculated through G*power software 3.1.9.6 version, taking into consideration a low Cohen's d effect value (0.2), 5% significance level, and 80% test power.

We excluded pregnant women under the age of 14 years and illiterate women. This study was approved by the Ethics Committee of UNIFESP (CAAE: 58959922.4.0000.5505), and all participants signed the consent form.

The pregnant women were paired, and they were evaluated at time 1, before reading the content on Instagram on the website of the Department of Obstetrics of the EPM-UNIFESP about the ECV, and at time 2, after reading, to check the evolution of knowledge on the topic after reading; in other words, the progress they were able to achieve from the content shared and adherence to the procedure. Data were collected in person through an anonymous questionnaire via Google Forms (available at: https://forms.gle/5Z5uAs8AWDJkqPvt9) that included qualitative variables divided into four sections. Section 1 contained seven questions about the socioeconomic profile of pregnant women. Section 2 contained 13 questions about the current and previous pregnancies. Sections 3 and 4 had the same four questions of basic level related to the ECV, i.e., important points for lay knowledge. Section 4 had an additional six questions about the level of satisfaction with the information provided. The pregnant women were given between 5 and 7 min to complete the questionnaire.

Before the intervention (reading the content displayed on Instagram on the website of the Department of Obstetrics of the EPM-UNIFESP), Sections 1, 2, and 3 of the questionnaires were applied. After the intervention, Section 4 of the questionnaire was applied. There were seven posts for Instagram. After reading the Patient Education Materials Assessment Tool for Audiovisual Materials (PEMAT-A/V), the content to be displayed on Instagram was developed taking into account the aspects assessed by the tool. The PEMAT-A/V was developed by the Agency for Healthcare Research and Quality as a systematic method for analyzing the level of usefulness and understandability of audio–visual materials developed for patients.

The questions in Sections 1 and 2, which are qualitative variables, were compared using chi-square, Fisher's exact, or likelihood ratio test, as appropriate. The questions in Sections 3 and 4 of the questionnaires were scored, with each question worth 1 point. The numerical variables were compared using the Wilcoxon signed-rank test at a 5% significance level. A positive association was considered to exist between the intervention and a higher number of correct answers if the pregnant women had more than 75% correct answers in Section 4 or a 50% increase in the number of correct answers from Sections 3 to 4. Analyses were performed with R software version 4.0.2.

RESULTS

In this study, 133 pregnant women were selected after the exclusion criteria. The prevalent profile of the participants was age between 30 and 39 years (n=60; 45.11%), mixed ethnicity (n=67; 50.38%), not in a stable union (n=106; 79.70%), and completed high school education (n=62; 46.62%). Most of the pregnant women had a history of ≥3 pregnancies (n=66; 49.62%), no previous delivery (n=47; 35.34%), and no history of miscarriages (n=90; 67.67%). The majority were between 27 and 41 weeks of gestation (n=69; 51.88%), had started prenatal care ≤12 weeks of gestation (n=114; 85.71%), and had high-risk pregnancies (n=105; 78.95%). Most of the participants desired a vaginal delivery (n=82; 61.65%) (Table 1).

When evaluating the evolution of the participants' knowledge of the ECV, a statistically significant difference was identified after reading the content made available on Instagram, with a positive evolution after reading ($p<0.001$) and, therefore more correct answers after reading the content (Table 2).

An individual analysis of the answers was also carried out according to the questionnaire. In question 1, about the correct interpretation of what a pelvic presentation would be, 34.59% of the participants (n=46) got the question wrong before reading the content and got it right after reading the

Table 1. Sociodemographic characteristics of the pregnant women.

Characteristics	Participants (n)	Percentage (%)
Age (years)		
16–19	5	3.76
20–29	52	39.10
30–39	60	45.11
>40	16	12.03
Ethnicity/race		
Asian	1	0.75
White	46	34.59
Mixed	67	50.38
Black	19	14.29
Marital status		
Stable union	27	20.30
No stable union	106	79.70
Education level		
Illiterate	1	0.75
Incomplete primary education	6	4.51
Complete primary education	9	6.77
High school incomplete	15	11.28
High school completed	62	46.62
Higher education incomplete	12	9.02
Higher education completed	28	21.05
Number of pregnancies		
1	41	30.83
2	26	19.55
≥3	66	49.62
Number of deliveries		
0	47	35.34
1	36	27.07
2	31	23.31
≥3	19	14.29
Miscarriages		
Yes	43	32.33
No	90	67.67
Gestational age (weeks)		
≤13	19	14.29
14–26	45	33.83
27–41	69	51.88
Classification of prenatal care		
Low risk	28	21.05
High risk	105	78.95
Start of prenatal care (weeks)		
≤12	114	85.71
13–25	16	12.03
26–32	2	1.50
≥33	1	0.75
Desired type of delivery		
Vaginal delivery	82	61.65
Cesarean section	51	38.35
Total	133	100.00

content (p<0.001). The same behavioral pattern was observed when analyzing the result of question 2, about the position in which it would be possible to offer the ECV to a pregnant woman, for which 32.33% of the participants (n=43) got the question wrong before reading the content and got it right after reading it (p<0.001). When asked about the purpose of the ECV, 31.58% of the participants (n=42) got it wrong initially but got it right after reading the content (p<0.001). Finally, when asked about the indications and contraindications of the procedure, 33.84% of the participants (n=45) got it wrong on the first attempt and got it right after reading the content (p<0.001) (Table 3).

The analysis of the trend showed that there was no statistically significant difference when comparing the different levels of education and type of delivery (p=0.507 and 0.366, respectively).

At the end of the questionnaire, the participants were asked about their particular views on the ECV procedure. Of the 133 participants, 100% felt that knowledge about the procedure should reach the major population of pregnant women, 131 (98.50%) opined that they would talk to other pregnant women about it, and 113 (84.96%) said that they would perform the procedure if they had indications for it.

DISCUSSION

From the study conducted, it was possible to observe that there was a positive evolution in the patient's knowledge of ECV after reading the content made available on the social network Instagram. We concluded that there was an increase of 1.015 in the patient's score before and after reading, confirming the hypothesis that Instagram contributed to the knowledge. In addition, in the final questions of the questionnaire, 133 participants were asked about their particular views on the ECV procedure. Of this sample, 100% felt that knowledge about the procedure should reach the major population of pregnant women, 131 (98.50%) opined that they will talk to other pregnant women about it, and 113 (84.96%) said that they would perform the procedure if they had indications for it.

Despite the positive results, it was possible to note during the questionnaire administration that some situations could influence the results of the survey. The first was the lack of concentration of some patients when it came to reading the content on Instagram. This was due to anxiety about going to the physician and leaving, discomfort due to pregnancy symptoms, or even having small children demanding their attention. In order to reduce the influence of this factor, the pregnant women were contacted before their appointment with the physician so that

Table 2. Scores before reading and after reading and participants' progress.

	Score			p-value*
	Before reading	After reading	Evolution	
Mean	1.805	2.820	1.015	<0.001
Standard deviation	0.899	0.968	1.066	
Minimum	0	1	−1	
Maximum	4	4	4	
Median	2	3	1	

*Wilcoxon test.

Table 3. Individual analysis of the answers according to the questions.

Answer before and after reading the content	How does the baby look when we talk about the breech presentation?	When can the ECV be offered to pregnant women?	What is the ECV for?	Which pregnant women can have the ECV?
Kept incorrect answer	39 (29.42)§	37 (27.82)	10 (7.52)	30 (22.5)
Correct answer to incorrect	14 (10.53)	17 (12.78)	5 (3.76)	5 (3.76)
Incorrect answer to correct	46 (34.59)	43 (32.33)	42 (31.58)	45 (33.84)
Kept correct answer	34 (25.56)	36 (27.07)	76 (57.14)	53 (39.85)
p-value*	<0.001	<0.001	<0.001	<0.001

*McNemar test. §Mean (standard deviation). ECV: external cephalic version.

they would not feel like they were wasting time answering the questionnaire but rather using the time they had to wait for the physician to call them. It is possible that the results would have been even better if the questionnaire had been administered at a time already scheduled and reserved for pregnant women. In addition, while analyzing the results, it was hypothesized that pregnant women who were more likely to need the ECV, who were more interested in it due to personal factors, and who had a higher level of education might have a better outcome than other women. However, this possible relationship was resolved by analyzing the relationship between the outcome and the education level and between the outcome and the desired delivery type. There was no statistically significant difference when comparing the different levels of education or different delivery type preferences.

According to a survey conducted by Comscore, Brazil is the third most social media-consuming country in the world. With a reach of 81.4%, Instagram is the third most accessed social media by Brazilian users[11]. The Internet will reach 90.0% of the country's households by 2021. People aged 25 to 29 years have the highest percentage of social media use, 94.5%, but all age groups between 14 and 49 years have percentages above 90%[12]. These data show how Instagram can be used as a tool for the population to identify their health aspirations and be equipped to deal with their environment[13]. Therefore, when health content is shared on Instagram, as was the case with the ECV, it opens an opportunity for the population to learn about an alternative other than those usually proposed, such as a cesarean section in the case of a breech presentation. In this way, pregnant women can bring this option to their appointment with the obstetrician, opening up a space for discussion about the different options, so that the physician feels the need to update himself on meeting the expectations of his pregnant women, and also so that the woman is an active part of her care process and not just someone who follows orders. There is evidence that engaged pregnant women are more compliant with the treatment process and are better informed to make treatment choices that fit their lifestyle and desired outcomes[14].

Something very important about Instagram, and social media in general, compared to other ways of promoting health knowledge, is their durability and reach. For example, if pamphlets had been used in the research as a way of disseminating information about ECV, the knowledge would only have reached the patients in our service, but by using Instagram as a method of disseminating knowledge, the reach was increased since the page on this social media is available to anyone looking for information on the subject. In addition, the pregnant women who participated in the research can recommend the page to their friends. For example, many of the pregnant women who responded to the questionnaire were asked to follow the

page so that they could read the content at home and show it to their friends. Therefore, social media can widen access to those who do not have easy access to health information through traditional methods, such as younger people, ethnic minorities, and lower socioeconomic groups[15]. And in addition to accessibility, social media are a cheaper way to disseminate information than more traditional methods, such as billboards, commercials, flyers, or posters.

In a study conducted by Rooyen[16] on the communication of science news through social media in South Africa, the author argues that, during the Ebola outbreak, social media played an extremely important role in the dissemination of science-related news and information. The author concluded that seemingly equal amounts of media coverage were devoted to the positive role that social media played in helping combat the pandemic and the negative role that social media played in enabling the rapid, rampant spread of misinformation about the disease.

CONCLUSION

This study provided a comprehensive overview of pregnant women's profile and knowledge about ECV, as well as the effectiveness of disseminating information through Instagram. In addition, pregnant women expressed a strong desire to share information about ECV with other pregnant women.

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AUTHORS' CONTRIBUTIONS

SPA: Data curation, Investigation. **RTA:** Formal Analysis. **CYY:** Data curation, Investigation. **JFKS:** Methodology. **EAJ:** Writing – original draft. **SYS:** Supervision, Writing – review & editing.

REFERENCES

1. Metzler JM, Kalaitzopoulos DR, Burla L, Schaer G, Imesch P. Examining the influence on perceptions of endometriosis via analysis of social media posts: cross-sectional study. JMIR Form Res. 2022;6(3):e31135. https://doi.org/10.2196/31135
2. Moorhead SA, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. J Med Internet Res. 2013;15(4):e85.https://doi.org/10.2196/jmir.1933
3. Comitê Gestor da Internet no Brasil. TIC Domicílios: Pesquisa sobre o uso de informação e comunicação nos domicílios brasileiros [internet]. 2020. p. 325. [cited on 2022 Mar 31]. Available from: https://www.cgi.br/media/docs/publicacoes/2/20211124201233/tic_domicilios_2020_ livro_eletronico.pdf
4. Pinto PA. Social and digital marketing of the Brazilian Ministry of Health on Instagram. Rev Eletron Comun Inf Inov Saude. 2019;13(4):817-30.
5. Alas A, Sajadi KP, Goldman HB, Anger JT. The rapidly increasing usefulness of social media in urogynecology. Female Pelvic Med Reconstr Surg. 2013;19(4):210-3. https://doi.org/10.1097/SPV.0b013e3182909872
6. Sánchez-Romero J, García-Soria V, Araico-Rodríguez F, Herrera-Giménez J, Blanco-Carnero JE, Nieto-Díaz A, et al. External cephalic version: is it an effective and safe procedure? J Vis Exp. 2020;(160). https://doi.org/10.3791/60636
7. Hofmeyr GJ, Kulier R, West HM. External cephalic version for breech presentation at term. Cochrane Database Syst Rev. 2015;2015(4):CD000083. https://doi.org/10.1002/14651858.CD000083.pub3
8. External cephalic version: ACOG practice bulletin, number 221. Obstet Gynecol. 2020;135(5):e203-12.
9. Melo P, Georgiou EX, Hedditch A, Ellaway P, Impey L. External cephalic version at term: a cohort study of 18 years' experience. BJOG. 2019;126(4):493-9. https://doi.org/10.1111/1471-0528.15475
10. Burgos J, Rodríguez L, Cobos P, Osuna C, Del Mar Centeno M, Larrieta R, et al. Management of breech presentation at term: a retrospective cohort study of 10 years of experience. J Perinatol. 2015;35(10):803-8. https://doi.org/10.1038/jp.2015.75
11. Scatamburlo B. Tendências de social media 2023. 2023. [cited on 2023 Sep 09]. Available from: https://static.poder360.com.br/2023/03/Tendencias-de-Social-Media-2023-1.pdf
12. Nery C, Britto V. Internet já é acessível em 90,0% dos domicílios do país em 2021. 2022. Brasilia: IBGE. [cited on 2023 Sep 10]. Available from: agenciadenoticias.ibge.gov.br/agencia-noticias/2012-agencia-de-noticias/noticias/34954-internet-ja-e-acessivel-em-90-0-dos-domicilios-do-pais-em-2021#:~:text=Em%202021%2C%20entre%20os%20183,a%20rede%20p%C3%BAblica% 20de%20ensino
13. Organização Mundial da Saúde. Carta de Ottawa da OMS para a promoção da saúde. [cited on 2023 Sep 14]. Available from: https://www.who.int/teams/health-promotion/enhanced-wellbeing/first-global-confer ence
14. Kubheka BZ, Carter V, Mwaura J. Social media health promotion in South Africa: Opportunities and challenges. Afr J Prim Health Care Fam Med. 2020;12(1):e1-7. https://doi.org/10.4102/phcfm.v12i1.2389
15. Moorhead SA, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. J Med Internet Res. 2013;15(4):e85. https://doi.org/10.2196/jmir.1933
16. Rooyen RS. Science communication and the nature of the social media audience: breaking and spreading of science news on Twitter in the South Africa context. Unpublished master's thesis Stellenbosch University; 2017. [cited on 2020 Mar 20]. Available from: http://scholar.sun.ac.za/handle/10019.1/100908

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The impact of body mass index on the diagnostic and surgical outcomes in primary hyperparathyroidism

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the influence of body mass index on the diagnostic and surgical outcomes in patients undergoing parathyroidectomy for primary hyperparathyroidism.

METHODS: A total of 446 patients with primary hyperparathyroidism were divided into four groups according to their body mass index: normal weight (body mass index<25 kg/m^2) (n=130), overweight (25≤body mass index<30 kg/m^2) (n=166), obese (30≤body mass index<35 kg/m^2) (n=112), and morbidly obese (body mass index≥35 kg/m^2) (n=38). Perioperative findings were compared between the groups.

RESULTS: The preoperative median parathormone level in the morbidly obese group (204 pg/mL, min:max 72:1,178) was significantly lower than that in the normal-weight (246 pg/mL, min:max 60:4,262) (p=0.026) and obese (251 pg/mL, min:max 74:2,094) (p=0.012) groups. The osteoporosis rate in the normal-weight group (51%) was higher than that in the overweight (35.4%) (p=0.041) and morbidly obese (25%) (p=0.023) groups. The symptomatic hypocalcemia rate in the normal-weight group (10.2%) was significantly higher than that in the obese group (1.8%) (p=0.017).

CONCLUSION: Normal-weight patients with primary hyperparathyroidism have higher blood parathormone values, higher rates of osteoporosis, and postoperative symptomatic hypocalcemia compared to patients with higher body mass index. For this reason, the surgeon should consider the possibility of symptomatic hypocalcemia after undergoing parathyroidectomy for primary hyperparathyroidism in normal-weight cases.

KEYWORDS: Body mass index. Obesity. Hyperparathyroidism. Parathyroidectomy.

INTRODUCTION

Worldwide, the incidence of obesity is increasing daily[1]. Consequently, the impact of body mass index (BMI) on the diagnostic and therapeutic outcomes of surgical diseases, including primary hyperparathyroidism (PHPT), has been extensively studied[2-6]. Studies show that patients with PHPT tend to have higher BMI compared to eucalcemic controls, and BMI has increased over time among these patients[5,6]. Limited studies on the effect of BMI on PHPT outcomes indicate no difference in blood Ca^{+2} levels between groups, but higher BMI correlates with elevated preoperative parathormone (PTH) levels and larger adenomas[5,7-9]. Additionally, osteoporosis is less common in obese patients compared to those with normal weight[8,9]. The clinical presentation of PHPT can be influenced by factors, such as vitamin D levels, age, genetics, ethnicity, and regional differences[10-17]. This study aims to investigate the effect of BMI on the perioperative findings in patients with PHPT.

METHODS

Cases consecutively operated due to PHPT between 2005 and 2015 were retrospectively investigated. The exclusion criteria were secondary and tertiary hyperparathyroidism (HPT), multiple endocrine neoplasia syndrome, previous parathyroidectomy or thyroidectomy, creatinine>1.4 mg/dL, and insufficient data on BMI. A total of 446 consecutive patients were included in the study. The patients were divided into four groups according to their BMI: normal weight (BMI<25 kg/m^2) (n=130), overweight (25≤BMI<30 kg/m^2) (n=166), obese (30≤BMI<35 kg/m^2) (n=112), and morbidly obese (BMI≥35 kg/m^2) (n=38). Eleven cases had a BMI <18 kg/m^2 These cases were included in the normal-weight group.

Preoperative laboratory findings such as PTH, Ca^{+2}, 25-OH-vitamin D, bone mineral density (BMD), ultrasonography (USG) and scintigraphy findings, intraoperative findings, and postoperative findings were compared between

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the groups. This was a retrospective review of a prospectively collected parathyroid database.

The results obtained from the dual-energy X-ray absorptiometry (DXA) measurements were defined as follows: normal: a T-score of -1 standard deviation (SD) or above, osteopenia: a T-score between -1.0 and -2.5 SD, and osteoporosis: a T-score of -2.5 SD or below.

The result of the imaging method was accepted as "successful" if the abnormal parathyroid gland(s) was (were) localized via USG or scintigraphy and if the outcomes were concordant with the operational findings.

The operations were performed by two surgeons experienced in the endocrine surgery field. The number of concomitant thyroidectomies, the number of abnormal parathyroid glands observed, and the adenoma sizes were compared when evaluating the intraoperative findings. The inability to detect the abnormal parathyroid gland during the surgery was accepted as a negative exploration. Parathyroid tumor dimension was determined as the longest dimension measured during the surgery. If there were more than one enlarged parathyroid gland, the larger one was used for comparison. Intraoperative PTH was routinely measured. The first measurement was performed just prior to the incision, and the second measurement was performed 10 min after the excision of the adenoma. The first PTH level was accepted as the basal value, and the percentage change (PC) in the PTH value in the second measurement, compared to the first, was compared between the groups.

The preoperative laboratory values of the patients were those measured 1 month before the surgery. When more than one laboratory value such as Ca^{+2} or PTH was documented preoperatively, the highest level was used for comparison. The postoperative PTH and Ca^{+2} values were those measured within the postoperative first 12–24 h. The normal limits in laboratory measurements were accepted as follows: PTH: 15–68 pg/mL, total Ca^{+2}: 8.4–10.2 mg/dL, urinary Ca^{+2}: 100–300 mg/24 h, alkaline phosphatase: 40–150 U/L, and 25-OH-vitamin D: 15–100 ng/mL.

When evaluating the postoperative complications, symptomatic cases were accepted as hypocalcemic, cases to be re-operated due to hematomas were accepted as cases with bleeding, and cases with voice loss were accepted as those with recurrent laryngeal nerve palsy. Local ethical committee approval was obtained for the study.

The IBM SPSS Statistics 22 program was used for statistical analysis. The suitability of the parameters to normal distribution was evaluated using the Shapiro-Wilk test. In addition to the descriptive statistic methods (mean, standard error, and frequency), the one-way analysis of variance test was used for the comparison of the quantitative data of the normally distributed parameters, and Tukey's honestly significant difference test was used for the detection of the group responsible for the difference. The Kruskal-Wallis test was used for the intergroup comparison of the non-normally distributed parameters. The Mann-Whitney U test was used for the comparison of two non-normally distributed parameters. The chi-square test, Fisher's exact test, and continuity (Yates) correction were used for the comparison of the qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

PHPT cases were distributed as follows: normal weight (n=130, 29.1%), overweight (n=166, 37.2%), obese (n=112, 25.1%), and morbidly obese (n=38, 8.5%). Statiscally significant differences in mean BMI (p=0.001) and ages were observed, with the normal-weight group being younger than the obese (p=0.002) and morbidly obese (p=0.023) groups. No statistically significant difference was observed between the other groups with regard to the mean ages (p>0.05). Gender distribution differed significantly (p=0.044), with fewer females in the normal-weight group compared to the obese (p=0.028) and morbidly obese (p=0.032) groups. No statistically significant difference was observed between the remaining groups (p>0.05). The preoperative blood PTH levels varied significantly (p=0.046), with the lowest levels in the morbidly obese group, significantly lower than in the normal-weight (p=0.026) and obese (p=0.012) groups. No statistically significant differences were found in the preoperative blood Ca^{+2}, vitamin D, alkaline phosphatase, and 24-h urine Ca^{+2} levels (p>0.05) (Table 1).

DXA results for 358 cases showed statistically significant differences (p=0.043), with the morbidly obese group having the highest number of patients with normal BMD. Osteoporosis rates were higher in the normal-weight group compared to the overweight (p=0.041) and morbidly obese (p=0.023) groups. No statistically significant difference was observed between the other groups with regard to the DXA results (p>0.05) (Table 2).

No statistically significant differences were found in USG and scintigraphy pre-detection rates between the groups (p>0.05). Additionally, there were no statistically significant differences in intraoperative parameters, adenoma size, operation duration, concomitant thyroidectomy rates, or intraoperative PTH measurements (p>0.05). The postoperative PTH levels at 12–24 h showed no statistically significant differences (p>0.05). However, the normal-weight group had a higher reduction in Ca^{+2} levels compared to the obese group (p=0.024). Transient hypocalcemia was more common in the normal-weight group compared to the obese group (p=0.017). No statistically significant

differences were found in transient hypocalcemia rates, postoperative bleeding, recurrent laryngeal nerve palsy, or hospital stay duration among the remaining groups (p>0.05) (Table 3).

DISCUSSION

The number of studies investigating the effect of BMI on PHPT in the literature is limited. Although these studies report no difference between groups with regard to blood Ca^{+2} levels, patients with higher BMI have been reported to have higher preoperative blood PTH levels and larger parathyroid adenomas[5,7-9]. However, there are some important differences between these studies and our study with regard to the characteristics of the BMI groups. In some of these studies, the BMI groups were observed to be similar with regard to age and gender[5,8,9]. However, in the study of Pitt et al.[7] and our study, the BMI groups were different with regard to age and gender. Pitt et al. reported that morbidly obese cases were younger than normal-weight cases and that the normal-weight group included more women than men. In contrast, patients in the normal-weight group were younger than the patients in the morbidly obese group and the rate of women was lower in our study. Furthermore, the mean age of all participants revealed a younger value among patients with PHPT in our study (mean age: 52 years) compared to that in other studies.

On the other hand, comparison of the groups with the highest and lowest BMI values revealed a significantly higher mean preoperative blood PTH level in the high BMI group in the present studies[5,7-9]. In contrast, the blood PTH levels in the normal-weight group were significantly higher than those in the morbidly obese group in our study.

There may be several reasons for the above-mentioned differences in the age and blood PTH of the patients between our study and other studies. As known, the clinical presentation of PHPT is more serious among young individuals[10,11,12]. On the other hand, the PTH levels were observed to be higher in the morbidly obese group in Pitt et al.'s study[7], whereas they were higher in the normal-weight group in our study, which may seem like different outcomes at the beginning. However, the common aspect of the morbidly obese group in Pitt et al.'s study

Table 1. Demographic and preoperative laboratory data of the groups.

	BMI<25	25≤BMI<30	30≤BMI<35	BMI≥35	p
	n=130	n=166	n=112	n=38	
BMI (kg/m^2)	22.2±0.19	27.4±0.11	32.2±0.13	38.1±0.48	**0.001**
Age (years)	49.4±1.35	53±0.9	55.1±0.91	55.8±1.32	**0.001**
Gender (male/female)	26/104	22/144	11/101	2/36	**0.044**
PTH (pg/mL)	246 (60:4,262)	230 (71:3,000)	251 (74:2,094)	204 (72:1,178)	**0.046**
Ca^{+2} (mg/dL)	11.2±0.1	11.1±0.07	11.2±0.1	11±0.15	0.329
25(OH)D (ng/L)	13.9 (4:338)	14.8 (2.8:68.9)	11.8 (4:47)	13.8 (5.2:34)	0.421
Ur.Ca^{+2} (mg/day)	314.2 (5.7:2,033)	332.5 (9:4,074)	300.7 (5.3:6,000)	174 (4.3:833)	0.098
ALP (U/L)	107 (28:1,665)	100 (10:416)	116 (18:701)	103.5 (63:117)	0.815

Data are presented as mean±SE, median (min:max). BMI: body mass index; PTH: parathormone; Ca^{+2}: calcium; Ur.Ca^{+2}: 24-h urine calcium; ALP: alkaline phosphatase; 25(OH)D: 25-OH-Vitamin D; SE: standard error. Statistically significant values are denoted in bold.

Table 2. Dual-energy X-ray absorptiometry findings of the groups.

	BMI<25	25≤BMI<30	30≤BMI<35	BMI≥35	P
	n=102	n=130	n=91	n=32	
Normal	12 (11.8)	15 (11.5)	13 (14.2)	8 (25)	**0.043**
Osteopenia	38 (37.2)	69 (53.1)	38 (41.8)	16 (50)	
Osteoporosis	52 (51)	46 (35.4)	40 (44)	8 (25)	
Lomber-T	-2.2 (-5.4:3.4)	-2 (-5.1:3.7)	-2 (-4.7:2.8)	-1.8 (-5.2:1.6)	0.249
Lomber-Z	-1.4 (-4.8:3.4)	-1.1 (-4.5:4.2)	-1 (-3.8:3.8)	-0.9 (-4.4:4)	**0.043**
Femur-T	-1.6 (-3.9:2.1)	-1.3 (-3.2:1.9)	-1.3 (-6.3:1.9)	-0.2 (-3:2)	**0.001**
Femur-Z	-0.9 (-3.6:2.2)	-0.3 (-3:4.2)	-0.4 (-5.5:2.3)	0.6 (-2.6:3)	**0.001**

Data were presented as n (%) and median (min:max). BMI: body mass index. Statistically significant values are denoted in bold.

Table 3. Success of preoperative imaging studies in identifying pathologic parathyroid and intra- and postoperative features belong to groups.

	BMI<25	25≤BMI<30	30≤BMI<35	BMI≥35	p
	n=130	n=166	n=112	n=38	
USG	114 (87.6)	138 (83.1)	96 (85.7)	33 (86.8)	0.743
Scintigraphy	115 (88.4)	145 (87.3)	103 (91.9)	31 (81.6)	0.351
Single adenoma	114 (87.7)	137 (82.5)	100 (89.3)	34 (89.5)	0.375
Double adenomas	6 (4.6)	19 (11.4)	10 (8.9)	2 (5.3)	
Triple adenomas	3 (2.3)	4 (2.4)	1 (0.9)	1 (2.6)	
Negative exploration	7 (5.4)	6 (3.6)	1 (0.9)	1 (2.6)	0.280
$IoPTH_{PC}$	-82 (-98: -15)	-80 (-99: -44)	-81 (-98: -16)	-79 (-97: -5)	0.980
Dimension[a] (mm)	20 (6:60)	20 (5:50)	20 (7:60)	19.5 (8:46)	0.363
Thyroidectomy[b]	23 (18.1)	35 (21.7)	20 (18.9)	11 (29.7)	0.443
Duration[c] (min)	60 (20:200)	65.5 (20:210)	60 (21:200)	75 (35:180)	0.272
$PTH_{po12-24\,h}$ (pg/mL)	21.5 (1.4:810)	25.8 (1.6:558)	26.2 (2:264.7)	21.3 (3:282.4)	0.437
$Ca^{+2}{}_{po12-24\,h}$ (mg/dL)	8.6±0.10	8.6±0.07	9.3±0.08	9.3±0.15	0.077
$Ca^{+2}{}_{PC}$	-23.5±0.76	-21.5±0.67	-20.4±0.64	-20.2±1.5	**0.021**
Bleeding	1 (0.8)	0 (0)	1 (0.9)	0 (0)	0.635
Hypocalcemia[d]	3 (10.2)	9 (5.5)	2 (1.8)	1 (2.7)	**0.036**
RLN palsy	1 (0.8)	1 (0.6)	4 (3.6)	0 (0)	0.129
Hosp. stay (day)	1 (1:8)	1 (0:18)	1 (0:6)	1 (1:2)	0.136

Data were presented as n (%) and median (min:max) and mean±SE. [a]Adenoma dimension; [b]Concomitant thyroidectomy; [c]Duration of surgery; [d]Symptomatic hypocalcemia. Hosp: hospital; Hematoma: bleeding requiring reoperation; Hypocalcemia: transient symptomatic hypocalcemia; $IoPTH_{PC}$: percent change of intraoperative parathormone between preexcision and postexcision measurements; $PTH_{po12-24\,h}$: parathormone values measured within the postoperative first 12–24 h; $Ca^{+2}{}_{po12-24\,h}$: calcium values measured within the postoperative first 12–24 h; RLN: recurrent laryngeal nerve; $Ca^{+2}{}_{PC}$: percent change of total blood calcium between preoperative and postoperative first day; BMI: body mass index; USG: ultrasonography. Statistically significant values are denoted in bold.

and the normal-weight group in our study was that they were the youngest groups in both studies. As mentioned above, the PTH levels were higher in younger patients. Thus, the higherPTH levels and the heavier glands observed in the morbidly obese group in the study of Pitt et al. may be due to the younger age of the group compared to other BMI groups.

Another factor that leads to the severity of the clinical presentation of PHPT is vitamin D insufficiency or deficiency[10]. A comparison of the present studies revealed that the 25-OH-vitamin D levels of the patients in our study (both of the groups with the lowest and highest BMI) were lower than those observed in the BMI groups of other studies. Younger age, higher blood PTH levels, and lower vitamin D levels observed in the normal-weight cases in our study are not compatible with the studies investigating the relationship between PHPT and BMI but in compliance with the literature on classical symptomatic PHPT.

There is not much data about BMD in the studies investigating the relationship between PTH and BMI. Tran[8] and Adam[9] observed a higher osteoporosis rate in normal-weight cases compared to obese patients. The outcomes obtained in our study were similar. Moreover, the tendency toward a reduction in the PC rate of postoperative blood Ca^{+2} level and the incidence of symptomatic hypocalcemia were found to be higher in the normal-weight cases compared to the obese patients in our study. This condition may be related to hungry bone syndrome, which occurs after parathyroid surgery due to the sudden uptake of minerals by the overactive bones, leading to a rapid drop in blood Ca^{+2} levels, particularly in patients with bone disease associated with long-standing HPT[13]. Besides, these findings were in compliance with the outcome that "the clinical presentation of PHPT is more serious among normal-weight individuals," which was determined in our study. However, the absence of a difference between the mean postoperative Ca^{+2} levels of the BMI groups and the partial subjectivity of symptomatic hypocalcemia partly support our conclusion.

Another reason for the differences in the findings may be the different frequency and severity of obesity in different geographical regions[1]. For example, the rate of high-BMI cases is lower in our study than that in other studies. In addition to these reasons, it should be considered that the clinical presentation of

PHPT may be affected by genetic, ethnic, economic, cultural, and climatic factors[14-17]. Depending on these factors, there may be differences between the cases with PHPT living in different geographical regions with regard to parameters, such as age, bone findings, blood PTH and vitamin D levels, and the adenoma size. However, the present studies in the literature investigating the relationship between PHPT and BMI are of USA origin, and no sufficient data is available for the other regions[5,7-9]. In our study, conducted in a region other than the USA, findings such as younger age, higher PTH levels, and lower vitamin D levels observed in our cases may indicate a more severe clinical course of PHPT. However, the asymptomatic PHPT rates in the USA are very high. Thus, the outcomes of this study suggest that the effect of age, vitamin D levels, and other factors leading to regional differences on the clinical presentation of PHPT is more than the effect of obesity.

CONCLUSION

We found that normal-weight patients with PHPT have higher blood PTH values, higher rates of osteoporosis, and postoperative symptomatic hypocalcemia compared to patients with higher BMI. For this reason, the surgeon should consider the possibility of symptomatic hypocalcemia after undergoing parathyroidectomy for PHPT in normal-weight cases. In addition to this, the results of this study suggest that the effect of factors such as age and vitamin D level and other possible factors that may lead to regional differences in the clinical presentation of PHPT is more than the effect of obesity.

AUTHORS' CONTRIBUTIONS

NSP: Data curation, Formal Analysis, Writing – original draft.
SÇE: Data curation, Formal Analysis, Writing – original draft.
TK: Data curation, Formal Analysis, Writing – original draft.

REFERENCES

1. Wong MCS, Huang J, Wang J, Chan PSF, Lok V, Chen X, et al. Global, regional and time-trend prevalence of central obesity: a systematic review and meta-analysis of 13.2 million subjects. Eur J Epidemiol. 2020;35(7):673-83. https://doi.org/10.1007/s10654-020-00650-3
2. Runkel M, Diallo TD, Lang SA, Bamberg F, Benndorf M, Fichtner-Feigl S. The role of visceral obesity, sarcopenia and sarcopenic obesity on surgical outcomes after liver resections for colorectal metastases. World J Surg. 2021;45(7):2218-26. https://doi.org/10.1007/s00268-021-06073-9
3. Khachfe HH, Hammad AY, AlMasri S, deSilva A, Kraftician J, Lee KK, et al. Obesity is associated with increased risk for adverse postoperative outcomes after distal pancreatectomy for pancreatic ductal adenocarcinoma. J Surg Res. 2023;284:164-72. https://doi.org/10.1016/j.jss.2022.11.050
4. Konishi T, Fujiogi M, Michihata N, Niwa T, Morita K, Matsui H, et al. Impact of body mass index on short-term outcomes after differentiated thyroid cancer surgery: a nationwide inpatient database study in Japan. Eur Thyroid J. 2022;11(1):e210081. https://doi.org/10.1530/ETJ-21-0081
5. Lin X, Fan Y, Zhang Z, Yue H. Clinical characteristics of primary hyperparathyroidism: 15-year experience of 457 patients in a single center in China. Front Endocrinol (Lausanne). 2021;12:602221. https://doi.org/10.3389/fendo.2021.602221
6. Pal R, Arya AK, Aggarwal A, Singh P, Dahiya D, Sood A, et al. Weight gain after curative parathyroidectomy predicts increase in bone mineral density in patients with symptomatic primary hyperparathyroidism. Clin Endocrinol (Oxf). 2020;93(1):28-35. https://doi.org/10.1111/cen.14195
7. Pitt SC, Panneerselvan R, Sippel RS, Chen H. Influence of morbid obesity on parathyroidectomy outcomes in primary hyperparathyroidism. Am J Surg. 2010;199(3):410-4;discussion 414-5. https://doi.org/10.1016/j.amjsurg.2009.08.024
8. Tran H, Grange JS, Adams-Huet B, Nwariaku FE, Rabaglia JL, Woodruff SL, et al. The impact of obesity on the presentation of primary hyperparathyroidism. J Clin Endocrinol Metab. 2014;99(7):2359-64. https://doi.org/10.1210/jc.2013-3903
9. Adam MA, Untch BR, Danko ME, Stinnett S, Dixit D, Koh J, et al. Severe obesity is associated with symptomatic presentation, higher parathyroid hormone levels, and increased gland weight in primary hyperparathyroidism. J Clin Endocrinol Metab. 2010;95(11):4917-24. https://doi.org/10.1210/jc.2010-0666
10. Rao SD, Miragaya J, Parikh N, Honasoge M, Springer K, Harn M, et al. Effect of vitamin D nutrition on disease indices in patients with primary hyperparathyroidism. J Steroid Biochem Mol Biol. 2020;201:105695. https://doi.org/10.1016/j.jsbmb.2020.105695
11. El-Hajj Fuleihan G, Chakhtoura M, Cipriani C, Eastell R, Karonova T, Liu JM, et al. Classical and nonclassical manifestations of primary hyperparathyroidism. J Bone Miner Res. 2022;37(11):2330-50. https://doi.org/10.1002/jbmr.4679
12. Kim SJ, Shoback DM. Sporadic primary hyperparathyroidism. Endocrinol Metab Clin North Am. 2021;50(4):609-28. https://doi.org/10.1016/j.ecl.2021.07.006
13. Carsote M, Nistor C. Forestalling hungry bone syndrome after parathyroidectomy in patients with primary and renal hyperparathyroidism. Diagnostics (Basel). 2023;13(11):1953. https://doi.org/10.3390/diagnostics13111953
14. Kandil E, Tsai HL, Somervell H, Dackiw AP, Tufano RP, Tufaro AP, et al. African Americans present with more severe primary hyperparathyroidism than non-African Americans. Surgery. 2008;144(6):1023-6;discussion 1026-7. https://doi.org/10.1016/j.surg.2008.08.021
15. Moosgaard B, Vestergaard P, Heickendorff L, Melsen F, Christiansen P, Mosekilde L. Vitamin D status, seasonal variations, parathyroid adenoma weight and bone mineral density in primary hyperparathyroidism. Clin Endocrinol (Oxf). 2005;63(5):506-13. https://doi.org/10.1111/j.1365-2265.2005.02371.x
16. Mercanoglu Efe E, Kirdak T, Aykut G, Kaya Argadal E, Kaya E, Ersoy C. Comparison of the effect of anesthetic agents on blood levels of parathyroid hormone and ionized calcium: a prospective randomized controlled trial. Int J Clin Pract. 2022;2022:7795004. https://doi.org/10.1155/2022/7795004
17. Broekhuis JM, Cote MP, Collins RA, Gomez-Mayorga JL, Chaves N, James BC. Association of patient-practitioner sex concordance with specialist referral in primary hyperparathyroidism. Surgery. 2024;175(1):19-24. https://doi.org/10.1016/j.surg.2023.08.048

ORIGINAL ARTICLE

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The effect of music-supported acceptance and commitment therapy on perceived stress and pain in cancer patients

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the effect of music-supported acceptance and commitment therapy on perceived stress and pain levels in cancer patients.

METHODS: A total of 79 cancer patients participated in this controlled, pre-test/post-test quasi-experimental study (experimental group: n=29; control group: n=50). The intervention group received eight sessions of acceptance and commitment therapy with music, while the control group received standard care. Data were collected using the Perceived Stress Scale and the West Haven-Yale Multidimensional Pain Inventory.

RESULTS: The post-test Perceived Stress Scale scores of the experimental group were statistically significantly lower compared to the control group (26.17±3.52 vs. 28.88±5.73, p<0.05), indicating a reduction in perceived stress. Additionally, there was a statistically significant difference in pain severity scores between the groups (9.62±2.33 in the experimental group vs. 8.06±3.14 in the control group, p<0.05). The effect size for stress reduction was moderate (Cohen's d=-0.54).

CONCLUSION: This study revealed that a music-supported acceptance and commitment therapy reduced perceived stress, pain severity, and pain interference in cancer patients. Nurses should actively involve non-pharmacological methods in pain and stress management planning in collaboration with patients and their families. They should create a therapeutic environment and take necessary measures to enable patients to benefit from non-pharmacological interventions.

KEYWORDS: Acceptance and commitment therapy. Cancer. Nursing. Pain. Psychological stress.

INTRODUCTION

Cancers continue to be a significant concern in terms of morbidity and mortality among chronic diseases worldwide. According to the World Health Organization, cancer is one of the leading causes of death globally, ranking second after cardiovascular diseases in many countries, regardless of their economic status[1]. According to the Turkish Statistical Institute, cancer caused the death of 49,946 men and 27,022 women in Turkey in 2015[2]. Cancer-related pain, which affects over half of the cancer patients at any stage, remains one of the most significant issues, negatively impacting their quality of life[3]. Psychological interventions like mindfulness have been shown to reduce distress levels and enhance the quality of life in cancer patients. Interest in implementing acceptance and mindfulness-based approaches for adults has rapidly increased in recent years. Studies suggest that these approaches are effective in improving physical health, managing stress, and aiding recovery[4]. Acceptance and commitment therapy (ACT) is a contemporary therapeutic approach that emphasizes accepting and committing to changes in response to traumatic events. Recent studies have demonstrated the significant role of therapies like ACT in enhancing the quality of life for cancer patients. The core principles of ACT provide a robust framework for effective cancer management interventions[5].

In the literature, there is a limited number of studies specifically examining the effectiveness of music-supported ACT in managing stress and pain among cancer patients. Recent research over the past few years has demonstrated the psychosocial benefits of ACT in managing chronic diseases, but there is a notable lack of data regarding its combination with music in oncology settings. Therefore, a more thorough investigation of the impact of music-supported ACT in this context is needed. This study aims to fill this gap and provide further insights into the effectiveness of non-pharmacological interventions for cancer patients.

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METHODS

Study design

This is a controlled pre-test/post-test quasi-experimental study.

Study population and sample

The study population consisted of all patients diagnosed with cancer, who received inpatient treatment between June 2019 and June 2020 and met the inclusion criteria for the study. All patients who met the study inclusion and exclusion criteria were randomly assigned to the intervention group (clinical treatment and practices+ACT and music) or the control group (clinical treatment and practices only) in a 1:2 ratio. The study was completed with 79 participants (29 in the experimental group and 50 in the control group).

Inclusion criteria:

- Agreeing to participate in the study;
- Willing to collaborate and communicate;
- Being 18 years old and above;
- Being diagnosed with cancer and undergoing treatment at the oncology clinic.

Exclusion criteria:

- Having psychotic symptoms;
- Having had a diagnosis of cognitive impairment;
- Having a lack of cognitive competence to continue the sessions during therapy.

Intervention

Music concert

The researcher provided patients with a portable MP3 player and headphones as the music-listening device. Patients in the experimental group listened to relaxing music for 30 min, featuring wave sounds accompanied by harp and violin melodies from the third section of the "Relaxation Exercises CD" prepared by the Turkish Psychological Association. This music was specifically chosen for its calming effects.

Acceptance and commitment therapy

The therapy was administered by the researcher in a total of eight sessions, each lasting 45–50 min, following the protocol prepared according to the study objectives.

Data collection

The data were collected through face-to-face interviews conducted by the researchers using a Personal Information Form, the Perceived Stress Scale (PSS), and the West Haven-Yale Multidimensional Pain Inventory (WHYMPI). The interviews were conducted in two stages: a pre-test before the intervention and a post-test at a 2-month follow-up.

- Personal Information Form: This form was prepared by the researchers and consists of questions to determine the patients' sociodemographic characteristics, as well as disease- and treatment-related features, including age, marital status, education level, type of cancer, and treatment modalities.
- PSS: The PSS was developed by Cohen et al. and consists of a total of 14 items designed to measure the extent to which certain situations in a given person's life are perceived as stressful. This is a 5-point Likert-type scale, scoring from "never (0)" to "very often (4)." Seven items contain positive statements and are scored in reverse. The total scale scores range from 0 to 56: Higher scores indicate greater perceived stress[6,7]. In this study, the Cronbach's alpha internal consistency coefficient for the PSS was found to be 0.64.
- WHYMPI: The WHYMPI was developed by Kerns et al. to assess relevant dimensions arising from the cognitive-behavioral theory for individuals with chronic pain. The scale is used to evaluate various clinical pains, such as cancer pain, fibromyalgia, headaches, temporomandibular disorders, chronic back pain, and chronic neck pain. It consists of three sections: "pain experience," "responses from significant others," and "daily activities," comprising a total of 60 items[8]. In this study, the Cronbach's alpha internal consistency coefficient for the WHYMPI was found to be 0.78.

Data analysis

The data were analyzed using the IBM SPSS V21 software package. The Shapiro-Wilk test was used to assess whether the data had a normal distribution. The analysis results were presented using mean±standard deviation and median (minimum–maximum) for quantitative data and frequency for categorical data. A p-value of<0.05 was considered statistically significant. The chi-square test was used to compare descriptive characteristics between the groups, the independent t-test for comparing mean scale scores of the groups, least significant difference for advanced analysis, and repeated-measures tests for comparing mean scale scores within the groups. Before conducting the statistical analyses, the demographic and health-related characteristics of the experimental and control groups were compared. It was found that there were no statistically significant differences between the groups in terms of key variables, such as age, gender, education level, marital status, and treatment

methods (p>0.05). These results indicate that the groups were homogeneous, minimizing the potential influence of confounding variables.

Ethics

For conducting the study, ethical approval was obtained from the Ethics Committee of the Faculty of Nursing, Atatürk University (reference number: 2019-1/13, date: 29.01.2019), and institutional permission was obtained from Firat University Hospital (number: 19003918/604.02, date: 13.03.2019-317546) where the study was conducted. Informed verbal and written consent was obtained from all patients who agreed to participate in the study. This study was conducted in accordance with the Declaration of Helsinki and complied with the ethical standards.

RESULTS

Table 1 compares the patients' demographic characteristics and health characteristics. There was no statistically significant difference between the groups' demographic characteristics and health characteristics (p>0.05); thus, the groups were homogeneous in terms of demographic characteristics and health characteristics.

Table 2 compares the groups' pre- and post-test mean scores of WHYMPI and PSS. The pre-test mean score of pain severity was 9.82±2.53 for patients in the experimental group and 8.06±3.14 for those in the control group; the difference between the groups' mean scores was statistically significant (p<0.05). There was no statistically significant difference between the groups' pre-test mean scores of other WHYMPI subscales, including pain interference, support of relatives, self-control, negative mood, punishing responses, solicitous responses, distracting responses, household chores, outdoor work, activities away from home, social activities, and general activities (p>0.05). In addition, the pain severity post-test mean score was 9.62±2.33 for patients in the experimental group and 8.06±3.14 for those in the control group, and the difference between the groups' mean scores was statistically significant (p<0.05). There was no statistically significant difference between the groups' other WHYMPI subscale post-test mean scores, including pain interference, support of relatives, self-control, negative mood, punishing responses, solicitous responses, distracting responses, household chores, outdoor work, activities away from home, social activities, and general activities (p>0.05). The pre-test mean score of PSS was 29.00±3.78 for patients in the experimental group and 28.06±6.27 for those in the control group, and the difference between the groups' mean scores was not statistically significant (p>0.05). However, the PSS post-test mean score was 26.17±3.52 for patients in the experimental group and 28.88±5.73 for those in the control group, and the difference between the groups' mean scores was statistically significant (p<0.05).

Table 3 compares the pre- and post-test mean scores of intragroup WHYMPI and PSS for patients in the experimental group. The pre- and post-test mean scores of their pain interference were 31.18±10.56 and 30.62±10.22, respectively; the difference between their mean scores was statistically significant in favor of the post-test (p=0.001). The pre- and post-test mean scores of their pain severity were 9.82±2.53 and 9.62±2.33, respectively; the difference between their mean scores was statistically significant in favor of the post-test (p<0.005). The pre- and post-test mean scores of their household chores were 3.60±4.46 and 6.29±3.56, respectively; the difference between their mean scores was statistically significant in favor of the post-test (p<0.005). The pre- and post-test mean scores of their outdoor work were 2.00±3.43 and 3.11±3.11, respectively; the difference between their mean scores was statistically significant in favor of the post-test (p<0.005). The pre- and post-test mean scores of their general activities were 11.08±12.48 and 14.87±11.22, respectively; the difference between their mean scores was statistically significant in favor of the post-test (p<0.005).

There was no statistically significant difference between the pre- and post-test mean scores (p>0.05) of their support of relatives, self-control, negative mood, punishing responses, solicitous responses, distracting responses, activities away from home, and social activities. The pre- and post-test PSS total mean scores of patients in the experimental group were 29.00±3.78 and 26.17±3.52, respectively; the difference between their mean scores was statistically significant in favor of the post-test (p<0.005).

DISCUSSION

The results of this study, which aimed to examine the effects of music-supported ACT on perceived pain and stress levels in individuals diagnosed with cancer, were discussed in relation to the relevant literature.

In this study, the pre-test PSS total mean score was 29.00±3.78 for patients in the experimental group and 28.06±6.27 for those in the control group. A descriptive study on the relationship between perceived stress and hope in cancer patients with chemotherapy found their PSS mean score as 29.27±5.88[9]. The results of the present study are consistent with those in the literature. This study found a statistically significant difference between the groups' pre- and post-test PSS mean scores, as well

Table 1. Comparison of the descriptive characteristics and health characteristics of the groups.

Characteristics	Experimental (n=29)		Control (n=50)		Test and p-value
	n	%	n	%	
Age					
20–54 years	11	38.0	20	40.0	χ^2=3.84 p=0.14
55–64 years	13	44.8	13	26.0	
65 years and above	5	17.2	17	34.0	
Gender					
Female	18	62.1	29	58.0	χ^2=0.12 p=0.72
Male	11	37.9	21	42.0	
Education level					
Illiterate	10	34.5	12	24.0	χ^2=1.06 p=0.78
Only literate	8	27.6	16	32.0	
Secondary education	5	17.2	11	22.0	
High school and above	6	20.7	11	22.0	
Marital status					
Married	20	69	42	84	χ^2=2.45 p=0.11
Single	9	31	8	16	
Occupation					
Homemaker	14	48.3	27	54.0	χ^2=1.00 p=0.60
Retired	8	27.6	9	18.0	
Other	7	24.1	14	28.0	
Number of children					
2 or fewer	8	27.6	12	24.0	χ^2=1.69 p=0.42
3–4	8	27.6	21	42.0	
5 and more	13	44.8	17	34.0	
Health status					
Good	3	10.3	7	14.0	χ^2=0.76 p=0.68
Moderate	18	62.1	26	52.0	
Poor	8	27.6	17	34.0	
Cancer in the family					
Yes	12	41.4	36	72.0	χ^2=1.48 p=0.22
No	17	58.6	14	28.0	
Presence of helper					
Yes	26	89.7	44	88.0	χ^2=1.00 p=0.56
No	3	10.3	6	12.0	
Presence of metastases					
Yes	7	24.1	7	14.0	χ^2=1.29 p=0.25
No	22	75.9	43	86.0	
Treatment methods					
Chemotherapy	11	38.0	25	50.0	χ^2=1.87 p=0.39
Radiotherapy	3	10.3	2	4.0	
Multiple treatment modalities	15	51.7	23	46.0	

Table 2. Comparison of the intergroup WHYMPI and PSS mean scores.

	Groups	WHYMPI													PSS
		Pain experience					Responses from significant others			Daily activities					
		Pain interference	Support of relatives	Pain severity	Self-control	Negative mood	Punishing responses	Solicitous responses	Distracting responses	Household chores	Outdoor work	Activities away from home	Social activities	General activities	
Pre-test	Experimental	31.18±10.56	10.28±2.78	9.82±2.53	5.77±2.34	7.81±2.52	5.72±3.24	20.84±8.81	8.37±3.63	3.60±4.46	2.00±3.43	2.13±2.67	2.06±2.64	11.08±12.48	29.00±3.78
	Control	28.52±8.76	9.89±3.79	8.06±3.14	5.00±2.25	8.04±2.92	6.56±4.85	19.24±8.14	9.74±4.37	5.90±6.50	4.41±5.89	4.23±4.66	4.58±4.95	21.68±21.53	28.06±6.27
	Test and p-value	t=−1.20, p=0.23	Z=−0.15, p=0.98	t=0.37, **p=0.01**	Z=−1.77, p=0.07	Z=−0.43, p=0.66	Z=−0.44, p=0.65	t=−0.81, p=0.41	t=0.22, p=0.13	Z=−1.16, p=0.24	Z=−1.60, p=0.10	Z=−1.53, p=0.12	Z=−1.73, p=0.08	Z=−1.81, p=0.07	Z=−1.43, p=0.15
Post-test	Experimental	30.62±10.22	10.28±2.78	9.62±2.33	5.77±2.34	7.81±2.52	5.72±3.24	20.84±8.81	8.37±3.63	6.29±3.56	3.11±3.11	2.13±2.67	2.06±2.64	14.87±11.22	26.17±3.52
	Control	28.52±8.76	9.89±3.79	8.06±3.14	5.00±2.25	8.04±2.99	6.56±4.85	19.24±8.13	9.74±4.37	5.90±6.50	4.41±5.89	4.23±4.66	4.58±4.95	21.68±21.51	28.88±5.73
	Test and p-value	t=−0.96, p=0.33	Z=−0.15, p=0.98	t=0.16, **p=0.01**	Z=−1.77, p=0.07	Z=−0.40, p=0.68	Z=−0.45, p=0.64	t=−0.81, p=0.41	t=0.22, p=0.13	Z=−1.42, p=0.15	Z=−1.19, p=0.23	Z=−1.53, p=0.12	Z=−1.73, p=0.08	Z=−0.51, p=0.61	Z=−2.44, **p=0.01**

PSS: Perceived Stress Scale; WHYMPI: West Haven-Yale Multidimensional Pain Inventory; statistically significant values are denoted in bold.

Table 3. Intragroup comparison of the experimental group's West Haven-Yale Multidimensional Pain Inventory and Perceived Stress Scale mean scores.

Scales		Pre-test	Post-test	Test and p-value
		$\bar{X}$±SD	$\bar{X}$±SD	
WHYMPI	Pain interference	31.18±10.56	30.62±10.22	Z=−3.55, **p=0.001**
	Support of relatives	10.28±2.78	10.28±2.78	Z=0.001, p=1.00
	Pain severity	9.82±2.53	9.62±2.33	Z=−2.12, **p=0.03**
	Self-control	5.77±2.34	5.77±2.34	Z=0.001, p=1.00
	Negative mood	7.81±2.52	7.81±2.52	Z=0.001, p=1.00
	Punishing responses	5.72±3.24	5.72±3.24	Z=0.001, p=1.00
	Solicitous responses	20.84±8.81	20.84±8.81	Z=0.001, p=1.00
	Distracting responses	8.37±3.63	8.37±3.63	Z=0.001, p=1.00
	Household chores	3.60±4.46	6.29±3.56	Z=−4.58, **p=0.001**
	Outdoor work	2.00±3.43	3.11±3.11	Z=−4.23, **p=0.001**
	Activities away from home	2.13±2.67	2.13±2.67	Z=0.001, p=1.00
	Social activities	2.06±2.64	2.06±2.64	Z=0.001, p=1.00
	General activities	11.08±12.48	14.87±11.22	Z=−4.72, **p=0.001**
PSS		29.00±3.78	26.17±3.52	Z=−4.47, **p=0.001**

SD: standard deviation; PSS: Perceived Stress Scale; WHYMPI: West Haven-Yale Multidimensional Pain Inventory; statistically significant values are denoted in bold.

as between the experimental group's pre- and post-test intragroup PSS mean scores (p<0.05). The music-supported ACT intervention was effective in reducing the perceived stress levels of cancer patients. Music itself is not a stand-alone treatment, but when used for patients who are suffering, experiencing pain and stress, seeking help, and looking for a way to express themselves through music, it exhibits therapeutic properties[10]. The intervention of enjoyable music for cancer patients reduced their stress levels[11]. Stress begins as soon as patients learn about their cancer diagnosis, and they need psychological interventions. A study of 107 cancer patients with ACT reported a statistically significant difference between their pre- and post-test scores regarding the acceptance of the disease, stress management, well-being, and meaning in life[12]. A study about the effects of an eight-session ACT intervention on stress, anxiety, and depression in breast cancer patients found that the intervention led to a decrease in all areas[13]. A randomized controlled study of women with breast cancer reported that ACT improved their perceived stress, depression symptoms, and marital satisfaction[14]. A study on the effectiveness of ACT on quality of life and perceived stress in cancer patients has shown that the therapy significantly improved the quality of life and reduced perceived stress in cancer patients[15].

The present study found a statistically significant difference in the experimental group's pre- and post-test mean scores of their pain severity and pain interference in favor of the post-test (p=0.001). The music-supported ACT intervention decreased both pain severity and interference among patients in the experimental group. The ACT is a psychosocial intervention with the potential to reduce symptom-related pain in cancer

patients[16]. A study of women with breast cancer reported that ACT has positive effects on pain and anxiety[17]. A study of 70 patients with chemotherapy found that music interventions effectively reduced the severity of chemotherapy symptoms such as pain, fatigue, and nausea, and improved the comfort of patients undergoing chemotherapy[18].

The present study also found a statistically significant difference in the experimental group's pre- and post-test mean scores of their household chores, general activities, and outdoor work in favor of the post-test ($p<0.005$). The music-supported ACT intervention increased daily activities among patients in the experimental group (Table 3). The ACT aims to increase awareness, reduce pain caused by diseases, alleviate exhaustion, address sleep problems and sedentary lifestyle, and evaluate post-traumatic growth[19]. The present study's results may reflect the effects of ACT.

CONCLUSION AND RECOMMENDATIONS

While this study provides valuable insights into the effectiveness of music-supported ACT in reducing stress and pain among cancer patients, it has certain limitations. The small sample size and quasi-experimental design limit the generalizability of the findings. Future studies should aim to conduct randomized controlled trials with larger sample sizes to validate these results and explore the long-term effects of music-supported ACT, as well as its applicability to other patient populations or chronic conditions. Despite these limitations, the intervention was effective in decreasing perceived stress, pain severity, and pain interference in cancer patients. Therefore, when planning pain and stress management strategies, nurses should actively incorporate non-pharmacological methods into the care process, collaborating with both cancer patients and their families. Creating a therapeutic environment is essential to maximize the benefits of such interventions. Additionally, nurses should educate patients and their families on pain and stress management techniques, participate in developing multidisciplinary treatment plans, and take on evolving roles in patient care and education before, during, and after treatment. Supporting the use of evidence-based, non-pharmacological interventions and contributing to the establishment of standards for their implementation are also critical responsibilities for nursing professionals.

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INSTITUTE WHERE THE RESEARCH WAS CONDUCTED

This study was conducted at the Department of Oncology, Fırat University Hospital, Elazığ, Turkey.

ETHICS APPROVAL

For conducting this study, ethical approval was obtained from the Ethics Committee of the Faculty of Nursing, Atatürk University (reference number: 2019-1/13, date: 29.01.2019), and institutional permission was obtained from Fırat University Hospital (number: 19003918/604.02, date: 13.03.2019-317546) where the study was conducted. Informed verbal and written consent was obtained from all patients who agreed to participate in the study. This study was conducted in accordance with the Declaration of Helsinki and complied with the ethical standards.

AUTHOR' CONTRIBUTIONS

MT: Conceptualization, Formal Analysis, Supervision. **SAK:** Conceptualization, Formal Analysis, Supervision. **ME:** Conceptualization, Formal Analysis, Supervision. **FE:** Conceptualization, Data Curation, Formal Analysis, Writing – original draft. **AA:** Data curation.

REFERENCES

1. World Health Organization. Cancer. 2022. [cited on 2024 Jul 18]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer
2. Turkish Statistical Institute (TÜİK). Cancer statistics report (2011-2015). Turkish Statistical Institute. 2017. [cited on 2021 Jan 12]. Available from: https://www.tuik.gov.tr
3. Lin J, Hsieh RK, Chen JS, Lee KD, Rau KM, Shao YY, et al. Satisfaction with pain management and impact of pain on quality of life in cancer patients. Asia Pac J Clin Oncol. 2020;16(2):e91-8. https://doi.org/10.1111/ajco.13095
4. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. The effectiveness of mindfulness-based interventions among cancer patients and survivors: a systematic review and meta-analysis. Support Care Cancer. 2023;138(1):41-64. https://doi.org/10.1007/S00520-022-07105-0
5. Jiang X, Sun J, Song R, Wang Y Li J, Shi R. Acceptance and commitment therapy reduces psychological distress in patients with cancer: a systematic review and meta-analysis of randomized controlled trials. Front Psychol. 2024;14:1253266. https://doi.org/10.3389/fpsyg.2023.1253266

6. Eskin M, Harlak H, Demirkıran F, Dereboy Ç. Algılanan stres ölçeğinin türkçeye uyarlanmasi: güvenirlik ve geçerlik analizi. New/Yeni Symposium J. 2013;51(3):132-40.
7. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96. PMID: 6668417
8. Kerns RD, Turk DC, Rudy TE. The west haven-yale multidimensional pain inventory (WHYMPI). Pain. 1985;23(4):345-56. https://doi.org/10.1016/0304-3959(85)90004-1
9. Erol, HC. Kemoterapi alan hastalarda algilanan stresin umutla ilişkisi. Yüksek Lisans Tezi. İstanbul: Marmara Üniversites; 2009.
10. Lafcı D. Meme kanseri, uyku ve müzik tedavisi. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2018;44(1):61-4.
11. Lee YJ, Kim MA, Park HJ. Effects of a laughter programme with entrainment music on stress, depression, and health-related quality of life among gynaecological cancer patients. Complement Therap Clin Pract. 2020;39:101118. https://doi.org/10.1016/j.ctcp.2020.101118
12. Datta A, Aditya C, Chakraborty A, Das P, Mukhopadhyay A. The potential utility of acceptance and commitment therapy (ACT) for reducing stress and improving wellbeing in cancer patients in Kolkata. J Cancer Educ. 2016;31(4):721-9. https://doi.org/10.1007/s13187-015-0935-8
13. Mohabbat-Bahar S, Maleki-Rizi F, Akbari ME, Moradi-Joo M. Effectiveness of group training based on acceptance and commitment therapy on anxiety and depression of women with breast cancer. Iran J Cancer Prev. 2015;8(2):71-6. PMID: 25960844
14. Mahdavi A, Aghaei M, Aminnasab V, Tavakoli Z, Besharat M, Abedin M. The effectiveness of acceptance-commitment therapy (act) on perceived stress, symptoms of depression, and marital satisfaction in women with breast cancer. Arch Breast Cancer. 2017;16-23.
15. Mohammadi SY, Soufi A. The effectiveness of acceptance and commitment treatment on quality of life and perceived stress in cancer patients. Q J Health Psychol. 2020;8(32):57-72. https://doi.org/10.30473/hpj.2020.45019.4308
16. Mosher CE, Secinti E, Li R, Hirsh AT, Bricker J, Miller KD, et al. Acceptance and commitment therapy for symptom interference in metastatic breast cancer patients: a pilot randomized trial. Support Care Cancer. 2018;26(6):1993-2004. https://doi.org/10.1007/s00520-018-4045-0
17. Hadlandsmyth K, Dindo LN, Wajid R, Sugg SL, Zimmerman MB, Rakel BA. A single-session acceptance and commitment therapy intervention among women undergoing surgery for breast cancer: a randomized pilot trial to reduce persistent postsurgical pain. Psychooncology. 2019;28(11):2210-7. https://doi.org/10.1002/pon.5209
18. Bilgiç Ş, Acaroğlu R. Effects of listening to music on the comfort of chemotherapy patients. West J Nurs Res. 2017;39(6):745-62. https://doi.org/10.1177/0193945916660527
19. Samet BAŞ, Dirik G. Kanser tanisi olan kişilerde kabul ve kararlilik terapisi uygulamalari: sistematik bir derleme. Psikoloji Çalışmaları. 2019;39(2):459-85. https://doi.org/10.26650/SP2019-0025

ORIGINAL ARTICLE

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The mediating role of loneliness in the effect of social media addiction on aesthetic procedures in women

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SUMMARY

OBJECTIVE: The aim of this study was to determine the mediating role of loneliness in the effect of women's social media addiction on aesthetic procedure behavior.

METHODS: The study was carried out with a total of 1,166 women. The data were evaluated by correlation and SPSS PROCESS macro 4 regression analysis with the Introductory Information Form, Social Media Addiction Scale-Adult Form, Social Media and Changing Perception of Aesthetic Procedures in Society Scale, and Ruls-6 Loneliness Scale.

RESULTS: When the mediating role of loneliness was examined in the effect of social media addiction on having aesthetic procedures, it was determined that both social media addiction (β=0.481) and loneliness (β=0.075) significantly positively affected the perception of having social media aesthetic procedures. A positive relationship was determined between Social Media Addiction Scale-Adult Form, Social Media and Changing Perception of Aesthetic Procedures in Society Scale total score, sub-factor mean scores, and Ruls-6 Loneliness total scores ($p<0.001$).

CONCLUSION: It was found that loneliness had a low-level effect on the effect of social media addiction on aesthetic behavior.

KEYWORDS: Social media. Social media addiction. Esthetics. Loneliness.

INTRODUCTION

Societies all over the world have been affected by the changes in social media, and the positive and negative effects of social media have been discussed in this article. Among the positive effects of social media on individuals is the ability of the masses to come together in a virtual environment, reducing the feeling of loneliness, providing an environment for fast access to information, and sharing ideas[1]. On the contrary, many negative emotions are caused by the misuse of social media. Perfect lives shared on social media, which are often unrealistic, cause individuals to question their lives and feel a sense of inadequacy[2]. One of these deviations from reality is beauty. The perfect face and body lines shared and appreciated on social media have started to increase the importance people attach to their bodies or all their physical characteristics[3].

The increasing influence of social media on daily life increases the tendency of users to compare and evaluate themselves with other people[4]. Social media interactions shape people's communication, interests, and moods, and this plays a decisive role in their aesthetic perceptions. Images of perfect lives that are frequently shared on social media platforms can cause individuals to question their own lives and experience a sense of inadequacy[3]. This situation paves the way for the concepts of aesthetics, beauty, and the perfect body to be easily communicated through social media and direct individuals to aesthetic procedures[3]. Studies examining the relationship between social media use and mental health problems have revealed that it may be associated with problems such as anxiety and depression. In addition, research also shows that social media use differs according to gender and that women are more affected than men[5,6]. Women's intense addiction to social media and the filtered and flawless beauty image they are constantly exposed to may cause them to seek perfection in their own bodies. It is thought that especially women may associate coping with the feeling of loneliness, social acceptance, socialization, and appreciation with their appearance[6]. For this reason, it is more possible to have aesthetic procedures that are not needed. In recent years, social media has become an important tool that shapes individuals' lives and body perceptions[3,5]. Especially women tend to feel inadequate due to the perfect beauty standards they frequently encounter on social media platforms. This may have increased the tendency toward aesthetic procedures. The perceptions of ideal beauty that women are exposed to through social media may trigger bodily dissatisfaction and the search for aesthetic intervention. Social media

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causes individuals to compare themselves with others and feel low self-esteem as a result of these comparisons. In this regard, this study aims to examine the mediating role of loneliness in the effect of social media addiction on the perception of having aesthetic procedures in women. It is thought that the findings will contribute to understanding the complex relationships between social media use, body perception, and mental health.

METHODS

This descriptive and cross-sectional study was conducted with an online survey in May–June 2024. Before starting data collection, necessary permissions were obtained from the Non-Interventional Clinical Research Ethics Committee (ethics number: E14679147-663.05-710841). The population of the study consisted of women over the age of 18 years who use at least one social media application. Since maximum diversity was targeted in the study, it was completed with 1,166 women. The principles of the Declaration of Helsinki were complied with in the study. Research data were collected through an online form (Google Form). Participants were invited to participate in the study through the researchers' social media channels (LinkedIn, Instagram, Facebook, and WhatsApp). An informed consent form on the first page informed women about the research's purpose and confidentiality. Those who selected "I agree" could proceed, while those who chose "I do not agree" were unable to participate.

Social Media Addiction Scale-Adult Form (SMAS-AF): The scale is a 5-point Likert-type scale consisting of 20 items and two sub-dimensions (virtual tolerance and virtual communication). The highest score that can be obtained from this scale is 100, and the lowest score is 20. The Cronbach's alpha reliability coefficient of the scale was found to be 0.94[7].

Social Media and Changing Perception of Aesthetic Procedures in Society Scale (SMCPAPSS): The scale consists of 16 items and 4 sub-dimensions. There are no reverse items in the scale. The scoring of this scale varies between 18 and 90. The Cronbach's alpha reliability coefficient of the scale was found to be 0.90[8].

Ruls-6 Loneliness Scale: The scale is a 4-point Likert-type scale consisting of six items and one sub-dimension. The lowest score is 6, and the highest score is 24. The Cronbach's alpha reliability coefficient of the scale was found to be 0.84[9,10].

In our study, the Cronbach's alpha value of the SMAS-AF was 0.93, the SMCPAPSS was 0.95, and the Ruls-6 Loneliness Scale was 0.85.

In descriptive statistics, mean, standard deviation, minimum, and maximum values were given for numerical variables, while number and percentage values were given for categorical variables. A t-test was performed to test whether there was a significant difference between the groups. Differences between three or more groups were analyzed by one-way analysis of variance (ANOVA). SPSS PROCESS macro 4 regression analysis was used.

RESULTS

The mean age of the women who participated in the study was 29.17±10.01 years (min–max: 18–65 years). Among the women, 49.7% were between the ages of 18 and 25, 41.2% were university graduates or higher, 66.3% were single, 70.8% were employed, and 49.1% had a poor income. Of the women, 40.4% reported that they spent 5 h or more on social media per day (Table 1).

The effect of the mediating role of loneliness on the effect of women's social media addiction status on the perception of having social media aesthetic procedures is shown in Figure 1. According to the results of the analysis, both social media addiction (β=0.481) and loneliness (β=0.075) have a significant positive effect on the perception of having social media aesthetic procedures. According to another finding, loneliness has a mediating role in the effect of social media addiction on the perception of having social media aesthetic procedures (β=0.022), and this role has a low level of mediation effect. Loneliness further increases the positive effect of social media addiction status on having social media aesthetic procedures (β=0.503).

It was determined that the participants in our study were moderately dependent on the average score they received from the social media addiction scale (52.41±14.69), the average score they received from the social media aesthetic perception scale, and the effect of social media on the desire to have aesthetic procedures at a low level (38.35±15.13) and the score they received from the Ruls-6 Loneliness Scale and they felt loneliness at a moderate level (14.13±4.15).

It was found that there was a relationship between the total scores and sub-factors of SMAS-AF and SMCPAPSS and the total scores of the Ruls-6 Loneliness Scale, and the relationship levels are given in Table 2 ($p<0.05$).

DISCUSSION

We found that women with higher levels of education had lower social media addiction but similar levels of loneliness. Burkovik et al. explained the effect of education level on social media use by the development of individuals' cognitive skills

and self-control mechanisms. It has been reported that highly educated women are more resistant to the negative effects of social media and have a lower risk of developing addiction[11]. In our study, it was also observed that advanced age decreased social media addiction and desire for aesthetic procedures in women. This result may indicate that women are more concerned with menopause-related problems[12].

On the other hand, the similar loneliness levels of women, regardless of education level, suggest that loneliness may be related to more complex social and psychological factors independent of social media use. In conclusion, the current research findings point to the protective role of education level on social media addiction, while its effect on loneliness is more limited.

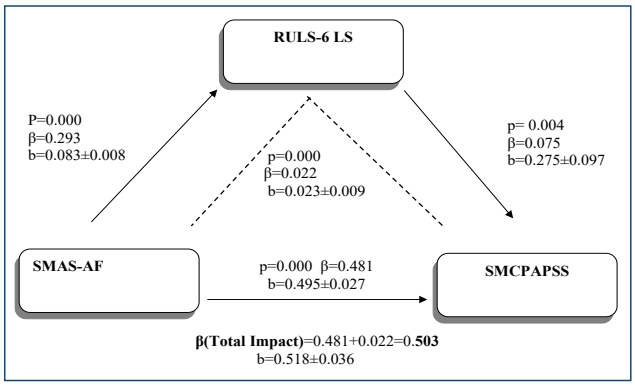

Figure 1. Research model. SMAS-AF: Social Media Addiction Scale; SMCPAPSS: Social Media and Changing Perception of Aesthetic Procedures in Society Scale; Ruls-6 Loneliness: Ruls-6 Loneliness Scale.

Table 1. Socio-demographic characteristics of women and their relationship with scales.

Variables (n: 1,166)	n	%	SMAS-AF	Test and significance	SMCPAPSS	Test and significance	Ruls-6 Loneliness	Test and significance
			$\bar{X} \pm SD$		$\bar{X} \pm SD$		$\bar{X} \pm SD$	
Age								
18–25 (1)	580	49.7	54.51±16.10	F: 10.830 **p: 0.000 (1-2, 1-3, 1-4)**	38.74±15.28	F: 0.978 p: 0.402	14.54±4.23	F: 8.935 **p: 0.000 (1-3, 1-4, 2-4)**
26–35 (2)	303	26.0	51.24±13.59		38.36±15.41		14.31±3.80	
36–45 (3)	191	16.4	50.77±14.90		38.30±14.21		13.36±4.07	
≥46 (4)	92	7.9	46.37±14.44		35.83±15.10		12.54±4.31	
Education								
≤Secondary school graduate (1)	220	18.9	49.00±16.73	F: 5.907	38.25±15.11	F: 0.118	13.50±4.51	F: 3.226
High school graduate (2)	466	40.0	54.00±16.34	**p: 0.003**	38.12±15.26	p: 0.889	14.35±4.01	**p: 0.040**
≥University graduate (3)	480	41.2	51.93±14.83	**(2-1)**	38.60±15.03		14.20±4.08	**(2-1)**
Marital status								
Married	393	33.7	49.57±15.50	t: -4.741	37.87±15.01	t: -0.759	13.14±4.05	t: -5.866
Single	773	66.3	53.85±15.89	**p: 0.000**	38.58±15.19	p: 0.448	14.63±0.10	**p: 0.000**
Employment status								
Not working	340	29.2	52.02±15.46	t: -0.570	39.28±15.18	t: 1.354	13.70±3.90	t: -2.288
Working	826	70.8	52.569±16.01	p: 0.569	3.96±15.10	p: 0.176	14.30±4.23	**p: 0.022**
Income status								
Poor (1)	573	49.1	52.90±16.33	F: 0.733	38.92±15.85	F: 1.254	14.67±4.30	F: 10.003
Medium (2)	454	38.9	51.79±15.45	p: 0.481	37.47±14.48	p: 0.286	13.69±3.94	**p: 0.000**
Good (3)	139	11.9	52.33±15.13		38.83±14.09		13.35±3.8	**(1-2, 1-3)**
Time spent on social media Daily								
0–2 h (1)	297	25.5	46.27±15.03	F: 50.380	34.32±13.59	F: 17.334	13.22±4.28	F: 16.919
4–6 h (2)	398	34.1	51.87±14.79	**p: 0.000**	38.40±14.96	**p: 0.000**	13.88±3.80	**p: 0.000**
≥5 h (3)	471	40.4	56.72±16.16	**(2-1, 3-1, 3-2)**	40.83±15.67	**(2-1, 3-1, 3-2)**	14.92±4.21	**(3-1, 3-2)**

F: Anova test, t: Student's t-test, 1-2-3-4: groups with differences. SD: standard deviation. SMAS-AF: Social media addiction scale, SMCPAPSS: Social Media and Changing Perception of Aesthetic Procedures in Society Scale, Ruls-6 Loneliness: Ruls-6 Loneliness Scale.
Statistically significant values are indicated in bold.

In this study, a significant positive correlation was found between women's social media addiction (SMAS-AF) and their perception of social media aesthetic procedures (SMCPAPSS). Accordingly, as women's social media addiction levels increased, their perception of having aesthetic procedures through social media also increased. Boursier et al. examined the effect of social media use on body dissatisfaction and plastic surgery tendency in women. In the study, it was determined that women who received insufficient attention and negative feedback on social media were concerned about their appearance and turned to aesthetic interventions[13]. This supports the relationship between social media addiction and the perception of having aesthetic procedures. Similarly, McComb and Mills emphasized that perfect beauty images on social media can negatively affect individuals' perceptions of their own bodies, which may increase the desire to have aesthetic procedures[3]. It can also be used to increase the sexual attractiveness of women with their bodies and to ensure that they are recognized[14]. In this context, with the increasing use of social media, it is observed that women focus more on their physical appearance and increase their plastic surgery preferences in order to ensure social acceptance.

Table 2. The relationship between Social Media Addiction Scale-Adult Form, Social Media and Changing Perception of Aesthetic Procedures in Society Scale total score and sub-factors mean scores, and Ruls-6 Loneliness total scores.

		SMAS-AF total score	SMAS-AF Sub 1	SMAS-AF Sub 2	SMCPAPSS total score	SMCPAPSS Sub 1	SMCPAPSS Sub 2	SMCPAPSS Sub 3	SMCPAPSS Sub 4	Ruls-6 LS total score
SMAS-AF total score	r	**1**								
	p									
SMAS-AF sub-factor 1	r	**0.926****	1							
	p	0.000								
SMAS-AF sub-factor 2	r	**0.928****	**0.718****	1						
	p	0.000	0.000							
SMAS Total score	r	**0.503****	**0.478****	**0.453****	1					
	p	0.000	0.000	0.000						
SMCPAPSS sub-factor 1	r	**0.486****	**0.470****	**0.430****	**0.952****	1				
	p	0.000	0.000	0.000	0.000					
SMCPAPSS sub-factor 2	r	**0.402****	**0.357****	**0.387****	**0.842****	**0.735****	1			
	p	0.000	0.000	0.000	0.000	0.000				
SMCPAPSS sub-factor 3	r	**0.384****	**0.390****	**0.322****	**0.786****	**0.661****	**0.580****	1		
	p	0.000	0.000	0.000	0.000	0.000	0.000			
SMCPAPSS sub-factor 4	r	**0.445****	**0.412****	**0.413****	**0.862****	**0.737****	**0.656****	**0.675****	1	
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000		
Ruls-6 LS	r	**0.294****	**0.306****	**0.238****	**0.216****	**0.223****	**0.137****	**0.180****	**0.184****	1
Total score	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	

r=Pearson correlation coefficient, **p<0.001, SMAS-AF: Social media addiction scale, SMCPAPSS: Social Media and Changing Perception of Aesthetic Procedures in Society Scale, Rulls-6 Loneliness: Rulls-6 Loneliness Scale.

r= correlation values. Significant values are those in bold and dark-colored bold.

SMA S-AF Sub 1: Social media addiction scale subfactor virtual tolerance.

SMA S-AF Sub 2: Social media addiction scale subfactor virtual communication.

SMCPA PSS Sub 1: Social Media and Changing Perception of Aesthetic Procedures in Society Scale subfactor need.

SMCPA PSS Sub 2: Social Media and Changing Perception of Aesthetic Procedures in Society Scale subfactor domain.

SMCPA PSS Sub 3: Social Media and Changing Perception of Aesthetic Procedures in Society Scale subfactor accessibility.

SMCPA PSS Sub 4: Social Media and Changing Perception of Aesthetic Procedures in Society Scale subfactor visibility.

The decrease in daily social communication with the increase in social media use causes individuals to feel lonely[15]. It is quite remarkable that women turn to aesthetic procedures to cope with loneliness. According to the results of the research, loneliness was found to have a low-level mediating role in the effect of social media addiction on having aesthetic procedures. In a study, it was determined that women who received insufficient attention and negative feedback on social media tended to undergo aesthetic interventions. It was also found that loneliness played a low level mediating role in this relationship[13]. In the results of this research, we found that social media addiction and loneliness have significant effects on women's perception of having aesthetic procedures. Understanding the complex relationships between social media use, body perception, loneliness, and psychological factors such as having aesthetic procedures is critical for women's mental health and well-being. Due to the growing influence of social media, women are more prone to constantly compare and evaluate themselves, resulting in increased feelings of body dissatisfaction and loneliness.

Limitations

As this was a cross-sectional study, it may not have been possible to identify causal relationships between variables fully. A longitudinal research design would have provided a better understanding of how variables change over time and the dynamics in the relationships. The sample consists of women only. A comparative study including men would have provided an opportunity to examine the relationships between social media use, aesthetic procedures, and loneliness in a more in-depth gender context. The data collection process was carried out only through an online survey. The fact that the study was conducted on a Turkish sample only limits the generalizability of the results to different cultural contexts. Due to these constraints, there are some limitations regarding the generalizability of the findings and the full elucidation of the causal relationships between the variables.

CONCLUSION

It is important to examine the relationship between social media use, body perception, and mental health more comprehensively and holistically. Specifically, we need to gain a better understanding of the psychological needs and challenges faced by women in this context. Additionally, it is important to investigate the psychological well-being of women who seek aesthetic procedures and the motivations behind their choices. Understanding the reasons why some women pursue unnecessary or excessive aesthetic procedures can help us avoid situations that may lead to regret.

AUTHORS' CONTRIBUTIONS

EYA: Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **MAŞ:** Conceptualization, Data curation, Formal Analysis, Validation. **ÖT:** Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft.

REFERENCES

1. Ostic D, Qalati SA, Barbosa B, Shah SMM, Galvan Vela E, Herzallah AM, et al. Effects of social media use on psychological well-being: a mediated model. Front Psychol. 2021;12:678766. https://doi.org/10.3389/fpsyg.2021.678766
2. Tiggemann M, Hayden S, Brown Z, Veldhuis J. The effect of Instagram "likes" on women's social comparison and body dissatisfaction. Body Image. 2018;26:90-7. https://doi.org/10.1016/j.bodyim.2018.07.002
3. McComb SE, Mills JS. Young women's body image following upwards comparison to Instagram models: the role of physical appearance perfectionism and cognitive emotion regulation. Body Image. 2021;38:49-62. https://doi.org/10.1016/j.bodyim.2021.03.012
4. Kıran S, Küçükbostancı H, Emre İE. Sosyal medya kullanımının kişiler üzerindeki etkilerinin incelenmesi. Bilişim Teknolojileri Dergisi. 2020;13(4):435-41. https://doi.org/10.17671/gazibtd.693331
5. Karim F, Oyewande AA, Abdalla LF, Chaudhry Ehsanullah R, Khan S. Social media use and its connection to mental health: a systematic review. Cureus. 2020;12(6):e8627. https://doi.org/10.7759/cureus.8627
6. Uslu M. Türkiye'de sosyal medya bağımlılığı ve kullanımı araştırması. Turk Acad Res Rev. 2021;6(2):370-96. https://doi.org/10.30622/tarr.933479
7. Şahin C, Yağcı M. Sosyal medya bağımlılığı ölçeği-yetişkin formu: geçerlilik ve güvenirlik çalışması. KEFAD. 2017;18(1):523-38.
8. Türk GD, Bayrakçı S. Sosyal medya ve toplumda değişen estetik işlem yaptırma algısı. Bilişim Teknolojileri Online Dergisi. 2019;10(39). https://doi.org/10.5824/ajit-e.2019.04.005
9. Wongpakaran N, Wongpakaran T, Pinyopornpanish M, Simcharoen S, Suradom C, Varnado P, et al. Development and validation of a 6-item Revised UCLA Loneliness Scale (RULS-6) using Rasch analysis. Br J Health Psychol. 2020;25(2):233-56. https://doi.org/10.1111/bjhp.12404
10. Inanç A, Eksi H. Adaptation of RULS-6 loneliness scale (6-item short form) into Turkish: a validity and reliability study. Contemp Educ Res J. 2022;12(4):197-203. https://doi.org/10.18844/cerj.v12i4.7466
11. Burkovik T, Bjelobrk D, Turk T. The relationship between social media addiction, loneliness, and educational level among women. Druš Istraž. 2021;30(1):85-103.

12. Zangirolami-Raimundo J, Sorpreso ICE, Rebouças CMP, Bezerra PCL, Costa LMPRD, Baracat EC, et al. Depression in women in climacteric period: a brief review. Rev Assoc Med Bras (1992). 2023;69(7):e20230385. https://doi.org/10.1590/1806-9282.20230385

13. Boursier V, Gioia F. Griffiths MD. Do selfie-expectancies and social appearance anxiety predict adolescents' problematic social media use? Comput Hum Behav. 2020;110:1-8. https://doi.org/10.1016/j.chb.2020.106395

14. Firmino Murgel AC, Santos Simões R, Maciel GAR, Soares JM, Baracat EC. Sexual dysfunction in women with polycystic ovary syndrome: systematic review and meta-analysis. J Sex Med. 2019;16(4):542-50. https://doi.org/10.1016/j.jsxm.2019.01.313

15. Cataldo I, Lepri B, Neoh MJY, Esposito G. Social media usage and development of psychiatric disorders in childhood and adolescence: a review. Front Psychiatry. 2021;11:508595. https://doi.org/10.3389/fpsyt.2020.508595

ORIGINAL ARTICLE

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The role of inflammatory indices for the prediction of preeclampsia in the first trimester: a case-control study from a tertiary center

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the role of systemic inflammation response index, systemic immune-inflammation index, platelet/hemoglobin ratio, and other defined low-grade inflammatory indices in predicting preeclampsia.

METHODS: The presented retrospective case-control study was conducted on 304 patients diagnosed with preeclampsia and 240 low-risk pregnant women who gave birth between 2019 and 2021 in Ankara Bilkent City Hospital, a tertiary center. Patient information was obtained from the hospital database. Patients diagnosed with preeclampsia, along with possible predictive indices in the first trimester, were evaluated to predict the development of preeclampsia. The indices were neutrophil/lymphocyte ratio, AST/platelet ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, platelet/hemoglobin ratio, creatinine/platelet ratio, systemic immune-inflammation index (neutrophil×platelet/lymphocyte), and systemic inflammation response index (neutrophil×monocyte/lymphocyte). These indices were calculated from the first-trimester routine blood test results and compared between preeclampsia and control groups. The indices were also evaluated for the predictive value regarding the severity and onset time of the disease.

RESULTS: In the first trimester, hemoglobin counts were lower in the preeclampsia group, whereas creatinine and monocyte counts were higher. The platelet/hemoglobin count ratio was significantly higher in the preeclampsia group, with a p-value of 0.025. According to receiver operating characteristic analyses, a platelet/hemoglobin count ratio of 21.41 was identified as the optimal cut-off value for the disease prediction.

CONCLUSION: Systemic inflammation response index and platelet/hemoglobin ratio were evaluated along with the other indices to predict preeclampsia. The platelet/hemoglobin ratio was found to be higher in the preeclampsia group in the first trimester, making it a promising index for preeclampsia prediction.

KEYWORDS: Preeclampsia. First trimester. Inflammation.

INTRODUCTION

Preeclampsia is a multisystem disorder encountered in 2–8% of pregnancies. The disease mostly occurs after mid-pregnancy, leading to maternal and fetal mortalities and morbidities[1]. Improving the outcome of preeclampsia necessitates the earliest identification of high-risk pregnancies for the most appropriate and early management. Preeclampsia was considered a disorder characterized by defective placentation and low-grade inflammation. Low-grade inflammation refers to increased proinflammatory cell counts without a sign of inflammatory disease[2]. The proinflammatory biomarkers were mentioned in preeclampsia as the causes of endothelial dysregulation and increased lymphocyte and neutrophil responses[3].

Systemic inflammatory response markers were available from readily taken simple blood tests and were widely used to diagnose many diseases. In the literature, hemogram-derived indices have been used and considered valuable inflammation markers in various conditions such as survival in intensive care, gastrointestinal diseases, thyroiditis, bowel diseases, and COVID-19 infection[4-7]. In obstetrics, inflammatory indices were also evaluated for conditions that were thought to underline inflammatory etiology, such as preterm delivery and intrahepatic cholestasis of pregnancy[8,9].

Preeclampsia is also considered an inflammatory origin disease. However, the published studies remained controversial for preeclampsia diagnosis and prediction, and the published results were predelivery evaluations of already occurring diseases[2,10].

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The aim of this study was to compare all possible low-grade inflammatory indices in preeclampsia and determine the most efficient predictive marker for the first trimester. There was no such comprehensive study for predicting preeclampsia in the first trimester. Using previously obtained blood parameters for prediction is inexpensive, rapid, and easily applicable in clinical practice.

METHODS

The present retrospective case-control study was conducted on pregnant women diagnosed with preeclampsia and low-risk pregnant women as the control group. Patient information was obtained from the hospital database. Patients diagnosed with preeclampsia, who gave birth between 2019 and 2021, had a singleton pregnancy, were between 17 and 45 years of age, and had no systemic diseases other than hypertension, were included. The control group consisted of low-risk pregnant women with no chronic disease or medication use, who gave birth during the same timeline as the preeclampsia group included in the study. Mild and severe preeclampsia criteria were determined based on ACOG guidelines[11]. This study was approved by the "Institutional Review Board of the University of Health Sciences Turkey, Ankara Bilkent City Hospital Ethics Committee" (approval number: E2-22-2376).

The possible predictive indices were determined as NLR (neutrophil/lymphocyte count ratio), PLR (platelet/lymphocyte count ratio), LMR (lymphocyte/monocyte ratio), APRI (AST/platelet count ratio), platelet/hemoglobin count ratio, creatinine/platelet count ratio, **systemic immune-inflammation index** (SII) (neutrophil×platelet/lymphocyte), and **systemic inflammation response index** (SIRI) (neutrophil×monocyte /lymphocyte count). The indices were calculated from the first-trimester routine blood test results in the first antenatal visit and compared between groups. Then, the preeclampsia group was divided according to the disease severity and diagnosis time. The indices were also compared between subgroups.

The statistical analyses were carried out using USA's Statistical Package for the Social Sciences version 23. The normality analysis of parameters was done based on the Shapiro-Wilk test. Descriptive statistics were presented as the median and interquartile range (IQR) due to the inconsistency with a normal distribution. The Mann-Whitney U test was used to compare the parameters between the groups. Categorical variables were presented as numbers and percentages. The chi-square test was used to compare categorical variables between groups. A receiver operating characteristic (ROC) analysis was used to assess the predictive performance of the platelet/hemoglobin count ratio in preeclampsia development. The Youden Index was used to determine optimal cut-off values. Statistical significance was defined as a p-value of 0.05 with a 95% confidence interval.

RESULTS

The study was conducted on 544 participants, including 304 patients as the preeclampsia group and 240 low-risk pregnant women as the control group. Maternal demographic characteristics for the preeclampsia and the control groups are shown in Table 1.

Laboratory parameters required for index calculations were evaluated in the first trimester and compared between groups. Hemoglobin counts were significantly lower, whereas creatinine and monocyte counts were significantly higher in the preeclampsia group, with p-values of 0.005, 0.035, and 0.004, respectively. Neutrophil, lymphocyte, WBC, platelet, AST, and ALT counts were obtained similarly between the groups (Table 1).

When the indices were compared between the groups, SIRI, SII, APRI, LMR, NLR, PLR, and creatinine/platelet ratios were similar. The only statistically different index was the platelet/hemoglobin count ratio, with a p-value of 0.025 (Table 1).

Then, the preeclampsia group was further divided into subgroups according to the timing of diagnosis such as early-occurring and late-occurring preeclampsia. Eighty-nine early-occurring preeclampsia patients were diagnosed before 32 gestational weeks and 215 late-occurring preeclampsia patients. None of the determined indices was observed to be significantly different between groups in the first trimester (Table 2).

The preeclampsia subgroups included 122 severe and 182 mild preeclampsia patients. The indices were evaluated for severity prediction, and none of them was found to be significantly different. p-values are shown in Table 2.

ROC analyses were performed to determine optimal platelet/hemoglobin count ratio cut-off values. The optimal cut-off value of 21.41 was found to predict preeclampsia in the first trimester (Figure 1).

DISCUSSION

In the present study, increased platelet, creatinine, and decreased hemoglobin counts were obtained in the preeclampsia group. The platelet/hemoglobin ratio was significantly higher in the preeclampsia group in the first trimester. SIRI or none of the other commonly used inflammation indices were found to be similar between groups. The platelet/hemoglobin ratio or other indices were found to be insufficient in predicting discriminating cases, according to the severity or occurring time in the evaluation of the first trimester.

Table 1. Maternal demographic characteristics and laboratory findings and index comparison between preeclampsia and control groups.

Variable	Control group (n=240)	Preeclampsia group (n=304)	p
Maternal indices			
Maternal age (years)	27 (7)	30 (10)	**0.001**
Gravidity	2 (2)	2 (3)	0.242
Parity	1 (1)	1 (2)	0.573
Laboratory parameters			
Hemoglobin (g/dL)	13.0 (1.2)	12.6 (1.4)	**0.005**
WBC (10^9/L)	8.70 (2.8)	8.74 (2.8)	0.068
Platelet (10^9/L)	265.5 (68.0)	272.0 (81.0)	0.138
AST (U/L)	17.0 (6.0)	16.9 (5.8)	0.973
ALT (U/L)	15.0 (9.0)	15.0 (11.0)	0.954
Creatinine (mg/dL)	0.53 (0.1)	0.56 (0.1)	**0.035**
Neutrophil (10^9/L)	5.98 (2.3)	6.09 (2.5)	0.169
Lymphocyte (10^9/L)	1.91 (0.7)	1.98 (0.8)	0.201
Monocyte (10^9/L)	0.44 (0.2)	0.49 (0.3)	**0.004**
Indices			
SIRI	1.30 (1.06)	1.48 (1.04)	0.072
SII	787.97 (535.8)	814.75 (501.0)	0.475
APRI	0.630 (0.03)	0.605 (0.03)	0.295
NLR	3.025 (1.73)	3.005 (1.53)	0.829
PLR	130.51 (55.76)	135.11 (64.21)	0.820
LMR	4.33 (2.10)	4.14 (1.93)	0.073
Creatinine/platelet	0.002 (0)	0.002 (0)	0.692
Platelet/hemoglobin	20.81 (5.92)	21.49 (7.84)	**0.025**

All variables were presented as medians and interquartile ranges (IQR). ALT, alanine aminotransferase; AST, aspartate aminotransferase; SIRI, systemic inflammation response index; SII, systemic immune-inflammation index; APRI, AST/platelet ratio index; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; WBC, white blood count.
Statistically significant p values are expressed in bold in the table.

Table 2. Index comparison between early and late preeclampsia subgroups and between mild and severe preeclampsia subgroups.

Indices	Early preeclampsia (n=89)	Late preeclampsia (n=215)	p^a-value	Mild preeclampsia (n=182)	Severe preeclampsia (n=122)	p^b-value
SIRI	1.52 (1.13)	1.46 (0.98)	0.647	1.46 (1.0)	1.50 (1.0)	0.573
SII	877.94 (664.9)	799.44 (429.7)	0.432	807.29 (472.8)	821.09 (529.8)	0.692
APRI	0.063 (0.04)	0.060 (0.03)	0.939	0.059 (0.03)	0.063 (0.03)	0.347
NLR	3.00 (1.86)	3.00 (1.45)	0.774	3.07 (1.47)	2.96 (1.74)	0.909
PLR	144.31 (74.62)	134.13 (60.51)	0.546	133.03 (61.06)	144.83 (68.03)	0.163
LMR	4.16 (2.04)	4.00 (1.73)	0.680	4.25 (2.04)	3.94 (1.87)	0.089
Creatinine/platelet	0.002 (0)	0.002 (0)	0.425	0.002 (0)	0.002 (0)	0.115
Platelet/hemoglobin	21.56 (9.98)	21.49 (7.07)	0.326	21.56 (7.96)	21.45 (7.18)	0.957

All variables were presented as medians and interquartile ranges (IQR). p^a-value indicates comparisons between early and late preeclampsia groups, and p^b-value indicates comparisons between comparisons between mild and severe preeclampsia groups. SIRI, systemic inflammation response index; SII, systemic immune-inflammation index; APRI, AST to platelet ratio index; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio.

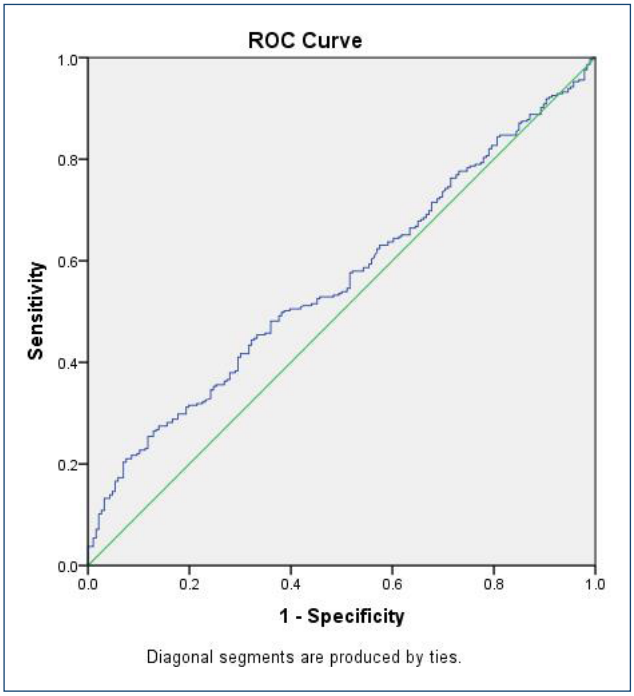

Figure 1. Receiver operating characteristic curve of platelet/hemoglobin count ratio on predicting preeclampsia development in the first trimester. The area under the curve was 0.561 (95% confidence interval=0.509–0.612, p=0.025). The optimal cut-off value of the platelet/hemoglobin count ratio was 21.41 (sensitivity=50%, specificity=60%).

Current findings indicated that preeclampsia was a vascular endothelial multisystem disorder, accompanied by platelet-induced microvascular thrombosis, capillary permeability increase, and hypertension[12]. The underlying disease etiology was suggested as placental hypoxia, leading to erythropoietic stimulation of bone marrow. Increased activated platelets and neutrophils accumulate in the intervillous space, stimulating endothelial dysfunction[13]. Increased inflammation and altered immune response act as etiological cofactors[14].

Preeclampsia risk identification before clinical disease occurrence is an essential task due to its major complications, leading to fetal-maternal morbidity and mortality. Many studies about the inflammatory etiology of preeclampsia suggest that the inflammatory process occurs in early pregnancy, much before the clinical diagnosis of the disease. In the literature, an increased inflammatory process in the decidua was demonstrated in the first trimester of preeclampsia. Altered platelet reactivity was reported as an early marker for preeclampsia[15,16].

In light of the first-trimester inflammation findings, studies focused on preeclampsia prediction and discrimination of high-risk pregnant women as early as possible. Commonly used blood parameters were evaluated and suggested as low-grade inflammation indicators. The PLR, LMR, NLR, APRI, and SII indices were frequently reported as valuable markers in predicting and diagnosing many diseases with inflammatory etiologies, including preeclampsia.

In the literature, conflicting results were reported on PLR. Some studies reported higher platelet and neutrophil counts and increased PLR in the preeclampsia group[2,10,14]. In the present study, the PLR between the groups did not differ, in discordance from the studies performed with smaller groups of patients in the literature. The platelet counts and lymphocyte counts were comparable between groups in concordance with recent studies that observed similar PLR counts in the preeclampsia group[17,18].

LMR was found to be an indicator of subclinical inflammation and a prognostic marker for several diseases. In a study conducted on patients diagnosed with preeclampsia, predelivery LMR values were found to be significantly higher in the preeclampsia group[19,20]. The only study with a restricted patient number on LMR in the first trimester reported significantly lower LMR values for the preeclampsia group[21]. In this study, which was conducted as a complement to the study in the literature with a larger number of patients, monocyte counts were found to be lower. However, LMR values did not differ between the groups.

In most studies, NLR values were found to be elevated in the preeclampsia group, while in some studies, these values were similar[14,22]. In a small number of studies with a limited number of patients, NLR was found to be significantly different[23]. The presented study found that NLR values of the control and preeclampsia groups were similar.

The APRI score was reported as a better marker than AST alone for predicting HELLP syndrome[24]. APRI in preeclampsia was explored and found to be significant in the prediction of preeclampsia under 20 weeks of gestation[25]. We obtained comparable AST and ALT counts, like platelet counts, between groups. The APRI scores of the groups and subgroups were also similar. In our opinion, these parameter differences might occur later than the first trimester.

SII and SIRI indices may be considered relatively new markers that have been investigated in various diseases with an inflammatory etiology. These markers have been reported to be more efficient for predicting low-grade inflammation than traditional markers. In a recent study on 63 pregnant women diagnosed with preeclampsia, an elevated SII score was reported in the first-trimester evaluation[21]. To the best of our knowledge, this study was the first to explore SIRI in the prediction of preeclampsia. No significant difference was observed in SII or SIRI between groups or subgroups.

In the present study, creatinine counts were significantly higher in the preeclampsia group. Although the creatinine/platelet ratio was not found different between groups, increased

creatinine might be an early indicator factor for preeclampsia's occurrence and an indicator of renal sensitivity of preeclampsia.

Lower hemoglobin counts were observed in the preeclampsia group, and this result was concordant with other studies in the literature[10]. Lower hemoglobin might be an early causative factor for the occurrence of preeclampsia. The platelet-to-hemoglobin ratio might be a useful index in the prediction of preeclampsia. In our study, this new ratio was significantly higher in the preeclampsia group compared to the control group.

This study was the first to explore SIRI, creatinine/platelet ratio, and platelet/hemoglobin ratio with the other commonly used inflammatory markers in the prediction of preeclampsia in the first trimester. One of the major strengths of this study was the evaluation time of blood parameters in the first trimester to predict subsequent preeclampsia. The relatively large sample size further strengthened the study. The possible limitation of this study was its retrospective design.

CONCLUSION

Preeclampsia is a pregnancy-specific multisystem disorder that might lead to maternal-fetal morbidities and mortalities. Therefore, recent studies focused on predicting disease as early as possible. In this innovative study, the hypothesis was that the underlying inflammatory etiology of preeclampsia might begin to occur in the first trimester. The aim of this study was to evaluate possible inflammatory markers for prediction and to find the most appropriate marker or index. To the best of our knowledge, this was the first study to explore SIRI, creatinine to platelet ratio, and platelet to hemoglobin ratio with other inflammatory indices for the prediction of preeclampsia. The platelet/hemoglobin ratio was found to be a promising index predicting preeclampsia in the first trimester;,however, further studies are needed to confirm these findings.

AUTHORS' CONTRIBUTIONS

Gİ: Investigation, Methodology, Writing – original draft. **AT:** Formal Analysis, Writing – review & editing. **NG:** Investigation, Methodology, Writing – original draft. **ZA:** Investigation, Methodology, Writing – original draft. **AP:** Investigation, Formal Analysis, Methodology. **ÖK:** Formal Analysis, Writing – review & editing. **DŞ:** Validation, Supervision, Writing – review & editing.

REFERENCES

1. Milosevic-Stevanovic J, Krstic M, Radovic-Janosevic D, Stefanovic M, Antic V, Djordjevic I. Preeclampsia with and without intrauterine growth restriction-two pathogenetically different entities? Hypertens Pregnancy. 2016;35(4):573-82. https://doi.org/10.1080/10641955.2016.1212872
2. Kirbas A, Ersoy AO, Daglar K, Dikici T, Biberoglu EH, Kirbas O, et al. Prediction of preeclampsia by first trimester combined test and simple complete blood count parameters. J Clin Diagn Res. 2015;9(11):QC20-3. https://doi.org/10.7860/JCDR/2015/15397.6833
3. O□lak SC, Aydın MF. Are neutrophil to lymphocyte ratio and platelet to lymphocyte ratio clinically useful for the prediction of early pregnancy loss? Ginekol Pol. 2020;91(9):524-7. https://doi.org/10.5603/GP.a2020.0082
4. Karagoz I, Aktas G, Yoldas H, Yildiz I, Ogun MN, Bilgi M, et al. Association between hemogram parameters and survival of critically ill patients. J Intensive Care Med. 2019;34(6):511-3. https://doi.org/10.1177/0885066617703348
5. Buse Balci S, Aktas G. A comprehensive review of the role of hemogram derived inflammatory markers in gastrointestinal conditions. Iranian J Colorectal Res. 2022;10(3):75-86. https://doi.org/10.30476/acrr.2022.97244.1160
6. Aktas G, Sit M, Dikbas O, Erkol H, Altinordu R, Erkus E, et al. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto's thyroiditis. Rev Assoc Med Bras (1992). 2017;63(12):1065-8. https://doi.org/10.1590/1806-9282.63.12.1065
7. Aktas G. Hematological predictors of novel coronavirus infection. Rev Assoc Med Bras (1992). 2021;67(Suppl 1):1-2. https://doi.org/10.1590/1806-9282.67.Suppl1.20200678
8. Yuce E. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can predict spontaneous preterm birth? J Inflamm Res. 2023;16:2423-9. https://doi.org/10.2147/JIR.S414305
9. Silva J, Magenta M, Sisti G, Serventi L, Gaither K. Association between complete blood count components and intrahepatic cholestasis of pregnancy. Cureus. 2020;12(12):e12381. https://doi.org/10.7759/cureus.12381
10. O□lak SC, Tunç □, Ölmez F. First trimester mean platelet volume, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio values are useful markers for predicting preeclampsia. Ochsner J. 2021;21(4):364-70. https://doi.org/10.31486/toj.21.0026
11. Espinoza J, Vidaeff A, Pettker CM, Simhan H. ACOG practice bulletin no. 202: gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133(1):1. https://doi.org/10.1097/AOG.0000000000003018
12. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. Circ Res. 2019;124(7):1094-112. https://doi.org/10.1161/CIRCRESAHA.118.313276
13. Romero R, Chaiworapongsa T. Preeclampsia: a link between trophoblast dysregulation and an antiangiogenic state. J Clin Invest. 2013;123(7):2775-7. https://doi.org/10.1172/JCI70431
14. Gezer C, Ekin A, Ertas IE, Ozeren M, Solmaz U, Mat E, et al. High first-trimester neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are indicators for early diagnosis of preeclampsia. Ginekol Pol. 2016;87(6):431-5. https://doi.org/10.5603/GP.2016.0021
15. Sacks GP, Seyani L, Lavery S, Trew G. Maternal C-reactive protein levels are raised at 4 weeks gestation. Hum Reprod. 2004;19(4):1025-30. https://doi.org/10.1093/humrep/deh179

16. Nagashima M, Takeda Y, Saitoh S, Sabrina S, Araki A, Nagase S, et al. A loss of tuning of both pro-coagulant and inflammatory responses in monocytes in patients with preeclampsia. J Reprod Immunol. 2024;166:104334. https://doi.org/10.1016/j.jri.2024.104334

17. Braester A, Bilyk A, Suriu C, Akria L, Dally N, Barhoum M. Can blood inflammatory markers identify pregnant women with preeclampsia? Still a controversial issue. Isr Med Assoc J. 2024;26(8):500-3. PMID: 39254410

18. Qiang T, Ding X, Ling J, Fei M. Is platelet to lymphocyte ratio predictive of preeclampsia? A systematic review and meta-analysis. J Obstet Gynaecol. 2023;43(2):2286319. https://doi.org/10.1080/01443615.2023.2286319

19. Wang J, Zhu QW, Cheng XY, Liu JY, Zhang LL, Tao YM, et al. Assessment efficacy of neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in preeclampsia. J Reprod Immunol. 2019;132:29-34. https://doi.org/10.1016/j.jri.2019.02.001

20. Cui HX, Chen C, Jung YM, Guo ZY, Dong CY, Lee SM, et al. Neutrophil-to-lymphocyte ratio (NLR) as a predictive index for liver and coagulation dysfunction in preeclampsia patients. BMC Pregnancy Childbirth. 2023;23(1):4. https://doi.org/10.1186/s12884-022-05335-1

21. Maziashvili G, Juliana K, Siva Subramania Pillai Kanimozhi V, Javakhishvili G, Gurabanidze V, Gagua T, et al. The use of systemic inflammatory markers from routine blood tests in predicting preeclampsia and the impact of age on marker levels. Cureus. 2023;15(3):e35836. https://doi.org/10.7759/cureus.35836

22. Yücel B, Ustun B. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia. Pregnancy Hypertens. 2017;7:29-32. https://doi.org/10.1016/j.preghy.2016.12.002

23. Panwar M, Kumari A, Hp A, Arora R, Singh V, Bansiwal R. Raised neutrophil lymphocyte ratio and serum beta hCG level in early second trimester of pregnancy as predictors for development and severity of preeclampsia. Drug Discov Ther. 2019;13(1):34-7. https://doi.org/10.5582/ddt.2019.01006

24. ?a?maz M?, Ayvaz MA, Dülger AC, Kuday Kaykısız EK, Güven R. Aspartate-aminotransferase to platelet ratio index score for predicting HELLP syndrome. Am J Emerg Med. 2020;38(3):459-62. https://doi.org/10.1016/j.ajem.2019.02.014

25. Ozkan D, Ibanoglu MC, Adar K, Ozkan M, Lutfi Tapisiz O, Engin-Ustun Y, et al. Efficacy of blood parameters in predicting the severity of gestational hypertension and preeclampsia. J Obstet Gynaecol. 2023;43(1):2144175. https://doi.org/10.1080/01443615.2022.2144175

ORIGINAL ARTICLE

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The usefulness of serum procalcitonin levels in predicting surgical intervention in patients with tubo-ovarian abscess

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SUMMARY

OBJECTIVE: Pelvic inflammatory disease is one of the most common gynecological diseases, and 15% of cases are accompanied by tubal-ovarian abscesses. The aim of this study was to evaluate the usefulness of abscess mass size, serum procalcitonin, and other biochemical markers in patients with tubo-ovarian abscesses in predicting surgical intervention.

METHODS: This case–control study included 113 women who were diagnosed with tubo-ovarian abscess, hospitalized, and started on antibiotic treatment. Demographic characteristics, biochemical markers, ultrasound findings, and length of hospital stay were recorded during medical treatment.

RESULT: In terms of demographic characteristics, there was no significant difference between cases requiring complete recovery with medical treatment and cases requiring surgery for complete recovery. While serum cancer antigen 125 level was not statistically significant, there was a significant difference among biochemical markers: serum white blood cell level (18,007.0±6,406.3; p=0.001), C-reactive protein level (261.2±122.2; p<0.001), procalcitonin level (0.88±0.46; p<0.001), and abscess mass size (6.1±1.2; p<0.001) in cases that required surgery for full recovery. The highest sensitivity variable predicting surgical intervention in tubo-ovarian abscess patients was abscess mass size (cut-off value>5.25 cm and area under the curve 0.768) with a sensitivity of 72.2%. The second highest sensitivity variant, procalcitonin (cut-off value>0.635 ng/mL and area under the curve 0.756), showed a sensitivity of 70.4%.

CONCLUSION: Although procalcitonin provides information about the severity of the disease in patients with tubo-ovarian abscesses, evaluation of the abscess mass size along with its size was useful in deciding surgical intervention.

KEYWORDS: Abscess. Biochemical markers. Pelvic inflammatory disease.Patient selection. Procalcitonin.

INTRODUCTION

A tubo-ovarian abscess (TOA) is an inflammatory mass that affects the ovary, fallopian tube, peritoneal tissue, and sometimes other nearby pelvic organs, including the bladder or bowel, and TOAs are often a consequence of pelvic inflammatory disease (PID)[1]. PID risk factors include having first sexual intercourse under the age of 25, having multiple sexual partners, using an intrauterine device, and having a low socioeconomic status[2,3]. While the diagnosis of PID is made by physical examination, some ultrasonographic classifications such as unilocular cystic structure, complex multicystic appearance, and pyosalpinx have been created to define the sonographic appearance of TOA[4]. Diagnosis is often difficult due to nonspecific symptoms and findings, and delayed diagnosis may cause TOAs to rupture, leading to life-threatening sepsis cases[5]. In addition, TOA often affects women of childbearing age and causes infertility, ectopic pregnancies, pelvic adhesions, and chronic pelvic pain[1].

The first treatment option for TOA is broad-spectrum parenteral antibiotic therapy. However, 25–30% of cases do not respond to medical treatment and require surgical intervention[6,7]. Advanced age, high white blood cell count (WBC), and cysts larger than 6 cm were found to be factors that lead to medical treatment failure in cases of TOA[8]. Although abdominal examination, fever measurement, and blood count are the basic components in the follow-up of the disease, it is known that the measurement of C-reactive protein (CRP) and serum procalcitonin (PCT) in the diagnosis and treatment follow-up gives information about the severity of the disease[9].

The aim of our study was to evaluate serum procalcitonin levels, other laboratory parameters, and abscess mass size in patients hospitalized with a diagnosis of TOA and investigate whether these parameters are associated with medical treatment failure and, therefore, whether they are effective in predicting surgical intervention.

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METHODS

Patients

We conducted this case–control study in patients hospitalized for TOA and started medical treatment in the gynecology department of a tertiary medical center between January 2019 and October 2023. Patients with a pelvic mass on ultrasonography diagnosed with TOA based on anamnesis, laboratory, and physical examination findings were included in the study. Pelvic inflammatory mass was evaluated according to the suggestions of the US Centers for Disease Control and Prevention criteria[10].

Data collection

The study was conducted with the institutional ethics committee (KAEK/2023.06.68) and in line with the Declaration of Helsinki. All patients gave written informed consent before enrolling in the study. TOA was diagnosed in patients presenting with lower abdominal and pelvic pain, vaginal discharge, and cervical motion tenderness during gynecological examination. Patients with incomplete data were not included in the study. Demographic data of all patients, laboratory parameters, pelvic ultrasonography findings, treatment method, and the length of hospital stay were recorded. All cases underwent an ultrasonography evaluation using a 6–10-MHz transvaginal probe (LOGIQ P5; GE Healthcare Inc., Milwaukee, WI). At sonographic examination, maximum diameters were recorded. Venous blood samples were obtained on admission to analyze serum WBC counts, CRP, and procalcitonin levels. Complete blood count was assessed with a cell counter (Abbott, Cell Dyn 3700, Abbott Diagnostics, 2010). Serum CRP concentrations were used as per standard methodology (Abbott, Acrhitecti1000sr, Abbott Diagnostics, 2012). Serum procalcitonin levels of the cases were analyzed (Wondfo, Finecare Multichannel, China, 2012).

Treatments

Hospitalization and intravenous antibiotics are suggested for all patients diagnosed with TOA. The antibiotic regimen included ceftriaxone 1.0 g IV every 12 h, metronidazole 500 mg IV every 8 h, and isepamicin 400 mg IV every 24 h. Surgical intervention was considered in cases of acute clinical deterioration such as persistent fever, sepsis, enlarging TOA, worsening pelvic tenderness, ruptured abscess, or widespread peritonitis despite 72 h of antibiotic treatment. Postoperative antibiotics were continued until clinical improvement was achieved. The surgical technique was determined according to the surgical exploration findings (drainage, uni/bilateral salpingectomy/salpingo-oophorectomy, or total abdominal hysterectomy combined with uni/bilateral salpingectomy/salpingo-oophorectomy).

Statistics

Ultrasonographic findings, demographic and laboratory parameters of women who had completely recovered with medical treatment, and women who had undergone surgical treatment were compared. All analyses were performed with the SPSS 20 program package (SPSS Inc., Chicago, IL). Mean and standard deviation were used for descriptive statistics. The characteristics of the two groups were compared using independent t-test and the chi-square test. The correlations were assessed using Spearman's correlation coefficient, along with the related p-values. A binary logistic regression was performed for significant variables in the univariate analysis. All statistical tests were two-sided, and a p-value of <0.05 was considered significant. A receiver operating characteristic (ROC) curve was used to determine the cut-off of clinical characteristics about the need for surgical intervention. The 95% confidence interval (CI) of the area under the curve (AUC) was determined. The optimum diagnostic threshold was chosen by using the ROC curve. The sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and odds ratio of significant variables were calculated to predict the risk of surgical intervention in patients with TOA. Significant variables in the multivariate analysis were also combined to maximize the predictability of surgical intervention.

RESULTS

During the study period, 243 people were diagnosed with PID. Of these, 113 patients received a final diagnosis of TOA. Of the patients, 58 were treated with intravenous antibiotics (in the conservative treatment group) and 55 did not respond to medical treatment and required further surgery or abscess drainage (surgical intervention group). Table 1 shows the patient demographic and clinical data for the two groups. While there was no significant difference between demographic characteristics, the mean (standard deviation) of biochemical markers WBC count, PCT, CRP, mass size, and hospital stay were higher in the surgical intervention group than in the conservative treatment group: 18,007.0 (6,406.3) µL and 14,669.3 (4,675.8) µL, $p=0.001$; 0.88 (0.46) ng/mL vs. 0.52 (0.28) ng/mL, $p<0.001$; 261.2 (122.2) mg/L vs. 184.2 (88.4) mg/L, $p<0.001$; 6.1 (1.2) cm vs. 4.9 (1.0) cm, $p<0.001$; and 11.4 (4.1) days vs. 8.0 (3) days, $p<0.001$, respectively.

In the 55 surgical intervention group patients, laparoscopy and laparotomy were performed in 34 (61.8%) and 21 (38.2%)

patients, respectively. In total, 41 patients underwent unilateral salpingectomy or unilateral salpingo-oophorectomy, and 10 patients underwent bilateral salpingectomy or bilateral salpingo-oophorectomy. Notably, four cases were identified who underwent total hysterectomy in addition to adnexal surgery. An appendectomy was performed in one patient because TOA had spread to the periappendix area.

Univariate analysis was performed using binary logistic regression. As shown in Table 2, three parameters remained significantly associated with the risk of surgical intervention: mass size (OR 2.951; 95%CI 1.665–5.229); WBC (OR 1.000; 95%CI 1.000–1.000), and PCT (OR 29.376; 95%CI 5.360–160.996). CRP showed no significance (p=0.806). In addition, no correlation was found between serum procalcitonin levels and WBC (r=-0.118, p=0.392, r: Pearson's rank correlation) and mass size (r=-0.083, p=0.392, r: Pearson's rank correlation), while a positive correlation was found between CRP levels (r=0.283, p=0.036, r: Pearson's rank correlation). The highest sensitivity variable predicting surgical intervention in TOA patients was abscess mass size (cut-off value>5.25 cm and AUC 0.768) with a sensitivity of 72.2%. The second highest sensitivity variant, PCT (cut-off value>0.635 ng/mL and AUC 0.756), showed sensitivity 70.4% (Table 3).

Mass size, WBC, CRP, and PCT were analyzed based on ROC curves as determinants of TOA. Sensitivity, specificity, accuracy, PPV, and NPV were calculated using the cut-off values. As a single variable, mass size (cut-off value>5.25 years and AUC 0.768) showed the highest sensitivity (72.2%) for predicting surgical intervention in TOA patients. However, the specificity of mass size was only 69%. The second highest sensitivity variable, PCT (cut-off value>0.635 ng/mL and AUC 0.756), showed sensitivity (70.4%) for predicting surgical intervention in TOA patients. Other parameters are shown in Table 3. To increase predictability, patients with mass sizes greater than the cut-off and PCT levels higher than the cut-off value were combined. The sensitivity of this group combination index was 92.7%, specificity 46.5%, accuracy 84.5%, PPV 62.1%, and NPV 87%.

Table 1. Comparison of some demographic and clinical characteristics between cases who responded and failed to respond to medical treatment.

	Full recovery with medical treatment (n=58)	Cases that required surgery for full recovery (n=55)	p-value
Age (year)	37.6±6.5	38.0±5.4	0.688[1]
Parity; nulliparous, n (%)	10 (17.2)	4 (7.3)	0.108[2]
BMI (kg/m^2)	26.4±4.9	27.2±3.8	0.329[1]
Previous cesarean section, n (%)	13 (22.4)	19 (34.5)	0.153[2]
Use of IUD, n (%)	29 (50)	27 (49.1)	0.923[2]
Smoking, n (%)	3 (5.2)	2 (3.6)	0.691[2]
Length of hospital stay (days)	8.0±3	11.4±4.1	***<0.001***[1]
Mass size (cm)	4.9±1.0	6.1±1.2	***<0.001***[1]
WBC count (uL)	14,669.3±4,675.8	18,007.0±6,406.3	***0.001***[1]
CRP (mg/L)	184.2±88.4	261.2±122.2	***<0.001***[1]
PCT (ng/mL)	0.52±0.28	0.88±0.46	***<0.001***[1]
CA-125 (Unit/mL)	58.4±43.2	56.6±33.5	0.808[2]

[1]Independent t-test. [2]Chi-square test. BMI: body mass index; IUD: intrauterine device; WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin; CA-125: cancer antigen 125. Statistically significant values are indicated in bold. Italicized p-values indicate statistical significance (p<0.05).

Table 2. Binary regression analysis for surgery management of the patient with tubo-ovarian abscess.

	OR	95%CI	p-value
Mass size (cm)	2.951	1.665–5.229	***<0.001***
WBC (μL)	1.000	1.000–1.000	***0.030***
CRP (mg/dL)	1.001	0.995–1.006	**0.806**
PCT (ng/mL)	29.376	5.360–160.996	***<0.001***

OR: odds ratio; CI: confidence interval; WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin. Statistically significant values are indicated in bold. Italicized p-values indicate statistical significance (p<0.05).

Table 3. Evaluation of the efficacy of mass size, white blood cell, C-reactive protein, and procalcitonin in need of surgery intervention.

	Cut value	AUC (95%)	p-value	Sensitivity (%)	Specificity (%)
Mass size (cm)	5.25	0.768 (0.683–0.854)	**<0.001**	72.2	69
WBC (μL)	21,660	0.640 (0.537–0.742)	**0.011**	27.8	96.6
CRP (mg/dL)	313.5	0.679 (0.581–0.777)	**0.001**	31.5	96.6
PCT (ng/mL)	0.635	0.756 (0.666–0.846)	**<0.001**	70.4	72.4

WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin; AUC: area under the curve. Statistically significant values are indicated in bold.

DISCUSSION

Early identification of the risk of antibiotic treatment failure in TOA may alert clinicians to the need for changes in treatment strategy, and early surgical intervention reduces acute and long-term complications of TOA[11,12]. Therefore, inflammatory markers and mass size can help the doctor focus his or her attention on people who will require surgical intervention. This study found that although mass size has the highest sensitivity in TOA, evaluation of mass size and PCT level together can predict the need for surgical intervention in TOA with 92.7% sensitivity.

Previous studies reported that CRP and WBC levels helped predict antibiotic treatment failure in TOA patients treated with antibiotics[13]. Nevertheless, according to another study, CRP levels did not differ between TOA patients who responded to antibiotic treatment and those who did not[8]. In our study, there was a significant difference in CRP levels between the TOA patient group that responded to antibiotics and the patient group that did not respond and required surgery, but its sensitivity in predicting the need for surgery was low (31.5%).

There are studies in the literature showing that high CA-125 serum levels are associated with the failure of parenteral antibiotic treatment in TOA[13]. In our study, it was found that serum Ca 125 levels did not have a significant value in surgical prediction.

Previous studies have shown that abscess size increases surgical treatment rates in TOA[14]. Similarly, it has been found that TOA abscess sizes over 8 cm increase the need for surgical intervention and the duration of hospitalization[15]. In another study, TOA abscess size greater than 6.5 cm was predictive of patients requiring surgical treatment[16]. In our study, the cut-off value for predicting the need for surgical intervention was found to be 5.25 cm, and the sensitivity was 72.2%. This mass size value was slightly lower than those in the literature.

When diagnosing sepsis and systemic infection, PCT is a helpful sign. Furthermore, a study addressing the usefulness of PCT in identifying TOA in female PID patients exists[9]. Nevertheless, there is little evidence in the literature regarding the PCT level's predictive power for surgical intervention in patients with TOA. In our study, the PCT cut-off value was calculated for predicting surgical intervention. This value was 0.636 ng/mL, and its sensitivity was 70.4%. This PCT value was found to be the parameter with the highest sensitivity after abscess size in predicting surgical intervention. We believe that when TOA mass size and serum procalcitonin level are evaluated together in TOA patients, they can be used to predict surgical treatment, which will provide additional advantages in terms of cost, and late complications can be prevented.

This study had some limitations. First, this is a retrospective design, and the sample size is relatively small. Second, because procalcitonin begins to increase markedly 8–12 h after illness onset, it may not accurately reflect clinical severity in patients hospitalized in the early stages of PID. Another limitation is that the diagnosis of TOA is made clinically. Finally, the lack of culture and antibiotic sensitivity test findings was one of the drawbacks, and all patients were treated with empirical antibiotics. The strength of the study is that, to the best of our knowledge, it is the first study to evaluate the prediction of surgical intervention PCT in TOA patients.

In conclusion, although PCT provides information about the severity of the disease in patients with TOA, its evaluation together with the size of the abscess mass was found to be more sensitive in deciding on surgical intervention and could be easily applied in clinical practice. Nowadays, inflammatory ratios (such as the SII) are becoming increasingly important in obstetrics and gynecology[17]. Therefore, randomized controlled trials with these ratios and procalcitonin could be conducted in the future.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

Ethical committee approval was obtained from the local ethical committee (approval number: KAEK/2023.06.68).

AUTHORS' CONTRIBUTIONS

OSG: Conceptualization, Writing – original draft. **AB:** Data curation, Formal Analysis, Writing – original draft.

REFERENCES

1. Wong TTC, Lau HCQ, Tan TC. Retrospective study on the efficacy and prognostic factors of conservative versus drainage of tubo-ovarian abscesses. Arch Gynecol Obstet. 2020;302(3):679-83. https://doi.org/10.1007/s00404-020-05640-0
2. Simms I, Stephenson JM, Mallinson H, Peeling RW, Thomas K, Gokhale R, et al. Risk factors associated with pelvic inflammatory disease. Sex Transm Infect. 2006;82(6):452-7. https://doi.org/10.1136/sti.2005.019539
3. Ulubay M, Ozturk M, Firatligil FB, Fidan U, Karaca RE, Yenen MC. Effects of levonorgestrel intrauterine system on patients with female sexual dysfunction. J Reprod Med. 2017;62(1-2):26-30. PMID: 29999278
4. Kinay T, Unlubilgin E, Cirik DA, Kayikcioglu F, Akgul MA, Dolen I. The value of ultrasonographic tubo-ovarian abscess morphology in predicting whether patients will require surgical treatment. Int J Gynaecol Obstet. 2016;135(1):77-81. https://doi.org/10.1016/j.ijgo.2016.04.006
5. Zhao WH, Hao M. Pelvic inflammatory disease: a retrospective clinical analysis of 1,922 cases in North China. Gynecol Obstet Invest. 2014;77(3):169-75. https://doi.org/10.1159/000358393
6. Ribak R, Schonman R, Sharvit M, Schreiber H, Raviv O, Klein Z. Can the need for invasive intervention in tubo-ovarian abscess be predicted? The implication of C-reactive protein measurements. J Minim Invasive Gynecol. 2020;27(2):541-7. https://doi.org/10.1016/j.jmig.2019.04.027
7. Bestel A, Günkaya OS, Aldıkactioglu Talmac M, Ballica Y, Colak Yuksek S, Gedik Ozkose Z, et al. Which treatment should we choose for tubo-ovarian abscesses? Results of an 8-year clinical training in a tertiary center. Ginekol Pol. 2024;95(5):350-5. https://doi.org/10.5603/gpl.96824
8. Akkurt MÖ, Yalçın SE, Akkurt İ, Tatar B, Yavuz A, Yalçın Y, et al. The evaluation of risk factors for failed response to conservative treatment in tubo-ovarian abscesses. J Turk Ger Gynecol Assoc. 2015;16(4):226-30. https://doi.org/10.5152/jtgga.2015.15123
9. Erenel H, Yilmaz N, Oncul M, Acikgoz AS, Karatas S, Ayhan I, et al. Usefulness of serum procalcitonin levels in predicting tubo-ovarian abscess in patients with acute pelvic inflammatory disease. Gynecol Obstet Invest. 2017;82(3):262-6. https://doi.org/10.1159/000449161
10. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. https://doi.org/10.15585/mmwr.rr7004a1
11. Chayachinda C, Rekhawasin T. Reproductive outcomes of patients being hospitalised with pelvic inflammatory disease. J Obstet Gynaecol. 2017;37(2):228-32. https://doi.org/10.1080/01443615.2016.1234439
12. Zhu S, Ballard E, Khalil A, Baartz D, Amoako A, Tanaka K. Impact of early surgical management on tubo-ovarian abscesses. J Obstet Gynaecol. 2021;41(7):1097-101. https://doi.org/10.1080/01443615.2020.1821620
13. Levin G, Herzberg S, Dior UP, Shushan A, Gilad R, Benshushan A, et al. The predictive role of CA-125 in the management of tubo-ovarian abscess. A retrospective study. Eur J Obstet Gynecol Reprod Biol. 2019;238:20-4. https://doi.org/10.1016/j.ejogrb.2019.05.004
14. Hwang JH, Kim BW, Kim SR, Kim JH. The prediction of surgical intervention in patients with tubo-ovarian abscess. J Obstet Gynaecol. 2022;42(1):97-102. https://doi.org/10.1080/01443615.2020.1867965
15. Chappell CA, Wiesenfeld HC. Pathogenesis, diagnosis, and management of severe pelvic inflammatory disease and tuboovarian abscess. Clin Obstet Gynecol. 2012;55(4):893-903. https://doi.org/10.1097/GRF.0b013e3182714681
16. Greenstein Y, Shah AJ, Vragovic O, Cabral H, Soto-Wright V, Borgatta L, et al. Tuboovarian abscess. Factors associated with operative intervention after failed antibiotic therapy. J Reprod Med. 2013;58(3-4):101-6. PMID: 23539877
17. Firatligil FB, Sucu ST, Tuncdemir S, Saglam E, Dereli ML, Ozkan S, et al. Evaluation of systemic immune-inflammation index for predicting late-onset fetal growth restriction. Arch Gynecol Obstet. 2024;310(1):433-9. https://doi.org/10.1007/s00404-024-07453-x

ORIGINAL ARTICLE

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Early detection and treatment of cardiac dysfunction in cancer patients improve overall survival

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SUMMARY

OBJECTIVE: The objective of this study was to analyze the impact of the early detection and treatment of cardiac dysfunction on overall survival in cancer patients.

METHODS: A retrospective analysis was conducted on clinical data from 60 cancer patients with concurrent cardiac dysfunction, admitted between January 2020 and November 2022. Patients were divided into an early treatment group (n=35), where treatment began within 24 h of diagnosis, and a late treatment group (n=25), where treatment started after 24 h. The clinical efficacy, early diastolic filling velocity, fractional shortening, left ventricular ejection fraction, and Quality of Life Questionnaire-Core 30 scores were compared before and after treatment. Adverse reactions, cardiovascular events, and 1-year survival rates were also evaluated.

RESULTS: The early treatment group showed higher total effective and survival rates compared to the late group ($p<0.05$). The post-treatment levels of early diastolic filling velocity, fractional shortening, left ventricular ejection fraction, and Quality of Life Questionnaire-Core 30 scores were statistically significantly higher in the early group ($p<0.05$), with no notable differences in adverse reactions ($p>0.05$). Kaplan-Meier analysis revealed a statistically significantly higher 1-year survival probability in the early treatment group (log-rank $p=0.02$).

CONCLUSION: Early detection and treatment of cardiac dysfunction in cancer patients can improve treatment efficacy and survival rate, better improve cardiac function and quality of life, and reduce the occurrence of adverse cardiovascular events.

KEYWORDS: Cancer. Heart failure. Quality of life. Cardiovascular diseases. Survival rate.

INTRODUCTION

Cancer progression, characterized by abnormal cell proliferation, invasiveness, and metastasis, is a complex process influenced by factors, such as smoking, genetic predisposition, and environmental conditions[1]. Cancer treatments, including chemotherapy and radiotherapy, can cause cardiac dysfunction, worsening patients' health and survival outcomes[2]. Cardiac dysfunction in cancer patients is defined by a reduction in left ventricular ejection fraction (LVEF), with a ≥10% decrease considered significant, as outlined by the American Society of Echocardiography and the European Association of Cardiovascular Imaging[3]. This condition often exacerbates patients' health, emphasizing the need for early detection and treatment to improve survival rates[4,5].

Cardiac dysfunction arises from the cardiotoxic effects of anticancer therapies. For instance, anthracyclines, commonly used in cancer treatment, are linked to dose-dependent cardiotoxicity, leading to left ventricular dysfunction and heart failure[6]. Additionally, targeted therapies, such as trastuzumab and tyrosine kinase inhibitors, can induce cardiac dysfunction[7]. Radiotherapy, especially when directed at the thoracic region, can also result in radiation-induced heart disease, contributing to conditions, such as myocardial fibrosis and coronary artery disease[8].

The impact of cardiac dysfunction on cancer patients' overall health is profound. A retrospective study found that pre-existing heart failure significantly increases mortality risk in breast cancer patients treated with trastuzumab. Furthermore, a systematic review by Lima et al. revealed a higher incidence of cardiac events and decreased survival in cancer patients who developed treatment-related cardiotoxicity[9]. These findings underscore the importance of early interventions to reduce the detrimental effects of cardiac dysfunction on cancer prognosis.

Early detection of cardiac dysfunction in cancer patients offers hope for improving survival by allowing timely interventions. LVEF assessments through echocardiography

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remain a key tool in monitoring cardiac function during cancer treatment. Emerging imaging techniques, such as global longitudinal strain (GLS) imaging, show promise in identifying early myocardial dysfunction, enabling interventions before irreversible damage occurs[9]. Additionally, cardiac biomarkers such as troponins and natriuretic peptides provide valuable insights for the early detection and management of cardiotoxicity[10].

In summary, early detection and treatment of cardiac dysfunction in cancer patients are vital for enhancing survival and quality of life. A multidisciplinary approach integrating advanced imaging and biomarkers into clinical practice can improve early detection and guide interventions, thereby mitigating the impact of cardiac dysfunction on cancer outcomes. This study aims to evaluate the impact of the early detection and treatment of cancer-related cardiac dysfunction on clinical outcomes, particularly survival rates, cardiac function, and quality of life. Using echocardiography-based cardiac function assessments and validated quality-of-life measures, we compare the efficacy of initiating treatment within 24 h of diagnosis versus delayed treatment. By identifying the benefits of timely interventions, we seek to provide evidence supporting early clinical management to improve the prognosis of cancer patients with cardiac dysfunction.

METHODS

Study population

In this retrospective analysis, the clinical data of 60 cancer patients with concurrent cardiac dysfunction admitted to our hospital from January 2020 to November 2022 were reviewed. Based on the time of diagnosis and initiation of treatment for cardiac dysfunction, the patients were divided into an early treatment group (diagnosis and treatment of cardiac dysfunction initiated within ≤24 h) consisting of 35 cases and a late treatment group (diagnosis and treatment initiated after >24 h of diagnosing cardiac dysfunction) consisting of 25 cases. The inclusion criteria were as follows: (1) confirmed diagnosis of cancer by histopathological examination; (2) absence of skin infection at the site of ultrasound probe placement and diagnosis of cardiac dysfunction by echocardiography; (3) age ≥18 years; and (4) availability of complete clinical data. The exclusion criteria were: (1) a history of previous cardiac surgery; (2) existence of cognitive impairment, psychiatric disorders, or non-compliance; and (3) pregnancy or lactation in females.

Intervention methods

Patients in the early treatment group received treatment within 24 h of diagnosing cardiac dysfunction, while the late group received treatment after 24 h. Cardiac dysfunction was detected via echocardiography using the Philips EPIQ7C Doppler ultrasound. Key parameters measured included early diastolic filling velocity (E), fractional shortening (FS), and left ventricular ejection fraction (LVEF), with a ≥,0% LVEF decrease indicating dysfunction. The patients were treated with sacubitril/valsartan tablets (Beijing Novartis), starting at 50 mg twice daily, increased to 100 mg after 2 weeks, and adjusted based on blood pressure and cardiac function, up to 200 mg, for a total of 10 weeks.

Outcome measures

1. Baseline characteristics: These include gender, age, body mass index (BMI), cancer type, and other relevant data for both groups[6].
2. Clinical efficacy: Marked improvement was defined as the restoration of LVEF to baseline levels, while improvement indicated partial LVEF recovery. The total effective rate was calculated as (marked improvement+improvement)/total cases×100%.
3. Cardiac function indicators: The pre- and post-treatment levels of E, FS, and LVEF were measured.
4. Quality of life: This was assessed using the Quality of Life Questionnaire-Core 30 (QLQ-C30), covering physical, role, emotional, cognitive, and social functioning, with scores out of 100[7].
5. Adverse reactions: These include monitored occurrences of nausea, vomiting, headache, renal impairment, edema, and hypotension.
6. Adverse cardiovascular events: These include tracked arrhythmia, angina, heart failure, and cardiogenic shock over 1 year.
7. Survival rate: This was calculated as survivors/total cases×100% after 1 year.

Statistical analysis

Data were analyzed using SPSS 25.0 (IBM, Armonk, NY, USA). Categorical data were expressed as n (%). For sample sizes ≥40 and number of categories (t)≥5, the chi-square test was applied. For t between 1 and 5, a chi-square test with correction was used, and for t<1 or sample sizes <40, the Fisher's exact test was employed. Continuous variables were presented as mean±standard deviation and analyzed using the t-test, with $p<0.05$ being considered statistically significant.

RESULTS

Comparison of baseline data between the two groups

As shown in Table 1, the early treatment group included 24 males and 11 females, with an age range of 50–72 years (mean±standard deviation: 61.38±5.40 years) and a BMI of 17.1–24.5 kg/m² (mean±standard deviation: 20.48±3.26). The late treatment group consisted of 15 males and 10 females, with an age range of 52–75 years (mean±standard deviation: 61.60±5.32 years) and a BMI of 16.5–24.0 kg/m² (mean±standard deviation: 20.25±3.58). Tumor types were similar across both groups, including liver, gastric, lung, breast, and colorectal cancers. No statistically significant differences in gender, age, BMI, or tumor types were observed between the groups (p>0.05), indicating that they were comparable.

Comparison of clinical efficacy between the two groups

In the early treatment group, 23 patients showed marked improvement, 10 patients showed improvement, and 2 patients did not show improvement, resulting in a total effective rate of 94.29%. In the late treatment group, 10 patients experienced marked improvement, 8 showed improvement, and 7 were classified as ineffective, giving a total effective rate of 72.00%. The total effective rate in the early treatment group was statistically significantly higher than that in the late treatment group (p<0.05), indicating that the early detection and treatment of cardiac dysfunction in cancer patients can lead to better treatment outcomes.

Comparison of cardiac function indicators before and after treatment between the two groups

As shown in Table 2, there were no statistically significant differences in the levels of E, FS, and LVEF before treatment between the two groups (p>0.05). However, the post-treatment levels of E, FS, and LVEF were statistically significantly higher in the early treatment group than those in the late treatment group (p=0.019, 0.006, and 0.013, respectively), indicating that the early detection and treatment of cardiac dysfunction in cancer patients can better improve their cardiac function.

Comparison of Quality of Life Questionnaire-Core 30 scores before and after treatment between the two groups

As depicted in Table 3, there were no statistically significant differences in the QLQ-C30 scores for physical, role, emotional, cognitive, and social functioning before treatment between the two groups (p>0.05). However, the post-treatment QLQ-C30 scores of physical, role, emotional, cognitive, and social

Table 1. Comparison of baseline data between the two groups.

Group	Gender		Age (years)	BMI (kg/m²)	Tumor types				
	Male	Female			Hepatocellular carcinoma	Gastric cancer	Lung cancer	Breast cancer	Colorectal cancer
Early treatment group (n=35)	24 (68.57)	11 (31.43)	61.38±5.40	20.48±3.26	9 (25.71)	7 (20.00)	8 (22.86)	5 (14.29)	6 (17.14)
Late treatment group (n=25)	15 (60.00)	10 (40.00)	61.60±5.32	20.25±3.58	6 (24.00)	5 (20.00)	6 (24.00)	5 (20.00)	3 (15.00)
χ^2/t	0.471		0.157	0.259	0.277				
p	0.493		0.876	0.797	0.991				

BMI: body mass index.

Table 2. Comparison of cardiac function indicators before and after treatment in the two groups.

Group	E (cm/s)		FS (%)		LVEF (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Early treatment group (n=35)	68.56±3.12	74.40±3.25	32.80±4.02	37.75±4.14	62.54±5.72	67.75±4.32
Late treatment group (n=25)	69.10±3.20	72.38±3.14	32.56±4.28	34.68±4.06	61.90±5.88	64.80±4.46
t	0.654	2.407	0.222	2.855	0.422	2.573
p	0.516	0.019	0.825	0.006	0.674	0.013

E: early diastolic filling velocity, FS: fractional shortening, LVEF: left ventricular ejection fraction.

Table 3. Comparison of Quality of Life Questionnaire-Core 30 scores before and after treatment in the two groups.

Group	Physical function		Role function		Emotional function		Cognitive function		Social function	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Early treatment group (n=35)	53.86±5.32	65.74±4.25	51.32±5.28	66.47±6.04	53.32±5.80	64.35±5.76	57.36±6.42	69.74±5.96	60.32±5.50	74.42±5.84
Late treatment group (n=25)	53.50±5.48	60.90±4.56	50.86±5.35	58.75±5.98	53.54±5.95	57.90±6.04	58.20±6.56	64.85±5.86	61.02±5.98	69.90±5.95
t	0.255	4.219	0.331	4.901	0.143	4.191	0.495	3.155	0.469	2.933
p	0.799	0.001	0.742	0.001	0.887	0.001	0.622	0.003	0.641	0.005

functioning were statistically significantly higher in the early treatment group than those in the late treatment group (p=0.001, 0.001, 0.001, 0.003, and 0.005, respectively), suggesting that the early detection and treatment of cardiac dysfunction in cancer patients can better enhance their quality of life.

Comparison of adverse reactions between the two groups

In the early treatment group, 8.57% of the patients experienced renal impairment, 8.57% had vasogenic edema, and 8.57% had hypotension. In the late treatment group, 8.00% of patients experienced nausea and vomiting and 8.00% had headaches and dizziness. There were no statistically significant differences in the occurrence of adverse reactions between the two groups (p>0.05), suggesting that the early detection and treatment of cardiac dysfunction in cancer patients does not increase the risk of adverse reactions, thereby demonstrating a similar safety profile between the groups.

Comparison of adverse cardiovascular events between the two groups

In the early treatment group, 5.71% of the patients experienced arrhythmia and angina. In contrast, the late treatment group had a higher occurrence of adverse cardiovascular events, with 28.00% of the patients experiencing arrhythmia, 16.00% experiencing angina, and 8.00% developing heart failure. The overall occurrence rate of adverse cardiovascular events was statistically significantly lower in the early treatment group compared to the late treatment group (p<0.05), indicating that the early detection and treatment of cardiac dysfunction in cancer patients can effectively reduce the risk of adverse cardiovascular events.

Comparison of survival rates between the two groups

A 1-year follow-up revealed a survival rate of 91.43% in the early treatment group, compared to 68.00% in the late treatment group. The survival rate in the early treatment group was statistically significantly higher than that in the late treatment group (p<0.05), suggesting that the early detection and treatment of cardiac dysfunction in cancer patients can significantly improve their survival rate.

DISCUSSION

The incidence of malignant tumors is rising in our country. While modern anti-tumor therapies have extended survival for cancer patients, they also introduce cardiac toxicity. Overall, the benefits of these treatments outweigh the risks[8]. Understanding cardiac toxicity mechanisms and minimizing high-risk factors are crucial for effective management[9]. The early detection of cardiac toxicity has gained increasing attention, with a focus on reducing long-term complications[10]. Cancer treatment-induced cardiac dysfunction is a major cause of morbidity and mortality, highlighting the importance of early detection and intervention to improve patient outcomes[11].

Early interventions offer distinct advantages by mitigating the progression of cardiotoxicity at an early stage, preventing irreversible myocardial damage[12]. This study similarly concludes that the early detection and treatment of cardiac dysfunction improves cardiac function and clinical outcomes in cancer patients. Sacubitril/valsartan inhibits neprilysin and blocks angiotensin II receptors, counteracting the renin–angiotensin–aldosterone system, delaying ventricular remodeling, and alleviating cardiac toxicity[13]. Administering sacubitril/valsartan within 24 h of diagnosis can reverse cardiac dysfunction and prevent deterioration. Onishi et al.[14] also found that the early evaluation and treatment of cancer-related cardiac dysfunction improves patients' quality of life, as early intervention lowers neprilysin, inhibits natriuretic peptide degradation, reduces aldosterone levels and blood pressure, promotes diuresis and vasodilation, and prevents myocardial remodeling. Sacubitril's antioxidant and anti-inflammatory properties further alleviate sodium retention and improve exercise tolerance, enhancing the quality of life. Early interventions may reduce systemic

inflammation and endothelial dysfunction caused by cancer therapies, both of which are linked to adverse cardiac outcomes. By maintaining vascular homeostasis and improving coronary blood flow, early treatment reduces the incidence of adverse cardiovascular events, such as arrhythmias and myocardial infarction.

Khoury et al.[15] found that the early treatment of cardiac dysfunction in cancer patients improves prognosis and survival rates by preventing the deterioration of cardiac function and reducing cardiovascular events. This study supports the conclusion that the early detection and treatment of cardiac dysfunction lowers the risk of adverse cardiovascular events. Importantly, no statistically significant difference in the incidence of adverse reactions between the early and late treatment groups was found ($p>0.05$), indicating that early treatment is safe and does not increase the risk of side effects.

In summary, the early detection and treatment of cardiac dysfunction in cancer patients can improve their effectiveness and survival rate, better enhance their cardiac function and quality of life, and reduce the occurrence of adverse cardiovascular events. First, the small sample size and single-center design in this study may limit the generalizability of the findings. Future research should include multi-centric, large-scale prospective studies to validate the observed benefits of early detection and treatment in broader patient populations. Such studies could employ randomized controlled trial designs to minimize potential biases and enhance the strength of the evidence. Second, the relatively short follow-up period restricts insights into the long-term impact of early interventions on survival and cardiac function. Extended follow-up periods, combined with longitudinal assessments, are recommended to better evaluate sustained outcomes and delayed adverse effects. Additionally, the reliance on echocardiographic parameters such as LVEF and GLS, while effective, could be supplemented with advanced imaging modalities like cardiac magnetic resonance to provide more comprehensive assessments of myocardial health. Incorporating biomarkers such as high-sensitivity troponins and natriuretic peptides may further improve the early detection and risk stratification of cardiac dysfunction in cancer patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethical Committee of Ningbo Fourth Hospital (21-NB-4H-03). Signed written informed consent was obtained from the patients and/or their guardians. This study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of China.

AUTHORS' CONTRIBUTIONS

LZ: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **JW:** Formal Analysis, Investigation, , Methodology. **MZ:** Resources, Software, Supervision.

REFERENCES

1. Tahir E, Azar M, Shihada S, Seiffert K, Goy Y, Beitzen-Heineke A, et al. Myocardial injury detected by T1 and T2 mapping on CMR predicts subsequent cancer therapy-related cardiac dysfunction in patients with breast cancer treated by epirubicin-based chemotherapy or left-sided RT. Eur Radiol. 2022;32(3):1853-65. https://doi.org/10.1007/s00330-021-08260-7
2. Terui Y, Sugimura K, Ota H, Tada H, Nochioka K, Sato H, et al. Usefulness of cardiac magnetic resonance for early detection of cancer therapeutics-related cardiac dysfunction in breast cancer patients. Int J Cardiol. 2023;371:472-9. https://doi.org/10.1016/j.ijcard.2022.09.025
3. Peleg Hasson S, Arnold J, Merdler I, Sivan A, Shamai S, Geva R, et al. Cancer therapeutics-related cardiac dysfunction in patients treated with immune checkpoint inhibitors: an understudied manifestation. J Immunother. 2021;44(5):179-84. https://doi.org/10.1097/CJI.0000000000000371
4. McGregor PC, Moura FA, Banchs J, Aragam JR. Role of myocardial strain imaging in surveillance and management of cancer therapeutics-related cardiac dysfunction: a systematic review. Echocardiography. 2021;38(2):314-28. https://doi.org/10.1111/echo.14944
5. Leerink JM, Feijen ELAM, Pal HJH, Kok WEM, Mavinkurve-Groothuis AMC, Kapusta L, et al. Diagnostic tools for early detection of cardiac dysfunction in childhood cancer survivors: methodological aspects of the Dutch late effects after childhood cancer (LATER) cardiology study. Am Heart J. 2020;219:89-98. https://doi.org/10.1016/j.ahj.2019.10.010
6. Mizuno T, Sakai T, Tanabe K, Kozaki K, Umemura T, Higashikawa M, et al. Identification of target small molecule tyrosine kinase inhibitors that need monitoring and clinical application of protocol for early detection of cancer therapeutics-related cardiac dysfunction using signal detection: an investigation of real world data. J Oncol Pharm Pract. 2021;27(4):804-14. https://doi.org/10.1177/1078155220930367
7. Heck SL, Mecinaj A, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): extended follow-up of a 2×2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Circulation. 2021;143(25):2431-40. https://doi.org/10.1161/CIRCULATIONAHA.121.054698
8. Murray J, Bennett H, Bezak E, Perry R. The role of exercise in the prevention of cancer therapy-related cardiac dysfunction in breast cancer patients undergoing chemotherapy: systematic review. Eur J Prev Cardiol. 2022;29(3):463-72. https://doi.org/10.1093/eurjpc/zwab006

9. Lima M, Brito H, Mitidieri GG, Souza EP, Sobral A, Melo H, et al. Cardiotoxicity in cancer patients treated with chemotherapy: a systematic review. Int J Health Sci-Ijh. 2022;16(6):39-46.
10. Merkx R, Leerink JM, Feijen ELAM, Kremer LCM, Baat EC, Bellersen L, et al. Echocardiography protocol for early detection of cardiac dysfunction in childhood cancer survivors in the multicenter DCCSS LATER 2 CARD study: design, feasibility, and reproducibility. Echocardiography. 2021;38(6):951-63. https://doi.org/10.1111/echo.15081
11. Oikonomou EK. Molecular imaging to guide precision diagnosis and prevention of cancer therapeutics-related cardiac dysfunction. Expert Rev Mol Diagn. 2020;20(4):355-8. https://doi.org/10.1080/14737159.2020.1717336
12. Sendur MA, Aksoy S, Altundag K. Cardiotoxicity of novel HER2-targeted therapies. Curr Med Res Opin. 2013;29(8):1015-24. https://doi.org/10.1185/03007995.2013.807232
13. Carlos El-Tallawi K, Alnabelsi T, Al-Mallah MH. Cardiac dysfunction in cancer survivors after thoracic irradiation: a necessary evil? J Nucl Cardiol. 2021;28(6):2988-91. https://doi.org/10.1007/s12350-020-02348-1
14. Onishi T, Fukuda Y, Miyazaki S, Yamada H, Tanaka H, Sakamoto J, et al. Practical guidance for echocardiography for cancer therapeutics-related cardiac dysfunction. J Echocardiogr. 2021;19(1):1-20. https://doi.org/10.1007/s12574-020-00502-9
15. Khoury K, Lynce F, Barac A, Geng X, Dang C, Yu AF, et al. Long-term follow-up assessment of cardiac safety in SAFE-HEaRt, a clinical trial evaluating the use of HER2-targeted therapies in patients with breast cancer and compromised heart function. Breast Cancer Res Treat. 2021;185(3):863-8. https://doi.org/10.1007/s10549-020-06053-y

ORIGINAL ARTICLE

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Comparison of the effect of cardioplegic solutions used in cardiac surgery on myocardial protection

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SUMMARY

OBJECTIVE: The aim of this retrospective study was to evaluate the effects of cardioplegic solutions on myocardial protection factors in patients undergoing cardiac surgery with cardiopulmonary bypass and to evaluate the relationship between these effects and early clinical outcomes.

METHODS: A total of 78 patients were included in the study. The data of patients who received del Nido cardioplegia (Group 1; n=39) and blood cardioplegia (Group 2; n=39) during the operation were grouped and compared. Preoperative and postoperative routine parameters such as creatine phosphokinase, troponin I, C-reactive protein, and demographic data were recorded, and statistical analyses were performed.

RESULTS: Perfusion time, cross-clamp time, act pump, preoperative C-reactive protein, preoperative creatine phosphokinase, preoperative troponin I, postoperative C-reactive protein, postoperative creatine phosphokinase, postoperative troponin I values were significantly different between del Nido and blood groups ($p<0.05$).

CONCLUSION: Del Nido cardioplegia provided myocardial protection and early postoperative favorable results compared to blood cardioplegia, which may make it a viable option for conventional cardiopulmonary bypass.

KEYWORDS: Cardiopulmonary bypass. Cardioplegia. Myocardial ischemia. Del Nido.

INTRODUCTION

The heart is the largest producer and consumer of energy compared to other organs in our body. It mainly oxidizes fatty acids and carbohydrates to produce energy in the form of adenosine triphosphate (ATP) and other high-energy phosphates. It has the potential to produce approximately 35 times its own weight in ATP in a day[1]. Therefore, a continuous supply of oxygen to the heart is required to maintain its contractile function. The interruption of blood flow to the heart is termed "ischemia," and this condition develops due to the interruption of both oxygen and substrate supply[2].

Myocardial protection is important during cardiac surgery. In cardiac surgery with cardiopulmonary bypass, the heart is usually stopped with cardioplegic solutions[3]. Stopping the heart in diastole with hyperkalemic solutions reduces myocardial oxygen consumption and allows the surgeon to work in an immobile and bloodless field. Cardioplegia solutions commonly used in adult cardiac surgery are multidose blood and single-dose del Nido cardioplegia solution (dNCS)[4].

Del Nido cardioplegia (DNC) is an extracellular solution developed by Pedro del Nido and his team at the University of Pittsburgh in the early 1990s[5]. dNCS was initially designed to enhance myocardial protection of immature cardiomyocytes and has been used in clinical practice for pediatric and infant patients. In recent years, it has been widely used in congenital heart surgery and has provided a well-tolerated myocardial protection time of over 90 min[6]. Aspects of dNCS use include single-dose administration, shorter aortic cross-clamp (AoX) and cardiopulmonary bypass (CPB) times, less need for defibrillations after AoX, and less release of postoperative cardiac enzymes[7]. dNCS is a crystalloid-based solution with approximately 75% less calcium (Ca2+) and contains magnesium sulfate and lidocaine, which limit intracellular Ca^{2+} accumulation and promote ventricular recovery[8].

The choice of cardioplegic solution in cardiac surgery depends on several factors, including the type of surgery and the surgeon's preference and expertise. Although blood cardioplegia is a traditional choice and continues to be widely used, dNCS is gaining popularity in adult cardiac surgery following its proven safety in pediatric cardiac procedures[9].. Although some congenital or acquired heart diseases are successfully treated, open heart surgery is sometimes required. Although cardioplegia is currently

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used in patients undergoing cardiac surgery, the ideal cardioplegic technique remains controversial. There is no consensus on best practices for myocardial protection assessment. First, there is no way to routinely perform real-time myocardial protection assessment. Second, myocardial protection is clinically assessed through a number of indirect factors, such as postoperative troponin I/T or creatine kinase MB levels, ischemic electrical signs on ECG or myocardial infarction, stroke, atrial fibrillation, myocardial function on echo, low cardiac output status, inotropic support, intra-aortic balloon pump, extracorporeal membrane oxygenation, as well as time to extubation and ICU stay[10].

In our study, we aimed to investigate the effects of del Nido and blood cardioplegia on myocardial protection in the postoperative period in patients who underwent cardiac surgery with cardiopulmonary bypass.

METHODS

This retrospective study used the data of patients who underwent cardiac surgery with cardiopulmonary bypass between January 2021 and December 2023 in the Cardiovascular Surgery Clinic of Harran University Hospital. It was approved by the Harran University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 27.05.2024, session 07, session 03. This study was conducted in accordance with the Declaration of Helsinki revised in 1989.

Data collection method

Data of the patients were obtained from computers, operating theater records, perfusion follow-up records, intensive care follow-up cards, and file records. The data of the patients obtained in this study were recorded and entered into the computer.

Statistical analysis

SPSS 25.0 (IBM, Chicago, IL, USA) software was used for data analysis and statistical evaluations. "Mann-Whitney U Test" was used for comparison and significance between two independent groups. Spearman's correlation analysis was used to examine the relationships within and between different groups. Data were presented as mean±standard deviation for numerical variables and number and percentage for categorical variables. A two-tailed p-value <0.05 was accepted as an indicator of a statistically significant difference.

RESULTS

According to Mann-Whitney U test, there was a significant difference between del Nido and blood groups in perfusion time, cross-clamp time, act pump, preoperative CRP, preoperative CK-MB, preoperative troponin I, postoperative CRP, postoperative CK-MB, and postoperative troponin I values ($p<0.05$) (Table 1).

According to the table, in the del Nido patients group, a negative significant correlation between height and preoperative CK-MB (r: -0.362, p: 0.024), a negative significant correlation between height and preoperative troponin I (r: -0.336, p: 0.037), a negative significant correlation between height and postoperative CK-MB (r: -0.448, p: 0.004), a negative significant correlation between BSA and preoperative CK-MB (r: -0.427, p: 0.007), a negative significant correlation between act pump and preoperative CK-MB (r: -0.445, p: 0.004), a negative significant correlation between act pump and preoperative troponin I (r: -0.319, p: 0.048), a positive significant correlation between act pump and postoperative CRP (r: 0.426, p: 0.007), a positive significant correlation between preoperative CRP and postoperative CK-MB (r: 0.399, p: 0.012), a positive significant correlation between preoperative CK-MB and preoperative troponin I (r: 0.839, p: 0.000), and a negative significant correlation between preoperative CK-MB and postoperative CRP (r: -0.326, p: 0.043) were observed.

According to Table 2, there was a positive significant correlation between preoperative CRP and postoperative CRP in the blood group (r: 0.408, p: 0.010), a positive significant correlation between preoperative CRP and postoperative CK-MB (r: 0345, p: 0,031), a positive significant correlation between preoperative CRP and postoperative troponin I (r: 0.394, p: 0,013), a positive significant correlation between preoperative CK-MB and postoperative troponin I (r: 0.774, p: 0.000), a positive significant correlation between preoperative troponin I and postoperative troponin I (r: 0.628, p: 0.000), and a positive significant correlation between postoperative CK-MB and postoperative troponin I (r: 0.620, p:0,000).

In the correlation of the two groups, a negative significant correlation (r: -0,248 p: 0,028) was found between perfusion time and preoperative CRP, a positive significant correlation between perfusion time and preoperative troponin I (r: 0.262, p: 0.021), a negative significant correlation between perfusion time and preoperative CRP (r: -0.228, p: 0.003), a negative significant correlation between cross-clamp time and preoperative CRP (r: -0.279, p: 0.013), a negative significant correlation between cross-clamp time and postoperative CRP (r: -0.344, p: 0.002), a negative significant correlation (r: -0.269, p: 0.017) was found between act pump and preoperative CK-MB, a negative significant correlation (r: -0.288, p: 0.011) was found between preoperative CRP and preoperative CK-MB, a negative significant correlation was found between preoperative

Table 1. Descriptive statistics for del Nido and blood cardioplegia group.

Del Nido cardioplegia group				
	Minimum	Maximum	Mean	Std. deviation
Age	34	79	52.23	10.289
Height	160	185	168.67	6.662
Weight	52	86	75.28	8.778
BSA	1.53	2.04	1.8433	0.12158
Flow	3,660	4,890	4,448.21	282.134
Perfusion time	51	221	124.05	36.687
Cross-clamp time	37	150	84.74	27.776
ACT pump	420	1,000	617.51	164.643
Preoperative CRP (mg/L)	0.05	37.37	3.5149	7.29675
Preoperative CK-MB (u/L)	0.39	69.54	27.2300	28.28622
Preoperative troponin I (ng/mL)	0.00	14,854.20	5,492.0910	6,116.40436
Postoperative CRP (mg/L)	0.10	130.18	17.5105	28.36096
Postoperative CK-MB (u/L)	0.20	9.13	2.1349	1.80895
Postoperative troponin I (ng/mL)	0.03	51.43	21.8670	20.34364
Blood cardioplegia group				
Age	22	76	59.95	10.224
Height	150	187	169.00	8.672
Weight	55	133	76.62	15.786
BSA	1.56	2.55	1.8715	0.21606
Flow	3,750	6,110	4,500.56	519.402
Perfusion time	60	249	105.92	39.783
Cross-clamp time	33	173	71.56	34.776
ACT pump	414	1,145	646.23	189.534
Preoperative CRP (mg/L)	0.16	126.82	14.7038	25.04534
Preoperative CK-MB (U/L)	0.59	189.58	21.6041	50.28994
Preoperative troponin I (ng/mL)	0.00	12,978.44	2,107.5348	4,558.43031
Postoperative CRP (mg/L)	0.29	194.81	78.6500	44.12288
Postoperative CK-MB (u/L)	0.00	150.10	11.6608	26.46399

ACT: activated clotting time; BSA: body surface area; CRP: C-reactive protein; CK-MB: creatine phosphokinase.

CRP and preoperative troponin I (r: -0.398, p: 0,000), and a positive significant correlation between preoperative CRP and postoperative CRP (r: 0.677, p:0.000).

According to Table 3, there was a positive significant correlation between preoperative CRP and postoperative CK-MB (r: 0.555, p: 0.000), a positive significant correlation between preoperative CK-MB and preoperative troponin I (r: 0.764, p: 0.000), a negative significant correlation between preoperative CK-MB and postoperative CRP (r: -0.402, p: 0.000), a positive significant correlation between preoperative CK-MB and preoperative troponin I (r: 0.249, p: 0.028), a negative significant correlation between preoperative troponin I and postoperative CRP (r: -0.537, p: 0.000), a positive significant correlation between preoperative troponin I and postoperative troponin I (r: 0.647, p: 0.000), a positive significant correlation between postoperative CRP and postoperative CK-MB (r: 0.421, p: 0.000), a negative correlation between postoperative CRP and postoperative troponin I (r: -0.267, p: 0.018).

DISCUSSION

Before heart surgery, it is necessary to stop the heart quickly. In order to better restore the function of the myocardium after ischemia, the concept of cardioplegia has been proposed. With the

Table 2. Correlation table of del Nido group and blood group.

Del Nido cardioplegia group		Preoperative CK-MB (U/L)	Preoperative troponin I (ng/mL)	Postoperative CRP (mg/L)	Postoperative CK-MB (u/L)
Height	r	-0.362*	-0.336*		-0.448**
	p	0.024	0.037		0.004
BSA	r	-0.427**			
	p	0.007			
ACT pump	r	-0.445**	-0.319*	0.426**	
	p	0.004	0.048	0.007	
Preoperative CRP (mg/L)	r				0.399*
	p				0.012
Preoperative CK-MB (U/L)	r		0.839**	-0.326*	
	p		0.000	0.043	
Blood cardioplegia group		**Preoperative troponin I**	**Postoperative CRP (mg/L)**	**Postoperative CK-MB (u/l)**	**Postoperative troponin I (ng/mL)**
Preoperative CRP (mg/L)	r		0.408**	0.345*	0.394*
	p		0.010	0.031	0.013
Preoperative CK-MB (U/L)	r	0.774**			
	p	0.000			
Preoperative troponin I (ng/mL)	r				0.628**
	p				0.000
Postoperative CK-MB (u/L)	r				0.620**
	p				0.000

ACT: activated clotting time, BSA: body surface area, CRP: C-reactive protein, CK-MB: creatine phosphokinase. *Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level.

Table 3. Correlation table in del Nido and blood group.

Del Nido and blood group		Preoperative CRP (mg/L)	Preoperative CK-MB (U/L)	Preoperative troponin I (ng/mL)	Postoperative CRP (mg/L)	Postoperative CK-MB (U/L)	Postoperative troponin I (ng/mL)
Perfusion time	r	-0.248*		0.262*	-0.328**		
	p	0.028		0.021	0.003		
Cross-clamp time	r	-0.279*			-0.344**		
	p	0.013			0.002		
ACT pump	r		-0.269*				
	p		0.017				
Preoperative CRP (mg/L)	r		-0.288*	-0.398**	0.677**	0.555**	
	p		0.011	0.000	0.000	0.000	
Preoperative CK-MB (U/L)	r			0.764**	-0.402**		0.249*
	p			0.000	0.000		0.028
Preoperative troponin I (ng/mL)	r				-0.537**		0.647**
	p				0.000		0.000
Postoperative CRP (mg/L)	r					0.421**	-0.267*
	p					0.000	0.018

ACT: activated clotting time, CRP: C-reactive protein, CK-MB: Creatine phosphokinase. *Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level.

development of cardiac surgery, myocardial protection research has been going on for decades, and the establishment of the general theoretical system of myocardial protection and clinical application methods are becoming more and more mature[11].

DNC is a type of single-dose cardioplegia. The initial infusion dose is usually 20 mL/kg and can be up to a maximum of 1 L, which can meet the cross-clamp time of 90 min. If the duration of cardiac arrest needs to be extended, the amount of intraoperative infusion is usually added at a dose of 10 mL/kg. The results of various studies have shown that the perfusion volume of DNC is significantly lower than that of blood-containing cardioplegia, requiring repeated perfusion[12].

Troponin is released from damaged cell membranes only after cardiac muscle cells have died, and both cardiac troponin values are ideal for detecting myocardial injury. CK-MB is an important biomarker in the diagnosis of myocardial injury and is used as a potential co-detection index along with troponin to reflect the degree of myocardial injury[13]. DNC was associated with lower troponin and CK-MB after cardiac surgery in a meta-study including only two randomized clinical trial (RCT) studies. A recent meta-analysis of del Nido cardioplegia for myocardial protection included three RCTs and showed no statistically significant difference in troponin levels 24 h after cardiac surgery between the DNC group and the CBC group. Among the 10 RCTs included in this study, there were three, four, and five studies with complete data including troponin I and CK-MB levels 24 h after surgery, respectively. The results showed that DNC significantly reduced troponin and CK-MB levels compared to blood cardioplegia. No significant difference was found in postoperative troponin I values[14].

In one study, DNC showed potential superiority in myocardial protection, as evidenced by detailed evaluation of both functional and biochemical markers. Postoperative LV ejection fraction changes, which serve as a functional indicator of myocardial protection, showed comparable results between the two groups, while the del Nido group outperformed the blood cardioplegia group in terms of changes in troponin I level, an important biochemical marker of myocardial protection[15]. In our study, the mean values of perfusion time, cross-clamp time, preoperative CK-MB, preoperative troponin I, and postoperative troponin I were higher in the dNCS group, while the mean values of preoperative CRP, postoperative CRP, and postoperative CK-MB were higher in the blood cardioplegia group. According to these results, the duration of operation, aortic cross-clamping time, and postoperative troponin I values were higher in the dNCS group, while postoperative CRP and CK-MB values were higher in the blood group.

CONCLUSION

In our study, preoperative troponin I value was in the same direction with preoperative CK-MB and perfusion time. Preoperative and postoperative CRP values were in the same direction with postoperative CK-MB values.

AUTHORS' CONTRIBUTIONS

MP: Conceptualization, Formal Analysis, Methodology, Resources, Software, Writing – original draft. **RD:** Data curation, Formal Analysis, Methodology, Resources, Software, Visualization, Writing – original draft. **EE:** Data curation, Resources, Validation, Writing – review & editing. **YH:** Resources, Software, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circ Res. 2013;113(6):709-24. https://doi.org/10.1161/CIRCRESAHA.113.300376
2. Lorca R, Jiménez-Blanco M, García-Ruiz JM, Pizarro G, Fernández-Jiménez R, García-Álvarez A, et al. Coexistence of transmural and lateral wavefront progression of myocardial infarction in the human heart. Rev Esp Cardiol (Engl Ed). 2021;74(10):870-7. https://doi.org/10.1016/j.rec.2020.07.007
3. Kağan As A, Engin M, Amaç B, Aydın U, Eriş C, Ata Y, et al. Effect of del Nido cardioplegia use on kidney injury after coronary bypass operations. Rev Assoc Med Bras (1992). 2021;67(9):1322-7. https://doi.org/10.1590/1806-9282.20210642
4. Luo W, Bouhout I, Demers P. The del Nido cardioplegia in adult cardiac surgery: reinventing myocardial protection? J Thorac Dis. 2019;11(Suppl 3):S367-9. https://doi.org/10.21037/jtd.2018.12.65
5. Timek TA, Beute T, Robinson JA, Zalizadeh D, Mater R, Parker JL, et al. Del Nido cardioplegia in isolated adult coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2020;160(6):1479-85.e5. https://doi.org/10.1016/j.jtcvs.2019.09.027
6. Charette K, Gerrah R, Quaegebeur J, Chen J, Riley D, Mongero L, et al. Single dose myocardial protection technique utilizing del Nido cardioplegia solution during congenital heart surgery procedures. Perfusion. 2012;27(2):98-103. https://doi.org/10.1177/0267659111424788
7. Ad N, Holmes SD, Massimiano PS, Rongione AJ, Fornaresio LM, Fitzgerald D. The use of del Nido cardioplegia in adult cardiac surgery: a prospective randomized trial. J Thorac Cardiovasc Surg. 2018;155(3):1011-8. https://doi.org/10.1016/j.jtcvs.2017.09.146
8. Garcia-Suarez J, Garcia-Fernandez J, Martinez Lopez D, Reques L, Sanz S, Carballo D, et al. Clinical impact of del Nido cardioplegia in adult cardiac surgery: a prospective randomized trial. J Thorac Cardiovasc Surg. 2023;166(5):1458-67. https://doi.org/10.1016/j.jtcvs.2022.01.044

9. Ali JM, Miles LF, Abu-Omar Y, Galhardo C, Falter F. Global cardioplegia practices: results from the global cardiopulmonary bypass survey. J Extra Corpor Technol. 2018;50(2):83-93. PMID: 29921986
10. Fan Y, Zhang AM, Xiao YB, Weng YG, Hetzer R. Warm versus cold cardioplegia for heart surgery: a meta-analysis. Eur J Cardiothorac Surg. 2010;37(4):912-9. https://doi.org/10.1016/j.ejcts.2009.09.030
11. Whittaker A, Aboughdir M, Mahbub S, Ahmed A, Harky A. Myocardial protection in cardiac surgery: how limited are the options? A comprehensive literature review. Perfusion. 2021;36(4):338-51. https://doi.org/10.1177/0267659120942656
12. Eris C, Engin M, Erdolu B, Kagan As A. Comparison of del Nido cardioplegia vs. blood cardioplegia in adult aortic surgery: is the single-dose cardioplegia technique really advantageous? Asian J Surg. 2022;45(5):1122-7. https://doi.org/10.1016/j.asjsur.2021.09.032
13. Xu C, Zhang T, Zhu B, Cao Z. Diagnostic role of postmortem CK-MB in cardiac death: a systematic review and meta-analysis. Forensic Sci Med Pathol. 2020;16(2):287-94. https://doi.org/10.1007/s12024-020-00232-5
14. Zhai K, Cheng X, Zhang P, Wei S, Huang J, Wu X, et al. Del Nido cardioplegia for myocardial protection in adult cardiac surgery: a systematic review and update meta-analysis. Perfusion. 2023;38(1):6-17. https://doi.org/10.1177/02676591211031095
15. Lee S, Jung JC, Chang HW, Lee JH, Kim DJ, Kim JS, et al. Comparative analysis of del Nido cardioplegia versus blood cardioplegia in isolate coronary artery bypass grafting. J Cardiothorac Surg. 2024;19(1):438. https://doi.org/10.1186/s13019-024-02853-1

ORIGINAL ARTICLE

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Evaluation of head posture in patients with temporomandibular joint disorders: a cross-sectional study

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SUMMARY

OBJECTIVE: This study evaluated head posture in patients with temporomandibular joint disorders and explored the effects of postural changes on clinical parameters.

METHODS: In total, 81 individuals diagnosed with temporomandibular joint disorders participated in this cross-sectional prospective study. Demographics, pain status, head posture, and jaw movement data were collected. Head posture was assessed using the Posture Screen Mobile application.

RESULTS: Results indicated moderate negative correlations between pain and mouth opening (rho=-0.437, p<0.001) and maximum mouth opening (rho=-0.427, p<0.001). Anterior translation showed weak positive correlations with mouth opening and maximum mouth opening, while right lateral translation exhibited a weak positive correlation with pain (rho=0.264, p=0.017). Posterior angulation showed weak significant correlations with pain, mouth opening, and maximum mouth opening.

CONCLUSION: These findings suggest that head posture has a significant influence on temporomandibular joint disorder symptoms. Treatment strategies addressing postural abnormalities may help alleviate symptoms and enhance the quality of life in temporomandibular joint disorder patients.

KEYWORDS: Jaw diseases. Pain. Posture. Temporomandibular joint disorders.

INTRODUCTION

The temporomandibular joint (TMJ) is a critical structure that enables essential functions such as chewing, speaking, and swallowing by coordinating complex jaw movements. TMJ disorders (TMD) are a group of functional impairments characterized by symptoms such as pain, restricted jaw movement, joint sounds, and muscle spasms. TMD significantly impacts patients' quality of life, often requiring a multidisciplinary approach for effective management[1,2].

Head posture plays a crucial role in maintaining musculoskeletal balance and proper body mechanics. Deviations in normal head posture, such as forward head posture or lateral translations, have been linked to various health issues, including neck pain, headaches, and even TMD[3,4]. Abnormal head posture is thought to exacerbate TMD symptoms by increasing strain on the TMJ and associated muscles[4,5].

Previous studies have explored the relationship between TMD and head posture, suggesting that postural deviations may worsen TMD symptoms[6,7]. However, the existing literature presents inconclusive findings, necessitating further research to clarify the impact of head posture on TMD. Understanding this relationship is critical for developing comprehensive treatment strategies that not only target the TMJ but also address postural abnormalities.

This study aims to evaluate head posture in patients with TMD and investigate the effects of these postural deviations on clinical symptoms such as pain and jaw movement limitations. By understanding this relationship, clinicians can develop targeted interventions to alleviate symptoms by correcting postural imbalances. We hypothesize that there is a significant relationship between head posture deviations, levels of pain, and the range of jaw movements in patients with TMD. Specifically, we expect that abnormal head posture will correlate with increased pain levels and restricted jaw mobility. Therefore, addressing postural abnormalities may help alleviate TMD symptoms and improve overall patient outcomes.

METHODS

Study design

This research was conducted as a cross-sectional prospective study. Approval for the study was granted by the Karamanoglu Mehmetbey University Faculty of Medicine Clinical Research

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Ethics Committee (Decision No. 05-2024/20). The study took place between May and June 2024 at the faculty hospital, involving 81 volunteer participants diagnosed with TMD. All procedures were carried out following the principles of the Declaration of Helsinki. This study was reported in accordance with the STROBE statement.

Participants

In total, 81 participants aged between 18 and 65 years, diagnosed with muscle-related TMD, were included in the study. Patients presenting with jaw pain, ear pain, or joint sounds were evaluated and diagnosed using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) developed by Dworkin and Leresche[8]. Exclusion criteria included participants with pre-existing skeletal disorders, intra-articular TMD, tumors, infections, psychiatric diagnoses, systemic diseases, bleeding disorders, fibromyalgia, and uncooperative behavior. All participants provided written informed consent before participation, and confidentiality was ensured by using unique identifiers for each participant.

A pilot study was conducted with 10 participants to determine the necessary sample size. Using the G*Power software (version 3.0.10, Franz Faul, University of Kiel, Germany), the effect size was calculated as r=0.31, based on the pilot results. A minimum of 73 participants was needed to achieve 80% power at a 0.05 significance level (α) and a type II error rate (β) of 0.20. To account for potential data loss, an additional 10% of participants were included, resulting in a total sample size of 81 participants (Figure 1).

Outcome measures

Sociodemographic information

Data on participants' age, gender, education level, income level, marital status, joint sounds during mouth opening and closing, protrusion levels, tooth wear, night guard use, ear pain, jaw locking, headaches, and occlusion angle were collected.

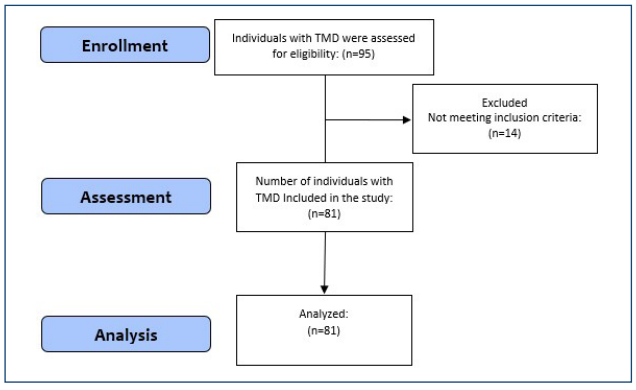

Figure 1. Flow diagram.

Pain

The Visual Analog Scale (VAS) was used to measure participants' pain levels. The VAS consists of a 10 cm line, with 0 representing "no pain" and 10 representing "the most severe pain imaginable." Participants marked their pain intensity on this line for both resting and functional states[9].

Posture

Posture was evaluated using the Posture Screen Mobile (PSM) (PostureCo Inc., Trinity, FL, USA) application, which is a validated and reliable tool for postural analysis. Calibration of the PSM was performed before each session to ensure accuracy. Participants were photographed from the front, back, right, and left lateral views while standing in a standardized position. Postural deviations were calculated using the craniovertebral angle, determined by the angle between the horizontal axis and a line connecting the tragus of the ear to the C7 spinous process. Parameters such as anterior and posterior translations, lateral translations, and angulations were assessed[10,11].

Jaw motions

Jaw movement measurements included maximum mouth opening, mouth opening, and lateral movements. Maximum mouth opening was defined as the maximum distance between the upper and lower incisors in millimeters. Lateral movements were measured using a digital caliper, which recorded the distance the jaw could move to the right and left from the midline[12].

Statistics

Statistical analyses were performed using IBM SPSS version 27 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Kolmogorov-Smirnov test and histogram analysis. Due to the non-normal distribution of the data, Spearman correlation tests were used to evaluate the relationships between pain, maximum mouth opening, and various postural parameters. Significance was set at $p<0.05$. Spearman correlation coefficients (r) were interpreted as follows: 0–0.19 very weak, 0.2–0.39 weak, 0.40–0.59 moderate, 0.6–0.79 strong, and 0.8–1 very strong[13].

RESULTS

In total, 81 participants, ranging in age from 22 to 58 years, were included in the study. Sociodemographic information for the participants is presented in Table 1.

Table 1. Participants' sociodemographic information and clinical parameters.

		n (%)	
Gender	Male	35 (43.2)	0.222
	Female	46 (56.8)	
Marital status	Married	36 (44.4)	0.317
	Single	45 (55.6)	
Education level	Primary school	2 (2.5)	<0.001*
	Middle school	15 (18.5)	
	High school	28 (34.6)	
	University	25 (30.9)	
	Graduate	11 (13.6)	
Income level	Low	33 (40.7)	<0.001*
	Medium	40 (49.4)	
	High	8 (9.9)	
Sound during mouth opening	Yes	72 (88.9)	<0.001*
	No	9 (11.1)	
Protrusion	1	3 (3.7)	<0.001*
	2	47 (58.0)	
	3	31 (38.3)	
Tooth wear	No wear	24 (29.6)	<0.001*
	Enamel	50 (61.7)	
	Dentin	7 (8.6)	
Night guard	Yes	19 (23.5)	<0.001*
	No	62 (76.5)	
Ear pain	Yes	50 (61.7)	0.035*
	No	31 (38.3)	
Headache	Yes	50 (61.7)	0.035*
	No	31 (38.3)	
Jaw locking	Yes	31 (38.3)	0.035*
	No	50 (61.7)	
Occlusion angle	1	29 (35.8)	0.010*
	2	37 (45.7)	
	3	15 (18.5)	

Chi-square test, *p<0.05. n: number of participants; %: percentage.

In this study, the relationships between various postural parameters and pain, mouth opening, and maximum mouth opening in patients with TMD were analyzed using Spearman correlation tests. According to the analysis results, a moderate negative and significant correlation was found between pain and mouth opening (rho=-0.437, p<0.001). Similarly, a moderate negative and significant relationship was identified between pain and maximum mouth opening (rho=-0.427, p<0.001).

A weak negative and significant relationship was found between anterior translation and pain (rho=-0.239, p=0.032). Additionally, weak positive and significant relationships were found between anterior translation and mouth opening (rho=0.224, p=0.044) and maximum mouth opening (rho=0.335, p=0.002).

No significant correlation was found between anterior angulation and the examined parameters. Right lateral translation showed a weak positive and significant correlation with

pain (rho=0.264, p=0.017). Furthermore, weak negative significant relationships were found between right lateral translation and maximum mouth opening (rho=-0.233, p=0.036) and anterior translation (rho=-0.396, p<0.001). Right lateral angulation showed a weak positive relationship only with right lateral translation (rho=0.232, p=0.037).

No significant correlation was found between posterior translation and the other examined parameters. Posterior angulation showed weak significant relationships with pain (rho=-0.239, p=0.032), mouth opening (rho=0.223, p=0.045), and maximum mouth opening (rho=0.259, p=0.020). Additionally, strong positive relationships were found with anterior translation (rho=0.524, p<0.001) and anterior angulation (rho=0.577, p<0.001). A weak negative correlation was observed with right lateral translation (rho=-0.416, p<0.001).

Left lateral translation showed weak positive relationships with anterior translation (rho=0.316, p=0.004), anterior angulation (rho=0.372, p<0.001), and posterior angulation (rho=0.343, p=0.002). Left lateral angulation exhibited weak positive relationships with left lateral translation (rho=0.298, p=0.007) and posterior angulation (rho=0.433, p<0.001) (Table 2).

DISCUSSION

The findings of this study indicate that the majority of participants were women, which may suggest a higher prevalence of TMD among females. Previous research has explored the relationship between sex steroid receptors in masticatory muscles, considering factors such as age and gender, and emphasized the role of hormones in TMD[14]. Hormonal fluctuations in women can increase muscle tension and pain sensitivity, potentially exacerbating TMD symptoms. Thus, gender differences should be taken into account in the assessment and management of TMD.

Table 2. The relationships between various postural parameters and pain, mouth opening, and maximum mouth opening.

Variables	Pain	Mouth opening	Maximum mouth opening
Pain	–	0.437***	-0.427***
Mouth opening	-0.437***	–	0.948***
Maximum mouth opening	-0.427***	0.948***	–
Anterior translation	-0.239*	0.224*	0.335**
Anterior angulation	-0.115	0.084	0.128
Posterior translation	0.004	0.035	0.041
Posterior angulation	-0.239*	0.223*	0.259*
Right lateral translation	0.264*	-0.209	-0.233*
Right lateral angulation	0.004	-0.052	0.009
Left lateral translation	-0.164	0.155	0.172
Left lateral angulation	-0.049	0.061	0.075

Spearman correlation; *p<0.05; **p<0.01; ***p<0.001.

A moderate negative and significant correlation was found between pain and mouth opening, as well as maximum mouth opening. This finding indicates that an increase in pain may lead to a decrease in mouth opening. The findings of this study are similar to the literature. The TMJ is associated with muscles and joint structures that control jaw movements, and dysfunction in these structures can lead to pain and restricted movement[15-17]. This aligns with previous research, such as the work by Minervini et al.[3], which demonstrated that increased TMD-related pain significantly restricts mandibular mobility. Furthermore, pain-induced muscle guarding and spasms are well-documented phenomena that exacerbate joint stiffness and limit functional capacity[18].

A weak negative relationship was found between anterior translation and pain. Additionally, weak positive relationships were found between anterior translation and mouth opening, as well as maximum mouth opening. The anterior translation is characterized by the forward displacement of the head, which can cause tension in the neck muscles, particularly the sternocleidomastoid and trapezius muscles. This tension can increase pressure on the TMJ, leading to pain and restricted movement. These findings are supported by studies in the literature[3,19]. Furthermore, forward head posture has been linked to altered biomechanics and increased strain on the cervical spine, which may further exacerbate TMD[6]. Corrective exercises aimed at improving head posture have shown promise in reducing TMD symptoms, highlighting the importance of addressing postural issues in clinical practice[20].

The weak positive correlation between right lateral translation and pain suggests that lateral shifts in head posture may exacerbate pain symptoms. The lateral translation is characterized by the sideways displacement of the head, creating asymmetric loading on the neck muscles and spinal alignment. Lateral postural changes can cause asymmetric tension in the TMJ and associated muscle groups, leading to pain and dysfunction. This asymmetry can hinder the proper alignment of the TMJ, causing pain and restrictions in jaw movements[21]. Additionally, this misalignment can contribute to compensatory mechanisms in the cervical spine and shoulder girdle, further complicating the clinical picture[22]. Clinicians should consider incorporating postural assessment and correction into the treatment protocols for TMD patients, as addressing these imbalances can potentially alleviate pain and improve overall functional outcomes[3].

The weak significant relationships between posterior angulation and pain, mouth opening, and maximum mouth opening indicate that posterior postural changes may also affect TMD symptoms. Posterior angulation is characterized by the backward tilt of the head, which can increase mechanical stress on the lower jaw and TMJ. This stress can lead to joint dysfunction and pain[23]. Such findings align with previous research indicating that abnormal head postures can contribute to altered mandibular dynamics and increased strain on the TMJ, exacerbating symptoms in participants with TMD[24]. Moreover, interventions focusing on correcting head posture have shown promising results in reducing TMJ pain and improving functional outcomes[3]. In addition, psychological factors like anxiety and stress may worsen TMD symptoms, as emotional stress can increase muscle tension and pain. Recent studies have shown that the COVID-19 pandemic, with its extended periods of social isolation, significantly affected individuals' emotional well-being, leading to increased levels of anxiety, depression, and stress. Research indicates that these psychological factors were linked to greater TMD-related pain, particularly among vulnerable groups such as students[25]. Therefore, it is plausible that emotional stress could intensify the impact of postural deviations on TMD symptoms.

The findings of this study emphasize the importance of evaluating head posture in patients with TMD. It should be considered that postural deviations can exacerbate TMD symptoms and restrict jaw functions. Therefore, strategies to correct head posture should be developed in the treatment of TMD.

Although this study is a significant step in understanding the relationship between TMD and head posture, larger sample sizes and long-term studies are necessary. Future research should compare the effects of different treatment methods on head posture and TMD symptoms. Furthermore, the relationship between head posture and other musculoskeletal disorders should be explored. Specifically, the role of the neck and shoulder muscles and their impact on TMD should be investigated in detail.

This study has several limitations. The cross-sectional design limits the ability to establish causality, indicating the need for longitudinal studies to explore these relationships further. Additionally, while the study assessed the link between head posture, pain, and jaw movements, the long-term effects remain uncertain. Including a control group of healthy participants would have enhanced comparative analysis. The use of subjective measures, such as the VAS for pain, may introduce potential bias. Although clinical tools like RDC/TMD are commonly used, their diagnostic accuracy can sometimes fall short, whereas advanced imaging techniques, such as magnetic resonance imaging, may provide more precise diagnostics in complex TMD cases[26].

CONCLUSION AND RECOMMENDATIONS

This study is among the first to evaluate head posture in TMD patients using a mobile posture analysis application. The findings indicate that head posture is a significant factor influencing TMD symptoms, with deviations exacerbating pain and limiting jaw function. Integrating postural assessments into clinical practice can help identify high-risk patients and guide targeted treatment approaches. Correcting head posture through targeted treatment approaches can help reduce patients' symptoms and improve their quality of life.

ETHICAL APPROVAL

This study was approved by the Karamanoglu Mehmetbey University Faculty of Medicine Clinical Research Ethics Committee (decision no. 05-2024/20). The study conformed to institutional ethical standards.

AUTHORS' CONTRIBUTIONS

EEO: Conceptualization, Data curation, Investigation, Project administration, Resources, Writing – original draft, Writing – review & editing. **BSU**: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Kapos FP, Exposto FG, Oyarzo JF, Durham J. Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management. Oral Surg. 2020;13(4):321-34. https://doi.org/10.1111/ors.12473
2. Wilkie G, Al-Ani Z. Temporomandibular joint anatomy, function and clinical relevance. Br Dent J. 2022;233(7):539-46. https://doi.org/10.1038/s41415-022-5082-0
3. Minervini G, Franco R, Marrapodi MM, Crimi S, Badnjević A, Cervino G, et al. Correlation between temporomandibular disorders (TMD) and posture evaluated trough the diagnostic criteria for temporomandibular disorders (DC/TMD): a systematic review with meta-analysis. J Clin Med. 2023;12(7):2652. https://doi.org/10.3390/jcm12072652
4. Oleksy Ł, Kielnar R, Mika A, Jankowicz-Szymańska A, Bylina D, Sołtan J, et al. Impact of cervical spine rehabilitation on temporomandibular joint functioning in patients with idiopathic neck pain. Biomed Res Int. 2021;2021:6886373. https://doi.org/10.1155/2021/6886373

5. Nota A, Pittari L, Lannes AC, Vaghi C, Calugi Benvenuti C, Tecco S. Analysis of cervical range of motion in subjects affected by temporomandibular disorders: a controlled study. Medicina (Kaunas). 2023;60(1):37. https://doi.org/10.3390/medicina60010037
6. Xiao CQ, Wan YD, Li YQ, Yan ZB, Cheng QY, Fan PD, et al. Do Temporomandibular disorder patients with joint pain exhibit forward head posture? A cephalometric study. Pain Res Manag. 2023;2023:7363412. https://doi.org/10.1155/2023/7363412
7. Miçooğulları M, Yüksel İ, Angın S. Effect of pain on cranio-cervico-mandibular function and postural stability in people with temporomandibular joint disorders. Korean J Pain. 2024;37(2):164-77. https://doi.org/10.3344/kjp.23301
8. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord. 1992;6(4):301-55. PMID: 1298767
9. Marvin JA. Pain assessment versus measurement. J Burn Care Rehabil. 1995;16(3 Pt 2):348-57. https://doi.org/10.1097/00004630-199505001-00003
10. Boland DM, Neufeld EV, Ruddell J, Dolezal BA, Cooper CB. Inter- and intra-rater agreement of static posture analysis using a mobile application. J Phys Ther Sci. 2016;28(12):3398-402. https://doi.org/10.1589/jpts.28.3398
11. Szucs KA, Brown EVD. Rater reliability and construct validity of a mobile application for posture analysis. J Phys Ther Sci. 2018;30(1):31-6. https://doi.org/10.1589/jpts.30.31
12. Mazzetto MO, Anacleto MA, Rodrigues CA, Bragança RM, Paiva G, Valencise Magri L. Comparison of mandibular movements in TMD by means of a 3D ultrasonic system and digital caliper rule. Cranio. 2017;35(1):46-51. https://doi.org/10.1080/08869634.2016.1149928
13. Swinscow TD. Statistics at square one: XVIII-Correlation. Br Med J. 1976;2(6037):680-1. https://doi.org/10.1136/bmj.2.6037.680
14. Galhardo APM, Mukai MK, Mori M, Carvalho KC, Baracat MCP, Simões MJ, et al. Influence of age and gender on sex steroid receptors in rat masticatory muscles. Sci Rep. 2019;9(1):18403. https://doi.org/10.1038/s41598-019-54774-y
15. Dahl AF, Bergem AK, Bjørnland T, Olsen-Bergem H. Temporomandibular pain and quality of life assessment in adolescents in a Norwegian cohort. Clin Exp Dent Res. 2023;9(3):481-90. https://doi.org/10.1002/cre2.733
16. Zúñiga-Herrera ID, Herrera-Atoche JR, Aguilar-Pérez FJ, Escoffié-Ramírez M. Malocclusion complexity in patients with myofascial pain with or without mouth-opening limitation: a case-control study. Biomed Res Int. 2022;2022:3594246. https://doi.org/10.1155/2022/3594246
17. Özmen EE, Durmuş E, Ünüvar BS, Kalaycı A. Mid- and long-term effect of kinesio taping on temporomandibular joint dysfunction: a randomised-controlled trial. Acibadem Univ Saglik Bilim Derg. 2022;13(4):579-86.
18. Merkle SL, Sluka KA, Frey-Law LA. The interaction between pain and movement. J Hand Ther. 2020;33(1):60-6. https://doi.org/10.1016/j.jht.2018.05.001
19. Yang S, Boudier-Revéret M, Yi YG, Hong KY, Chang MC. Treatment of chronic neck pain in patients with forward head posture: a systematic narrative review. Healthcare (Basel). 2023;11(19):2604. https://doi.org/10.3390/healthcare11192604
20. Armijo-Olivo S, Pitance L, Singh V, Neto F, Thie N, Michelotti A. Effectiveness of manual therapy and therapeutic exercise for temporomandibular disorders: systematic review and meta-analysis. Phys Ther. 2016;96(1):9-25. https://doi.org/10.2522/ptj.20140548
21. Jaeger JO, Oakley PA, Moore RR, Ruggeroli EP, Harrison DE. Resolution of temporomandibular joint dysfunction (TMJD) by correcting a lateral head translation posture following previous failed traditional chiropractic therapy: a CBP® case report. J Phys Ther Sci. 2018;30(1):103-7. https://doi.org/10.1589/jpts.30.103
22. Nejati P, Lotfian S, Moezy A, Moezy A, Nejati M. The relationship of forward head posture and rounded shoulders with neck pain in Iranian office workers. Med J Islam Repub Iran. 2014;28:26. PMID: 25250268
23. Prodoehl J, Thomas P, Krzak JJ, Hanke T, Tojanic J, Thomas J. Effect of starting posture on three-dimensional jaw and head movement. J Oral Maxillofac Res. 2022;13(1):e4. https://doi.org/10.5037/jomr.2022.13104
24. Joy TE, Tanuja S, Pillai RR, Dhas Manchil PR, Raveendranathan R. Assessment of craniocervical posture in TMJ disorders using lateral radiographic view: a cross-sectional study. Cranio. 2021;39(5):391-7. https://doi.org/10.1080/08869634.2019.1665227
25. Galhardo APM, Andrade PR, Andrade LP, Cury MAA, Mukai MK, Baracat EC, et al. Cross-sectional study of self-reported pain related to temporomandibular disorders and emotional state of medical school faculty and students: post-COVID-19 pandemic. PLoS One. 2024;19(8):e0308988. https://doi.org/10.1371/journal.pone.0308988
26. Galhardo AP, Costa Leite C, Gebrim EM, Gomes RL, Mukai MK, Yamaguchi CA, et al. The correlation of research diagnostic criteria for temporomandibular disorders and magnetic resonance imaging: a study of diagnostic accuracy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115(2):277-84. https://doi.org/10.1016/j.oooo.2012.10.020

ORIGINAL ARTICLE

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Is cesarean scar defect becoming history? The effect of uterotomy closure

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SUMMARY

OBJECTIVE: Isthmocele or cesarean scar *defect is* a pouch-like defect in the myometrium at the isthmic level that *is thought that it might occur* as a result of the *insufficient* healing process of the uterine incision after cesarean section. It is important not to underestimate isthmocele and its preventive measures since it might cause serious gynecologic and obstetric complications. However, the best suturing technique suitable for the prevention of isthmocele formation is yet to be identified. The aim of this study was to compare the effects of three different uterine closure techniques applied during cesarean section on isthmocele formation.

METHODS: In this prospective study, a total of 120 term (>37 weeks) pregnant women with no history of cesarean section and scheduled for primary cesarean section were *randomized* preoperatively *to three different* uterotomy closure *techniques (baseball*, single-*locked*, *and single-unlocked groups)*.

RESULTS: In a total of 43 patients, postoperative third-month sonography revealed isthmocele as an *anechoic triangular area with ≥1 mm* depth at the scar site. Compared with the single-locked and single-unlocked groups, isthmocele development was significantly lower in the baseball-type closure group (47.5% in the single-locked, 46.2% in the single-unlocked, and 15.4% in the baseball-type closure group). The group with the highest residual myometrial thickness, that is, 5.7 mm, was again the patients who underwent baseball sutures.

CONCLUSION: Uterotomy closure with baseball-type suturing seems to be an advantageous method as compared to the traditional techniques in terms of preserving the residual myometrial thickness and preventing isthmocele formation.

KEYWORDS: Niche. Caesarean section. Scar. Suture technics.

INTRODUCTION

Currently, the most common surgical procedure performed by obstetricians in women of reproductive age is the cesarean section (C/S)[1]. The increase in C/S numbers worldwide has become a global concern. Elective C/S has no proven feto–maternal benefits; on the contrary, it might result in adverse outcomes, such as cesarean scar defects (CSDs), bladder–bowel injuries, and intra-abdominal adhesions. CSD or isthmocele, also known as a niche, might occur as a result of the insufficient healing process of the uterine incision after C/S[2]. It is generally about a 1–2 mm pouch-like defect, leading to thinning of the anterior myometrium and may also lead to abnormal uterine bleeding, chronic pelvic pain, scar ectopic pregnancy, uterine rupture, placenta accreta spectrum disorders, and infertility[3]. The prevalence of isthmocele, which ranges between 19 and 84%, continues to increase worldwide with a decline in the vaginal birth rate[4,5].

Being an easily accessible, simple, non-invasive, and inexpensive method, transvaginal ultrasonography (TVUSG) typically detects isthmocele as an anechoic triangular defect at the isthmic level. The diagnosis can also be made with other modalities, such as magnetic resonance imaging (MRI), hysteroscopy (H/S), hysterography (HSG), and sonohysterography (SIS).

Isthmocele can be managed medically (e.g., levonorgestrel-releasing intrauterine system and oral contraceptives) or surgically (e.g., laparotomy, laparoscopy, H/S, and robotic or vaginal surgery). However, there is no consensus on which patients should be treated and how. While it is generally preferred by experts to treat only symptomatic patients, there is insufficient information about the success of the surgical management of isthmocele and its complications and recurrence after the surgery in the long term. Therefore, it would be reasonable to focus on taking preventive measures against isthmocele formation.

A retroverted uterus can cause more tension and thus might negatively impact the healing process. The uterine position and individual/genetic predisposition to insufficient wound healing can be considered patient-specific risk factors for isthmocele formation.

The best suturing technique suitable for the prevention of isthmocele formation is yet to be identified. The aim of this

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study was to compare the effects of three different uterine closure techniques applied during C/S on isthmocele formation.

METHODS

In this prospective study, a total of 149 pregnant women scheduled for primary C/S in the Gynecology and Obstetrics Department between March and September 2022 were evaluated. Informed consent was obtained from all participants. Only term (>37 weeks) pregnant women with no history of C/S who were planned to undergo a primary C/S were included in the study. The study exclusion criteria were as follows: presence of regular contractions and/or a cervical dilatation of more than 4 cm indicating the beginning of the active stage of labor, placental abnormalities, previous uterine surgery, multiple pregnancies, premature rupture of membranes, chorioamnionitis, preoperative hemoglobin level below 10 g/dL, body mass index (BMI) above 35 kg/m^2, any comorbidities (e.g., diabetes, hypertension, preeclampsia, and eclampsia), smoking and/or alcohol use, and the need for blood transfusion.

A total of 29 patients were excluded from the study because 12 patients did not fulfill the criteria and 17 refused to participate in the study. Finally, 120 women were eligible for the study and randomized preoperatively to three different uterotomy closure techniques (baseball, single-locked, and single-unlocked groups). In all three groups, No. 1 absorbable multifilament polyglactin 910 (Vicryl, Ethicon Inc., Somerville, NJ, USA) suture thread was used to close the uterine incision. When necessary, hemostatic additional sutures were applied using the same material. The three different suture techniques applied during uterotomy closure are as follows:

Group 1 (Baseball Suturing Technique): A corner suture was placed at the right corner of the incision. Next, the second stitch was placed at the apex of the left corner and tied with a knot. Then, the free end of the suture was cut and running baseball stitch pattern was started. The suturing pattern was performed by taking bites from the inside out through the upper and lower lips of the wound at approximately 1 cm intervals with a 1 cm margin from the wound edges.

Group 2 (Single-Layer Locked Continuous Suturing Technique): A corner suture was placed at the right corner of the incision. Next, the second stitch was placed at the apex of the left corner and tied with a knot. Then, the free end of the suture was cut and single-layer-locked continuous suturing was started. The suturing pattern was performed by taking bites from outside to inside through the lower lip and inside to outside through the upper lip of the wound. Each time, a lock was formed by passing through the loop formed by the previous suture. The suturing was performed at approximately 1 cm intervals with a 1 cm margin from the wound edges.

Group 3 (Single-Layer Unlocked Continuous Suturing Technique): The uterotomy line was closed in a single-layer continuous suturing pattern that is explained above as group 2 but without passing the needle through the loop formed by the previous sutures.

Three months after the operation, any presence of isthmocele and its anatomical location were evaluated by ultrasonography. Any presence of isthmocele would reveal itself by an anechoic triangular area with ≥1 mm depth at the scar site. Postpartum complaints and other data regarding maternal age, gestational week, gravida, parity, number of abortions, BMI, C/S indications, type of anesthesia, birth weight, operation time, preoperative–postoperative hemoglobin values, and whether or not additional sutures required during uterotomy closure were also recorded.

Statistical analysis

Based on power analysis, 37 patients in each group were required to assess statistical significance (power of 0.80 and α=0.05). The power calculation was based on residual myometrial thickness (RMT). The statistical power analysis program G Power software version 3.1.9.7 was used. Mean and standard deviations (SDs) were reported for the normally distributed continuous variables. Median and interquartile range (IQR/Q1–Q3) were obtained when the SD was greater than the mean. The Shapiro-Wilk test was used to evaluate whether the data were normally distributed. Frequencies and percentages were calculated for categorical variables and presented as n (%). Since the outcome was categorical/binary, comparisons between the three groups were made by the chi-square test. A "p-value" less than 0.05 was considered statistically significant. The analysis of all variables was done with the statistical software program R Studio 2022.07.2 Build 576.

Ethical aspects of the research

Ethics committee approval was obtained from Tokat Gaziosmanpaşa University Hospital before the study (date: March 17, 2022/project no. 22-KAEK-057). The study was conducted in accordance with the Declaration of Helsinki and the ethical standards of our country.

RESULTS

The demographic characteristics of the patients in the study are shown in Table 1.

Table 1. Demographic characteristics of the patients.

Variables	Baseball (n=39)	Locked (n=40)	Unlocked (n=39)
Age (years)	25.5±5	27.3±5.2	27.4±5.3
BMI (kg/m^2)	28.5±4.9	29.3±4.5	30.4±5.8
Gravida	39 (100)	40 (100)	39 (100)
1	23 (59)	24 (60)	24 (61.5)
2	7 (17.9)	6 (15)	9 (23.1)
3	5 (12.8)	4 (10)	3 (7.7)
4	3 (7.7)	3 (7.5)	1 (2.6)
5	0 (0)	1 (2.5)	1 (2.6)
6	0 (0)	1 (2.5)	1 (2.6)
7	0 (0)	0 (0)	0 (0)
8	1 (2.6)	0 (0)	0 (0)
9	0 (0)	0 (0)	0 (0)
10	0 (0)	1 (2.5)	0 (0)
Parity	39 (100)	40 (100)	39 (100)
Nulliparity	26 (66.7)	26 (65)	28 (71.8)
Multiparity	13 (33.3)	14 (35)	11 (28.2)
Grand multiparity (≥5)	0 (0)	0 (0)	0 (0)
Abortion	39 (100)	40 (100)	39 (100)
Present	7 (17.9)	5 (12.5)	8 (20.5)
Absent	32 (82.1)	35 (87.5)	31 (79.5)

Categorical data are presented as n (%) and numerical data are presented as mean±standard deviation. BMI: body mass index.

Table 2. 'Obstetric characteristics of the patients.

Variables	Baseball (n=39)	Locked (n=40)	Unlocked (n=39)
Gestational age (weeks)	37.9±5	38.4±1	38.9±1
Duration of operation (min)	25.9±5.5	24.4±5.8	24.7±5
Birth weight (kg)	39 (100)	40 (100)	39 (100)
2,000–2,500	7 (17.9)	1 (2.5)	2 (5.1)
2,500–3,000	8 (20.5)	17 (42.5)	10 (25.6)
3,000–3,500	18 (46.2)	11 (27.5)	20 (51.3)
3,500–4,000	5 (12.8)	9 (22.5)	7 (17.9)
4,000–4,500	1 (2.6)	2 (5)	0 (0)
Indications for C/S	39 (100)	40 (100)	39 (100)
Non-reactive NST	18 (46.2)	11 (27.5)	12 (30.8)
Cephalopelvic disproportion	7 (17.9)	10 (25)	15 (38.5)
Fetal distress	7 (17.9)	8 (20)	4 (10.3)
Abnormal lie or presentation	7 (17.9)	11 (27.5)	8 (20.5)
Additional suture used	39 (100)	40 (100)	39 (100)
Present	4 (10.3)	12 (30)	10 (25.6)
Absent	35 (89.7)	28 (70)	29 (74.4)
Type of anesthesia	39 (100)	40 (100)	39 (100)
Spinal	36 (92.3)	36 (90)	36 (92.3)
General	3 (7.7)	4 (10)	3 (7.7)

Categorical data are presented as n (%) and numerical data are presented as mean±standard deviation. C/S: cesarean section; Non-reactive NST: non-reactive nonstress test

Obstetric data such as gestational week, indications for CS, and number of additional sutures used in the operation are shown in Table 2.

A total of 43 (36.4%) patients were found to have isthmocele on TVUSG performed at postpartum week 12. Compared with the single-locked and single-unlocked groups, isthmocele development was statistically significantly lower in the baseball-type closure group (p-value=0.004) (Table 3).

Table 3. Comparison of the three different suture techniques on isthmocele development.

Variables	Baseball (n=39)	Locked (n=40)	Unlocked (n=39)	p-value
Isthmocele				
Present	6 (15.4)	19 (47.5)	18 (46.2)	0.004*
Absent	33 (84.6)	21 (52.5)	21 (53.8)	

*p-value <0.05 indicates statistically significant difference, on comparison of all groups.

DISCUSSION

Since the number of C/S is increasing over time, the rate of isthmocele and its complications are also increasing. This helps obtain wider data on this pathology. On the other hand, there is still no consensus on its definition since different sources provide different myometrial indentation values to meet the diagnosis[6]. Osser et al. emphasized that as the number of C/S increases, wound healing will be adversely affected due to the old scar tissue and thus the rate of isthmocele and its complications may also increase[7].

When randomly selected patients with a history of C/S were evaluated by TVUSG, the prevalence of isthmocele was found to be between 24 and 70%[5]. A previous cohort study had indicated isthmocele prevalence to be 43.4%[8]. In our study, the isthmocele incidence was found to be compatible with the literature. Osser et al. reported that the incidence of isthmocele after the first C/S was 61%, after the second C/S 81%, and after the third C/S 100%[4].

Bennich et al. proposed maternal age, uterine position, and induction of labor as risk factors for the formation of isthmocele. Studies have suggested four hypotheses regarding the etiology of isthmocele, mostly based on patient-specific and surgically induced factors. The first hypothesis is that cervical glandular structures impair healing when the uterine incision opening is too low. Two different studies confirmed this hypothesis by showing that the defect was located below the intact scar. The second hypothesis is related to impaired healing due to early adhesion development between the uterotomy scar and the anterior abdominal wall. A thinner inferior myometrial segment occurs after cervical effacement in advanced labor. This may result in less vascularization leading to isthmocele formation[5]. Ballopra et al. suggested that intraoperative cervical dilatation performed by obstetricians to reduce the tension around the cesarean incision by draining excess blood from the uterus was associated with a lower risk of isthmocele formation. An opposing view was that this might disseminate any existing vaginal infection to the surgical site. Any increase in the risk of endometritis and sepsis was not found in the mentioned study, nonetheless. The third hypothesis is related to the surgical technique that results in the uterine wall not closing completely. Therefore, hysterotomy closure technique is considered an important factor in scar healing. The differences in scar morphology have been described between single-layer and double-layer, locked and unlocked techniques. On the other hand, in a meta-analysis of nine studies, Di Spiezio et al. found no difference between single- and double-layer techniques in isthmocele incidence[9]. In a meta-analysis by Roberge et al. involving 5,810 women, similar results were reported between the groups in terms of isthmocele incidence; nonetheless, the advantages of the double-layer closure technique were emphasized[10]. Marchand et al. showed that double-layer sutures resulted in higher RMT without a lower isthmocele rate[11]. A meta-analysis of 20 studies by Stegwee et al. found that the single-layer-locked suturing technique was associated with lower RMT and an increase in isthmocele incidence[12]. In another study, Ceci et al. compared the single-layer-locked continuous technique with the single-layer-interrupted technique and reported that the locked technique was associated with a larger defect[13]. Bamberg et al. compared three different uterotomy closure techniques: continuous single-layer unlocked, continuous single-layer locked, and double-layer sutures. They observed that the isthmocele incidence and its depth were independent of these three techniques[14]. The uterine suturing technique seems to be an important factor during C/S, but it remains unclear which technique is best to reduce isthmocele formation. Our findings suggest that women with baseball-type uterine sutures are less likely to develop isthmocele than women with single-locked and unlocked sutures. According to our findings, it seems that surgeons can prefer baseball-type suturing during C/S to preserve the RMT and reduce isthmocele formation. The fourth hypothesis regarding isthmocele formation includes patient-specific factors, such as poor hemostasis, tissue ischemia, individual/genetic predisposition contributing to inflammation or adhesion formation, and impaired wound healing, which may influence the development of isthmocele.

Limitations and strengths of the study

There are studies in the literature investigating the effect of surgical closure technique on isthmocele formation. Nevertheless, the effect of baseball suturing on isthmocele formation has never been studied in the literature so far. This feature might be evaluated as the strong side of our study. Our findings suggest that uterotomy closure with baseball-type suturing seems to be an advantageous method as compared to the traditional techniques in terms of preserving the RMT and preventing isthmocele formation. On the flip side, as limitations of our study, the power was 80% and the comparisons were made at postpartum third month. Therefore, further studies with 90% power investigating the long-term complications regarding isthmocele are still needed.

CONCLUSION

It is important not to underestimate isthmocele and its preventive measures since it might cause serious short- and long-term complications. Our findings suggest that women with baseball-type uterine sutures are less likely to develop isthmocele than women with single-locked and unlocked sutures. According to our findings, it seems that surgeons can prefer baseball-type suturing during C/S to preserve the RMT and reduce isthmocele formation. Our results need to be supported by large-scale studies including long-term complications.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHORS' CONTRIBUTIONS

NG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **UU:** Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

REFERENCES

1. Dahlke JD, Mendez-Figueroa H, Maggio L, Sperling JD, Chauhan SP, Rouse DJ. The case for standardizing cesarean delivery technique: seeing the forest for the trees. Obstet Gynecol. 2020;136(5):972-80. https://doi.org/10.1097/AOG.0000000000004120
2. Cai Y, Pan H, Zhang J, Cheng W, Shi Y, Zeng M, et al. Efficacy of adjunctive azithromycin versus single-dose cephalosporin prophylaxis for caesarean scar defect: study protocol for a randomised controlled trial. BMJ Open. 2020;10(1):e032379. https://doi.org/10.1136/bmjopen-2019-032379
3. Kremer TG, Ghiorzi IB, Dibi RP. Isthmocele: an overview of diagnosis and treatment. Rev Assoc Med Bras (1992). 2019;65(5):714-21. https://doi.org/10.1590/1806-9282.65.5.714
4. Osser OV, Jokubkiene L, Valentin L. High prevalence of defects in Cesarean section scars at transvaginal ultrasound examination. Ultrasound Obstet Gynecol. 2009;34(1):90-7. https://doi.org/10.1002/uog.6395
5. Bij Vaate AJ, Voet LF, Naji O, Witmer M, Veersema S, Brölmann HA, et al. Prevalence, potential risk factors for development and symptoms related to the presence of uterine niches following Cesarean section: systematic review. Ultrasound Obstet Gynecol. 2014;43(4):372-82. https://doi.org/10.1002/uog.13199
6. Jordans IPM, Leeuw RA, Stegwee SI, Amso NN, Barri-Soldevila PN, Bosch T, et al. Sonographic examination of uterine niche in non-pregnant women: a modified Delphi procedure. Ultrasound Obstet Gynecol. 2019;53(1):107-15. https://doi.org/10.1002/uog.19049
7. Kulshrestha V, Agarwal N, Kachhawa G. Post-caesarean niche (Isthmocele) in uterine scar: an update. J Obstet Gynaecol India. 2020;70(6):440-6. https://doi.org/10.1007/s13224-020-01370-0
8. Pan H, Zeng M, Xu T, Li D, Mol BWJ, Sun J, et al. The prevalence and risk predictors of cesarean scar defect at 6 weeks postpartum in Shanghai, China: a prospective cohort study. Acta Obstet Gynecol Scand. 2019;98(4):413-22. https://doi.org/10.1111/aogs.13505
9. Spiezio Sardo A, Saccone G, McCurdy R, Bujold E, Bifulco G, Berghella V. Risk of cesarean scar defect following single- vs double-layer uterine closure: systematic review and meta-analysis of randomized controlled trials. Ultrasound Obstet Gynecol. 2017;50(5):578-83. https://doi.org/10.1002/uog.17401
10. Roberge S, Chaillet N, Boutin A, Moore L, Jastrow N, Brassard N, et al. Single- versus double-layer closure of the hysterotomy incision during cesarean delivery and risk of uterine rupture. Int J Gynaecol Obstet. 2011;115(1):5-10. https://doi.org/10.1016/j.ijgo.2011.04.013
11. Marchand GJ, Masoud A, King A, Ruther S, Brazil G, Ulibarri H, et al. Effect of single- and double-layer cesarean section closure on residual myometrial thickness and isthmocele - a systematic review and meta-analysis. Turk J Obstet Gynecol. 2021;18(4):322-32. https://doi.org/10.4274/tjod.galenos.2021.71173
12. Stegwee SI, Jordans I, Voet LF, Ven PM, Ket J, Lambalk CB, et al. Uterine caesarean closure techniques affect ultrasound findings and maternal outcomes: a systematic review and meta-analysis. BJOG. 2018;125(9):1097-108. https://doi.org/10.1111/1471-0528.15048
13. Ceci O, Cantatore C, Scioscia M, Nardelli C, Ravi M, Vimercati A, et al. Ultrasonographic and hysteroscopic outcomes of uterine scar healing after cesarean section: comparison of two types of single-layer suture. J Obstet Gynaecol Res. 2012;38(11):1302-7. https://doi.org/10.1111/j.1447-0756.2012.01872.x
14. Bamberg C, Hinkson L, Dudenhausen JW, Bujak V, Kalache KD, Henrich W. Longitudinal transvaginal ultrasound evaluation of cesarean scar niche incidence and depth in the first two years after single- or double-layer uterotomy closure: a randomized controlled trial. Acta Obstet Gynecol Scand. 2017;96(12):1484-9. https://doi.org/10.1111/aogs.13213

ORIGINAL ARTICLE

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Association between the physical activity level in the third trimester of pregnancy and the gestational age at birth

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the association between the physical activity level in the third trimester and the time of labor onset.
METHODS: Two hundred and sixty women with low-risk pregnancies, who gave birth at 37 weeks of gestation or beyond, and completed the Pregnancy Physical Activity Questionnaire were included in this prospective, cross-sectional study. According to the gestational age at delivery, the study population was divided into case (≥41 weeks) and control (37–40$^{6/7}$ weeks) groups. The clinical characteristics and the physical activity levels of the two groups were compared. The physical activity levels of the participants were also compared according to the delivery route.
RESULTS: The nulliparity rate (54.3 vs. 21.7%), the median gestational weight gain (10.5 [2–30] vs. 10 [2–25] kg), and the cesarean delivery rate (27.7 vs. 6.6%) were higher in the case group than the control group ($p<0.05$). While the median level of sedentary activity was higher, the median moderate-intensity activity level and the median household/caregiving activity level were lower in the case group than the control group ($p<0.05$). The level of sedentary activity was also higher in women who gave birth by a cesarean section than vaginally ($p<0.05$).
CONCLUSION: Physical activity in the third trimester was associated with the time of labor onset. Decreased moderate-intensity and household/caregiving activity levels and an increased level of sedentary activity in the last trimester of pregnancy were found in women who gave birth at ≥41 weeks of gestation. A decreased level of sedentary activity was observed in women who gave birth vaginally.
KEYWORDS: Physical activity. Labor onset. Prolonged pregnancy. Birth.

INTRODUCTION

Physical activity is the bodily movement caused by the contraction of skeletal muscles[1]. Physical activity during pregnancy has many benefits, such as preventing excessive gestational weight gain, reducing the risk of gestational diabetes and hypertension, decreasing cesarean section rates, and improving maternal and neonatal outcomes[1-5].

Labor is a physiological process that leads the fetus to be expelled from the uterus. The timing of labor is controlled by complex interactions between the fetus, mother, and placenta. Various paracrine/autocrine events and fetal hormonal changes trigger the parturition cascade that is responsible for the timely onset of labor[6,7]. Early or late initiation of the labor process leads to preterm birth or postterm pregnancies that could become the cause of serious maternal and perinatal adverse outcomes[8,9]. However, the factors influencing the physiological processes that regulate the labor process and onset time have not been fully revealed yet. The effects of exercise on endocrine hormones are known[10,11]. The hormonal changes caused by physical activity could have an effect on the labor onset in pregnant women.

There are limited reports investigating the association between physical activity and the time of labor onset in term pregnancies. Conflicting results have been reported in these studies. Owe et al.[12] found that exercising during pregnancy increases the risk of postterm birth. In other studies, it has been reported that there is no relationship between regular exercise during pregnancy and the delivery time[2,13,14]. In most of these studies, physical activity levels were evaluated by using questionnaires including only queries about leisure-time exercises, such as running, jogging, bicycling, swimming, and aerobics[12-14]. However, it is known that many women reduce their leisure-time physical activity during pregnancy[15], and the most energy-consuming activities are the household and caregiving activities in pregnant women[16]. For this purpose, we aimed to evaluate the association between the physical activity level and the time of labor onset by using a questionnaire including household and caregiving activities, i.e., Pregnancy Physical Activity Questionnaire (PPAQ)[17]. We also aimed to evaluate the association between the physical activity level in the third trimester and the delivery route as a secondary outcome.

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METHODS

This prospective, cross-sectional study was performed in the obstetrics unit of a tertiary care center between May 2022 and April 2023. The study protocol was approved by the local ethical committee (2022/57) and complied with the Helsinki Declaration. A signed informed consent form was obtained from all participants.

Women with low-risk pregnancies, who gave birth at 37 weeks of gestation or beyond, and completed the PPAQ were included in the study. Low-risk pregnancy was defined as a singleton pregnancy older than 18 years of age and without systemic diseases, malpresentation, placenta accreta spectrum, placenta previa, intrauterine growth restriction, polyhydramnios, preterm premature rupture of membrane, and preterm delivery. Women with high-risk pregnancies including the age under 18 years; having multiple pregnancies, polyhydramnios, intrauterine growth restriction, preeclampsia, hypertension, diabetes mellitus, systemic diseases, orthopedic and neurological diseases, malpresentation, placenta previa, and a history of previous uterine surgery or cesarean delivery; who gave birth at <37 weeks of gestation; who did not volunteer to participate in the research; and who do not speak Turkish language were excluded from the study.

The demographic and clinical characteristics of the women were obtained from the medical records. The gestational age of the participants was evaluated by using the last menstrual period and ultrasonography findings that were performed before 20 weeks of gestation. The type, duration, and frequency of the physical activities performed by the women in the third trimester of pregnancy were ascertained using a PPAQ[17] that had been validated for the Turkish language previously[18]. The questionnaire instructions and the Compendium-based metabolic equivalent of task (MET) values[19] were used to estimate the intensity of activities. The activities were classified according to their intensity: sedentary activity with a MET value of <1.5, light-intensity activity with a MET value of 1.5–3.0, moderate-intensity activity with a MET value of 3.0–6.0, and vigorous activity with a MET value of >6. The weekly energy expenditure (MET-h.wk^{-1}) was computed by multiplying the time spent on each activity by its intensity. The average numbers of MET-h.wk^{-1} in each intensity level (sedentary, light, moderate, vigorous, and total) and in each activity type (household/caregiving, occupational, and sports/exercise) were calculated.

According to the gestational age at delivery, the study population was divided into case and control groups: the case group included women who gave birth at ≥41 weeks of gestation and the control group included women who gave birth at 37–40$^{6/7}$ weeks of gestation. The physical activity levels, the average number of the MET-h.wk^{-1} expended, were compared between the two groups. The physical activity levels were also evaluated according to the delivery route.

A power analysis was carried out to determine the sample size. When the correlation coefficient between the gestational age and the level of physical activity is predicted to be r=-0.176, the sample size required for 80% power with a 5% type I error level is calculated as at least 251 people[20]. The statistical analysis was performed using IBM SPSS Statistics software version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as median (min–max) values for continuous variables and the number and percentage for categorical variables. The normality of continuous variables was evaluated by using Kolmogorov-Smirnov and Shapiro-Wilk tests. Mann-Whitney U test was used for the analysis of non-parametric data. The differences between the case and control groups in terms of categorical variables were examined using Pearson's chi-square test. The ability of physical activity levels to predict the gestational age at delivery was evaluated using receiver operating characteristic (ROC) analysis. Optimal cutoff points were estimated for the MET values of sedentary, moderate-intensity, and household/caregiving activities. p-values less than 0.05 were accepted as statistically significant. A multiple logistic regression analysis was carried out to determine the independent risk factors for the birth at ≥41 weeks of gestation.

RESULTS

During the study period, the medical records of 278 women who gave birth at ≥37 weeks of gestation and met the inclusion criteria were evaluated. Eighteen women were excluded from the study due to incomplete questionnaire and data. Hence, from the remaining 260 women, 94 who gave birth at ≥41 weeks of gestation and 166 who gave birth at 37–40$^{6/7}$ weeks of gestation were included in the study.

The demographic and clinical characteristics of the case and control groups are shown in Table 1. The median age and body mass index (BMI) of the two groups were similar (p>0.005). The nulliparity rate (54.3 vs. 21.7%, p<0.001) and the median gestational weight gain (10.50 [2.0–30.0] vs. 10.0 [2.0–25.0] kg, p=0.005) were higher in the case group than the control group. The cesarean delivery rate was higher in the case group than the control group (27.7 vs. 6.6%, p<0.001).

As shown in Table 2, the physical activity levels of the case and control groups were different. While the median level of sedentary activity was higher, the median moderate-intensity activity level and the median household/caregiving activity level were lower in the case group than the control group (p<0.05).

Table 1. Demographic and clinical characteristics of the case and control groups.

Characteristics	Case group (≥41 weeks) n=94	Control group (37–40$^{6/7}$ weeks) n=166	p-value
Age, years	26 (18–38)	26.5 (18–43)	0.123
BMI, kg/m^2	28.89 (21.45–41.52)	28.44 (19.47–40.37)	0.275
Parity	0 (0–5)	1 (0–6)	<0.001
Nulliparity	51 (54.3%)	36 (21.7%)	<0.001
Gestational weight gain, kg	10.5 (2–30)	10 (2–25)	0.005
Working	7 (7.5%)	7 (4.3%)	0.285
Smoking	6 (6.4%)	15 (9.6%)	0.380
Birth interval for multiparous women, years	5 (1–10)	3 (1–14)	0.025
Previous child birthweight, g	3,200 (1,300–4,100)	3,365 (1,300–4,800)	0.383
Labor induction	50 (53.2%)	–	
Labor induction method			
Balloon	25 (50.0%)	–	
Oxytocin	20 (40.0%)	–	
Misoprostol	2 (4.0%)	–	
Dinoprostone	3 (6.0%)	–	
Delivery route			<0.001
Vaginal	68 (72.3%)	155 (94.5%)	
Cesarean section	26 (27.7%)	11 (6.6%)	
Newborn birthweight, g	3,350 (2,460–4,430)	3,230 (2,310–4,250)	0.073

BMI: body mass index.

Table 2. Physical activity levels of the case and control groups.

Physical activity level	Case group (≥41 weeks) (MET-h.wk^{-1})	Control group (37–40$^{6/7}$ weeks) (MET-h.wk^{-1})	p-value
Total activity	169.39 (4.38–677.30)	173.78 (4.38–455.00)	0.953
Sedentary activity	49.70 (1.93–163.28)	25.11 (1.75–106.93)	<0.001
Light-intensity activity	94.06 (4.38–242.55)	86.28 (4.38–224.35)	0.807
Moderate-intensity activity	54.25 (0.80–299.50)	72.95 (2.40–266.00)	0.037
Vigorous-intensity activity	5.25 (1.63–37.25)	1.75 (1.63–16.25)	0.262
Household/caregiving activity	99.93 (4.38–405.65)	133.79 (4.38–45.00)	0.011
Occupational activity	75.25 (3.85–119.18)	100.01 (67.20–194.08)	0.286
Sports/exercise	7.30 (0.80–102.50)	4.80 (0.80–29.78)	0.013

According to the ROC analysis, the optimal sedentary activity cutoff level for predicting birth risk at ≥41 weeks of gestation was 35.70 MET-h.wk^{-1} (area under the curve [AUC], 0.712; 95%CI 0.637–0.787; sensitivity, 67.1%; specificity, 60.1%; p<0.001). A 64.02 MET-h.wk^{-1} cut-off level of moderate-intensity activity was found for predicting birth at < 41 weeks of gestation (AUC, 0.584; 95%CI, 0.505-–0.662; sensitivity, 58.6%; specificity, 55.7%; p = =0.037) and a 117.86 MET-h.wk^{-1} cut-off level of household/caregiving activity was found for predicting birth at < 41 weeks of gestation (AUC, 0.597; 95%CI, 0.523-–0.670; sensitivity, 60.4%; specificity, 57.8%; p = =0.011).

As shown in Table 3, the physical activity level in the third trimester was also associated with the delivery route. While the

Table 3. Physical activity levels of the women who gave birth vaginally and by a cesarean section.

Physical activity level	Vaginal delivery (n=223) (MET-h.wk^{-1})	Cesarean delivery (n=37) (MET-h.wk^{-1})	p-value
Total activity	175.30 (23.28–677.30)	177.72 (82.78–359.92)	0.545
Sedentary activity	32.99 (1.75–163.28)	50.84 (5.08–96.08)	0.011
Light-intensity activity	103.86 (5.43–242.55)	83.21 (36.75–224.35)	0.874
Moderate-intensity activity	74.80 (0.80–299.50)	63.73 (10.55–115.30)	0.128
Vigorous-intensity activity	4.88 (1.63–16.25)	5.25 (1.63–37.25)	0.932
Household/caregiving activity	108.90 (13.52–405.65)	75.60 (58.80–123.20)	0.061
Occupational activity	108.24 (67.20–194.08)	29.93 (3.85–56.00)	0.040
Sports/exercise	8.00 (5.18–29.78)	41.18 (3.55–4.80)	0.094

median level of sedentary activity was lower, the median occupational activity level was higher in the women who gave birth vaginally than by a cesarean section (p<0.005). The Association between demographic and clinical variables (parity, gestational weight gain, birth interval, level of sedentary activity, moderate-intensity activity level, and household/caregiving activity level) and delivery at ≥41 weeks of gestation was modeled by a logistic regression analysis. According to the multiple logistic regression analysis results, the level of sedentary activity (odds ratio [OR] 1.03; 95% CI 1.02–1.05) was an independent risk factor for the birth at ≥41 weeks of gestation.

DISCUSSION

The study results showed that while the level of sedentary activity was higher, the moderate-intensity activity level and the household/caregiving activity level were lower in women who gave birth at ≥41 weeks of gestation than at 37–40$^{6/7}$ weeks of gestation. The level of sedentary activity was lower in women who gave birth vaginally than by a cesarean section.

It is known that continued physical activity during pregnancy has many benefits for both the mother and the infant. Previous studies have reported a lower risk of preeclampsia, gestational diabetes mellitus, and cesarean delivery in physically active pregnant women[3-5]. Studies investigating the association between the physical activity level and the time of labor onset have shown that physical activity during pregnancy reduces the risk of preterm births[12]. There is a limited number of reports on the effect of physical activity during pregnancy on postterm pregnancies, and these studies have conflicting results[2,12,21]. In the series of Haakstad et al.[2] and Evenson et al.[21], no association was found between the postterm birth (≥42 weeks of gestation) and the physical activity level during pregnancy. On the other hand, Owe et al.[12] reported that women exercising 3–5 times per week in the gestational week of 17 were more likely to have a postterm birth. Differently, we investigated the relationship between the physical activity level in the third trimester and the time of labor onset. We found that the increased physical activity level in the third trimester reduced the birth risk at ≥41 weeks of gestation.

In most of the studies reporting the relationship between the physical activity level and the time of labor onset, the physical activity level of the cases had been evaluated by using questionnaires including queries about only leisure-time exercises[12-14]. However, studies have shown that most women do not continue their pre-pregnancy exercises during pregnancy[15,22]. In a study on 1,737 women, Fell et al.[22] reported the impact of pregnancy on the physical activity level, including household and caregiving activities, active living, sports, and exercise activities. They showed that the largest decrease occurred in sports and exercise activities during the first 20 weeks of pregnancy compared with the year prior to pregnancy. Therefore, physical activity questionnaires that do not include household and caregiving activities could lead to inaccurate determination of the physical activity level in pregnant women and misunderstanding about the correlation between the physical activity level and the outcomes. In our study, we used the PPAQ that includes queries about the household and caregiving activities and has good validity and reliability characteristics[23]. Unlike the research assessing only leisure-time exercises for the determination of the physical activity level during pregnancy, we evaluated the impact of different physical activity intensities and types on the time of labor onset. In our series, the moderate-intensity activity level and the household/caregiving activity level were lower and the level of sedentary activity was higher in women who gave birth at ≥41 weeks of gestation than at 37–40$^{6/7}$ weeks of gestation.

It has been previously reported that physical activity during pregnancy positively affects the labor and delivery outcomes. Watkins et al.[24] reported the shorter active labor duration and the reduced risk of prolonged first stage of labor in women with a high physical activity level in the third trimester of pregnancy. In a recent meta-analysis, decreased cesarean section rates were reported in physically active pregnant women[5]. Similarly, we found an association between the delivery route and the physical activity level in the third trimester. The median level of sedentary activity was lower and the median occupational activity level was higher in women who gave birth vaginally than by a cesarean section in the study cohort. According to the study results, increased physical activity in pregnant women during the last trimester could lead to a timely onset of labor and a decrease in the need for cesarean delivery, thus reducing the risk of adverse maternal and neonatal outcomes.

The present study is one of the limited studies in the literature reporting the association between the physical activity level and the time of labor onset. The homogeneous study population is one of the strengths of the study. Only low-risk term pregnancies were included in this study. Pregnant women with diseases that could affect the labor onset were excluded. The selected study population of low-risk term pregnancies may have influenced the study results and introduced potential bias. Studies with a larger sample size including all low- and high-risk pregnancies are required to confirm our results. Another strength of the study was the measurement method used for the assessment of physical activity. The validated PPAQ is a simple-to-use, cost-effective method to evaluate physical activity and it was designed specifically for pregnant women. Nevertheless, the PPAQ was also the major limitation of the study because this self-reported questionnaire reflected the perceptions of those attitudes rather than the actual attitudes on the subject and was prone to measurement error and bias.

CONCLUSION

The study results showed that the physical activity level in the third trimester was associated with the gestational age at birth. The increased moderate-intensity and household/caregiving activities and the decreased sedentary activities in the last trimester of pregnancy could prevent the delay in the onset of labor that could lead to severe maternal and perinatal adverse outcomes. The physical activity level in the third trimester was also associated with the delivery route. Women who gave birth vaginally had lower levels of sedentary activity and higher levels of occupational activity than women who underwent a cesarean section.

AUTHORS' CONTRIBUTIONS

TK: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **SAM:** Data curation, Formal Analysis, Writing – original draft. **RSK:** Conceptualization, Writing – review & editing. **YEU:** Conceptualization, Supervision, Writing – review & editing.

REFERENCES

1. Physical activity and exercise during pregnancy and the postpartum period: ACOG Committee Opinion, Number 804. Obstet Gynecol. 2020;135(4):e178-88. https://doi.org/10.1097/AOG.0000000000003772
2. Haakstad LAH, Voldner N, Bø K. Pregnancy and advanced maternal age-The associations between regular exercise and maternal and newborn health variables. Acta Obstet Gynecol Scand. 2020;99(2):240-8. https://doi.org/10.1111/aogs.13738
3. Do NC, Vestgaard M, Ásbjörnsdóttir B, Nichum VL, Ringholm L, Andersen LLT, et al. Physical activity, sedentary behavior and development of preeclampsia in women with preexisting diabetes. Acta Diabetol. 2020;57(5):559-67. https://doi.org/10.1007/s00592-019-01459-7
4. Xie W, Zhang L, Cheng J, Wang Y, Kang H, Gao Y. Physical activity during pregnancy and the risk of gestational diabetes mellitus: a systematic review and dose-response meta-analysis. BMC Public Health. 2024;24(1):594. https://doi.org/10.1186/s12889-024-18131-7
5. Weng YM, Green J, Yu JJ, Zhang HY, Cui H. The relationship between incidence of cesarean section and physical activity during pregnancy among pregnant women of diverse age groups: dose-response meta-analysis. Int J Gynaecol Obstet. 2024;164(2):504-15. https://doi.org/10.1002/ijgo.14915
6. Casey ML, MacDonald PC. Biomolecular processes in the initiation of parturition: decidual activation. Clin Obstet Gynecol. 1988;31(3):533-52. https://doi.org/10.1097/00003081-198809000-00005
7. Kota SK, Gayatri K, Jammula S, Kota SK, Krishna SV, Meher LK, et al. Endocrinology of parturition. Indian J Endocrinol Metab. 2013;17(1):50-9. https://doi.org/10.4103/2230-8210.107841
8. Dehaene I, Scheire E, Steen J, Coen K, Decruyenaere J, Smets K, et al. Obstetrical characteristics and neonatal outcome according to aetiology of preterm birth: a cohort study. Arch Gynecol Obstet. 2020;302(4):861-71. https://doi.org/10.1007/s00404-020-05673-5
9. Alkmark M, Wennerholm UB, Saltvedt S, Bergh C, Carlsson Y, Elden H, et al. Induction of labour at 41 weeks of gestation versus expectant management and induction of labour at 42 weeks of gestation: a cost-effectiveness analysis. BJOG. 2022;129(13):2157-65. https://doi.org/10.1111/1471-0528.16929
10. Hackney AC, Lane AR. Exercise and the regulation of endocrine hormones. Prog Mol Biol Transl Sci. 2015;135:293-311. https://doi.org/10.1016/bs.pmbts.2015.07.001

11. Nys L, Anderson K, Ofosu EF, Ryde GC, Connelly J, Whittaker AC. The effects of physical activity on cortisol and sleep: a systematic review and meta-analysis. Psychoneuroendocrinology. 2022;143:105843. https://doi.org/10.1016/j.psyneuen.2022.105843
12. Owe KM, Nystad W, Skjaerven R, Stigum H, Bø K. Exercise during pregnancy and the gestational age distribution: a cohort study. Med Sci Sports Exerc. 2012;44(6):1067-74. https://doi.org/10.1249/MSS.0b013e3182442fc9
13. Barakat R, Stirling JR, Lucia A. Does exercise training during pregnancy affect gestational age? A randomised controlled trial. Br J Sports Med. 2008;42(8):674-8. https://doi.org/10.1136/bjsm.2008.047837
14. Leiferman JA, Evenson KR. The effect of regular leisure physical activity on birth outcomes. Matern Child Health J. 2003;7(1):59-64. https://doi.org/10.1023/a:1022545718786
15. Amezcua-Prieto C, Olmedo-Requena R, Jímenez-Mejías E, Hurtado-Sánchez F, Mozas-Moreno J, Lardelli-Claret P, et al. Changes in leisure time physical activity during pregnancy compared to the prior year. Matern Child Health J. 2013;17(4):632-8. https://doi.org/10.1007/s10995-012-1038-3
16. Wojtyła C, Ciebiera M, Wojtyła-Buciora P, Janaszczyk A, Brzęcka P, Wojtyła A. Physical activity patterns in third trimester of pregnancy - use of pregnancy physical activity questionnaire in Poland. Ann Agric Environ Med. 2020;27(3):388-93. https://doi.org/10.26444/aaem/110480
17. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a pregnancy physical activity questionnaire. Med Sci Sports Exerc. 2004;36(10):1750-60. https://doi.org/10.1249/01.mss.0000142303.49306.0d
18. Çırak Y, Yılmaz GD, Demir YP, Dalkılınç M, Yaman S. Pregnancy physical activity questionnaire (PPAQ): reliability and validity of Turkish version. J Phys Ther Sci. 2015;27(12):3703-9. https://doi.org/10.1589/jpts.27.3703
19. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 Suppl):S498-504. https://doi.org/10.1097/00005768-200009001-00009
20. Çeliker Tosun Ö, Okyay RE. Gebelik sürecinde fiziksel aktivite değişimlerinin incelenmesi (Investigation of physical activity changes during pregnancy). Sağlık Bilimleri ve Meslekleri Dergisi. 2018;5:333-41.
21. Evenson KR, Siega-Riz AM, Savitz DA, Leiferman JA, Thorp JM. Vigorous leisure activity and pregnancy outcome. Epidemiology. 2002;13(6):653-9. https://doi.org/10.1097/00001648-200211000-00009
22. Fell DB, Joseph KS, Armson BA, Dodds L. The impact of pregnancy on physical activity level. Matern Child Health J. 2009;13(5):597-603. https://doi.org/10.1007/s10995-008-0404-7
23. Schuster S, Šklempe Kokić I, Sindik J. Measuring physical activity in pregnancy using questionnaires: a meta-analysis. Acta Clin Croat. 2016;55(3):440-52. https://doi.org/10.20471/acc.2016.55.03.13
24. Watkins VY, O'Donnell CM, Perez M, Zhao P, England S, Carter EB, et al. The impact of physical activity during pregnancy on labor and delivery. Am J Obstet Gynecol. 2021;225(4):437.e1-8. https://doi.org/10.1016/j.ajog.2021.05.036

ORIGINAL ARTICLE

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A new approach to osteoarthritis: gut microbiota

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SUMMARY

OBJECTIVE: Studies investigating the relationship between the gut microbiome and osteoarthritis have increased in recent years. However, data on the relationship between joints and the gut microbiome are limited. The aim of this study was to determine whether there is a relation between knee joint fluid and gut microbiota in patients with knee osteoarthritis.

METHODS: This study included 40 individuals, 20 of whom were diagnosed with knee osteoarthritis and 20 of whom were considered healthy controls. Joint-fluid and stool samples were taken from the participants. Bacteria isolated from the samples were identified using a matrix-assisted laser desorption ionization-time of flight-mass spectrometry device.

RESULTS: Twenty-nine different bacteria were isolated from the stool samples and five bacteria were isolated from the joint-fluid samples. In our study, the same types of microorganisms (*Enterococcus faecium* and *Staphylococcus hominis*) were isolated from the stool and joint-fluid samples.

CONCLUSION: The data obtained in our study shed light on the uncertainty of how microorganisms, especially those identified in the knee and hip in the literature, reach these regions. The presence of intestinal bacteria in the knee joint fluid of osteoarthritis patients indicates that intestinal bacteria, especially in individuals with a weak immune system, malnutrition, and obesity, pass through the intestinal wall and reach other parts of the body via the bloodstream, a condition also known as "leaky gut."

KEYWORDS: Knee osteoarthritis. Microbiota. Intestinal barrier permeability.

INTRODUCTION

Knee osteoarthritis (OA) is a chronic joint disease characterized by bone hyperplasia and inflammatory destruction[1]. While it usually manifests itself with pain, it can also show symptoms, such as limitation of movement, stiffness, swelling, locking, and numbness. Hip and knee OA, estimated to affect approximately 300 million people worldwide, develops under the influence of systemic, local, and genetic factors[2,3]. In addition to articular cartilage, OA can also affect other structures associated with the joint, such as subchondral bone, adjacent connective tissue, and synovial membrane. Chondrocyte cells, which form the structure of the cartilage, are immobile and cannot renew themselves; therefore, chondrocyte death has an important role in the pathogenesis of OA[4,5].

The gut microbiome is a system in which trillions of symbiotic bacteria colonize our body and is of vital importance for our health. These microorganisms play an active role in various biological processes, such as metabolism, immune system, and neurological functions[5,6]. Gut microbes play a critical role in maintaining metabolic balance, development of the immune system, building resistance to infections, and production of neurotransmitters. Imbalances in this microbiota can lead to serious health problems, such as obesity, diabetes, metabolic diseases, and cancer. When used in appropriate amounts, probiotic supplements provide significant benefits to host health[7]. Additionally, the gut microbiome is a source of important vitamins and helps maintain metabolic balance, immune system development, and neurotransmitter production. Within this microbial community, Firmicutes and Bacteroidetes are the most common groups, but other bacterial groups are also present[8,9].

It is observed that the intestinal microbiota may contribute to the pathogenesis of joint diseases, especially OA, by affecting bone metabolism. This can be explained as the intestinal microbiota may affect the etiopathology of OA at both systemic and local levels, contributing to the development of this disease by paving the way for the onset of immune-metabolic disorders[9]. Additionally, it should be noted that the intestinal microbiota may accelerate the progression of inflammation-related diseases and affect the pathophysiology of OA. More research is needed

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on how OA risk factors such as aging, dietary habits, and obesity affect the gut microbiota. It is thought that the gut–bone relationship may be a promising target in the prevention and treatment of OA[9-11]. Recent studies have provided concrete evidence of this connection, and to fully explain these mechanisms, the role of gut microbiome-derived immune-metabolic disorders in the pathogenesis of OA needs to be further investigated[12-15]. It is important to conduct new research to further understand the effects of gut microbiomes on health. A more in-depth study on the role of these microorganisms in metabolism, immune system, and neurological functions may help develop more effective strategies for the management of health problems[16]. Additionally, collecting more data on the complexity of the gut microbiome and the contribution of different groups of bacteria will help enrich scientific research in this field and develop new approaches for disease diagnosis and treatment. Our study aimed to determine whether there is a relationship between joints and gut microbiota in individuals with knee OA.

METHODS

Patient population

Patients with stage I, II, III, and IV knee OA, who were diagnosed according to the Kellgren-Lawrence system and the criteria set by the ACR, and who applied to the Department of Orthopedics and Traumatology between June and July 2024 were included in the study. This study was approved by the Clinical Research Ethics Committee of Gulhane Training and Research Hospital (decision no. 2024/264, dated: 28.05.2024), and all the study subjects participated voluntarily. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The sample size of individuals participating in the research was evaluated with G-power analysis. In this context, a total of 40 individuals were included in the study, 20 of whom were diagnosed with knee OA and 20 of whom were considered healthy controls.

In our outpatient clinic, joint fluids taken from patients diagnosed with knee OA during treatment and about to be discarded were placed in sterile Falcon tubes and stored at -20°C until the study was performed. To investigate clinical findings during diagnosis and treatment, routine stool examinations were requested from patients with gastrointestinal system complaints according to the anamnesis, and the stool samples of these patients were stored for use in microbiota analyses.

Bacterial culture

Stool samples taken from patients were diluted with phosphate-buffered saline (PBS) at concentrations of 10^1 and 10^5 before the study. The joint-fluid and diluted stool samples were spread on eosin-methylene blue (EMB), plate count agar (PCA), and de Man–Rogosa–Sharpe (MRS) agar from 10^4 and 10^5 dilutions. The plates of the stool samples were incubated in a 37°C oven for 16–24 h. The plates of the joint-fluid samples were incubated for 16–24 h in a 37°C oven with 5% CO_2.

The resulting bacterial colonies were analyzed both macroscopically and microscopically. Colony counts were made on the plates with growth after incubation, and the first stage of the analysis was carried out by evaluating the morphological characteristics of the colonies. Then, bacterial colonies with different morphologies were typed using microbiological staining techniques (Gram staining) and biochemically (catalase test, coagulase test, motility test, oxidase test, etc.). The bacteria isolated from the samples were identified by a matrix-assisted laser desorption ionization-time of flight-mass spectrometry device, and antimicrobial susceptibility examination was performed by the disk–diffusion method. A score of 2.0 or higher indicates high reliability at the species level, and a score of 1.7–2.0 indicates a match at the genus level[17].

Statistical analysis

Before the study, the sample size of individuals participating in the research was evaluated via G*Power analysis. The "Statistical Package for the Social Sciences" (SPSS) program version 22.0 (IBM Corp., Armonk, NY, USA) was used to evaluate the data obtained in the study. The data to normal distribution were examined by the Kolmogorov-Smirnov test. Parametric tests were used for data with normal distribution according to the Kolmogorov-Smirnov test result.. A value of $p<0.05$ was accepted as the level of statistical significance.

RESULTS

A total of 40 OA patients (24 females and 16 males) were included in this study. The age range of the patients was 51–73 years, with a mean age of 61.6±8.0 years. According to the obtained data, the number of samples from which bacteria were isolated (18 Females/8 Males) and from which they were not also evaluated according to gender (Figure 1). As a result of the analysis performed with these data using the "chi-square test" in the SPSS program, Pearson's value was calculated as 0.685. Based on this result, with a value of $p>0.05$, it was reported that there was no significant difference between the number of bacteria isolated from the samples taken from the OA patients included in the study and patient gender.

A total of 29 different types of bacteria were isolated from the stool samples. It was determined that the number of pathogenic and opportunistic pathogenic microorganisms increased in the intestinal flora of these patients. Also, another five types of bacteria were isolated from the stool samples. The obtained data are shown in Table 1. In our study, the same species were found in both the stool and joint-fluid samples. The most notable of these are *Enterococcus faecium* and *Staphylococcus hominis*. Patients were directed to treatment in the clinic after opportunistic pathogen bacteria were identified in the joint fluid. While some of the species detected in the stool were members of the normal flora, the presence of species found through food was also detected.

Among the isolated bacteria from the joint-fluid samples, bacteria thought to be biotechnologically effective, especially in the health field, were also identified. One of these is *Streptomyces lavendulae*. *Myroides odoratus/odoratimimus* detected in the joint fluid is generally found in soil and water, but it can be pathogenic in those with underlying diseases, especially in immunosuppressed patients. Species detected in the stool samples are generally members of the normal flora (*E. faecium*, *Lactobacillus acidophilus*, and *Levilactobacillus brevis*) or species transmitted through food.

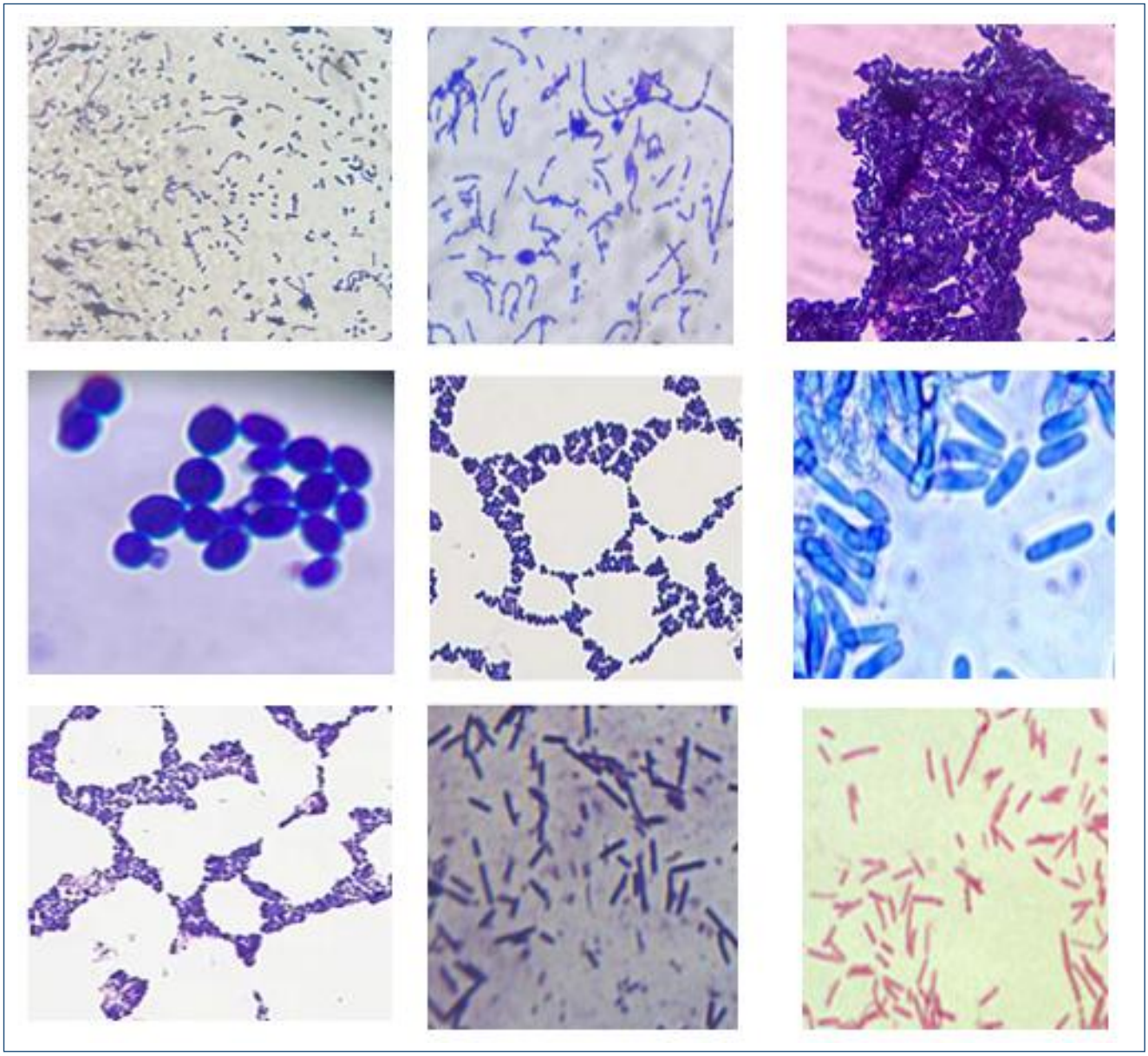

Figure 1. The light microscope images of some microorganisms from stool and joint-fluid samples (100×).

DISCUSSION

In the study of joint pain, the investigation of the connection between the musculoskeletal system and the intestinal system may be an interesting topic. Literature information suggests that intestinal permeability which plays an important role in many diseases may create a new diagnostic and treatment protocol in this regard. With time, individual intestinal health is increasingly becoming crucial in chronic diseases[18].

In recent years, in addition to genetic predisposition, physical inactivity, and nutritional disorders leading to obesity and metabolic syndrome, OA has become more common. The literature shows that all these conditions are closely related to the intestinal microbiota. Systemic and local inflammation plays an important role in the pathogenesis of OA. It has been reported in the literature that deteriorated cartilage may lead to the formation of inflammatory cytokines and metalloproteases[19,20]. Many studies have found several immune cells, including B cells, T cells, lymphoid follicles, granulocytes, and plasma cells, in the synovium of OA patients and have suggested that the innate/adaptive immune response has a central effect on the pathogenesis of OA[21]. To date, researchers have identified various risk factors for OA, such as age, gender, nutrition, obesity and metabolic syndrome, genetic background, inflammation, and intestinal microbiome[19,22]. However, pain relief or joint replacement is usually applied to OA

Table 1. Microorganisms from stool and joint-fluid samples.

Microorganisms from the stool sample	%	Microorganisms from the joint-fluid sample	%
Enterococcus faecium	8	*Streptomyces lavendulae*	20
Enterococcus mundtii	2	*Myroides odoratus/odoratimimus*	20
Enterococcus durans	2	*Colletotrichum gloeosporioides*	10
Candida albicans	3	*Enterococcus faecium*	20
Lactobacillus acidophilus	9	*Staphylococcus hominis*	30
Lacticaseibacillus paracasei	9		
Limosilactobacillus reuteri	10		
Lactobacillus gasseri	9		
Levilactobacillus brevis	12		
Staphylococcus hominis	10		
Stenotrophomonas maltophilia	1		
Escherichia coli	8		
Enterobacter hormaechei	1		
Enterobacter ludwigii	1		
Enterobacter asburiae	1		
Klebsiella pneumoniae	1		
Micrococcus luteus	1		
Pseudocitrobacter polychromogenes	1		
Pseudomonas putida	1		
Kluyveromyces marxianus	1		
Geodermatophilus bullaregiensis	1		
Microbacterium maritypicum	1		
Micrococcus luteus	1		
Peribacillus muralis	1		
Peribacillus simplex	1		
Secundilactobacillus malefermentans	1		
Kluyveromyces ascorbata	1		
Flavobacterium columnare	1		
Odoribacter splanchnicus	1		

patients. However, considering the studies and findings obtained, determining the treatment target of the disease is very important.

In our study, many normal flora members such as *E. faecium*, *L. acidophilus*, and *L. brevis* were detected, especially in stool samples. In addition to these, food pathogens and opportunistic pathogens were also observed to have a place in the flora. *Enterococci*, which are found in the natural flora of the intestine, oral cavity, and vagina, are known to be mostly avirulent in healthy individuals, but they often behave as pathogens in hospitalized patients[23,24]. *Kluyvera* is a relatively newly identified member of the Enterobacteriaceae family and rarely causes infection in humans[25]. In our study, it was detected in only one patient. *Odoribacter splanchnicus* is a Gram-negative anaerobic bacterium normally found in the intestines, known for its tumor-suppressive and immunomodulatory activities. It is an extremely rare pathogen of human infection, mainly reported with bacteremia infection[26,27]. Only a few cases of human infection have been reported, and it was detected in only one patient in our study. Some species, especially known as fish pathogens, can temporarily colonize the human intestinal system. Similar microorganisms (*Micrococcus luteus* and *Flavobacterium columnare*) were also detected in our study.

S. lavendulae produces mitomycin C (MC), and mitomycin is an important biotechnological agent used in anticancer therapy. *S. lavendulae* also produces complestatins and protease inhibitors with antiviral activities[19]. The other agent identified, *M. odoratimimus*, is an uncommon opportunistic pathogen, although it has been reported in the literature to be isolated from various bodily fluids. Since it is widely found in the environment, infections encountered may occur after contact with contaminated water[28]. *Colletotrichum* species are common pathogens, especially for plant anthracnose, but have recently been reported in the literature as opportunistic human pathogens causing keratitis and subcutaneous fungal infections, potentially leading to life-threatening systemic dissemination[29].

Strengths and limitations

Our study was limited in terms of the data obtained because it was conducted on OA patients only, and the small sample size of our study and the inclusion of only those who applied to the hospital constitute important limitations. However, it is an important study to determine the microbial situation in OA patients. Nevertheless, further studies on the subject and the inclusion of more patients will also increase statistical power.

CONCLUSION

Our study has drawn attention to the relationship between joint diseases and microbiota. The most important innovation that our study has added to the literature is the demonstration of intestinal flora bacteria in the joint fluids of patients with leaky gut syndrome. In addition, the imbalance in the intestinal flora in OA patients has been revealed and findings that will support the treatment of these patients have been reached.

The data obtained in our study shed light on the uncertainty of how microorganisms, especially those identified in the knee and hip in the literature, reach these regions. The presence of intestinal bacteria in the knee joint fluid of OA patients indicates that intestinal bacteria, especially in individuals with a weak immune system, pass through the intestinal wall and reach other parts of the body via the bloodstream, a condition also known as "leaky gut."

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (or Ethics Committee) of Gulhane Training and Research Hospital (decision no. 2024/264, dated: 28.05.2024).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

AUTHORS' CONTRIBUTIONS

MA: Conceptualization, Funding acquisition, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization. **GAA:** Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **UIY:** Investigation, Resources. **EA:** Investigation, Visualization.

REFERENCES

1. Wei Z, Li F, Pi G. Association between gut microbiota and osteoarthritis: a review of evidence for potential mechanisms and therapeutics. Front Cell Infect Microbiol. 2022;12:812596. https://doi.org/10.3389/fcimb.2022.812596
2. Du X, Liu ZY, Tao XX, Mei YL, Zhou DQ, Cheng K, et al. Research progress on the pathogenesis of knee osteoarthritis. Orthop Surg. 2023;15(9):2213-24. https://doi.org/10.1111/os.13809
3. Abramoff B, Caldera FE. Osteoarthritis: pathology, diagnosis, and treatment options. Med Clin North Am. 2020;104(2):293-311. https://doi.org/10.1016/j.mcna.2019.10.007

4. Nicola V. Degenerative osteoarthritis a reversible chronic disease. Regen Ther. 2020;15:149-60. https://doi.org/10.1016/j.reth.2020.07.007
5. Longo UG, Lalli A, Bandini B, Sire R, Angeletti S, Lustig S, et al. Role of the gut microbiota in osteoarthritis, rheumatoid arthritis, and spondylarthritis: an update on the gut-joint axis. Int J Mol Sci. 2024;25(6):3242. https://doi.org/10.3390/ijms25063242
6. Guan Z, Luo L, Liu S, Guan Z, Zhang Q, Li X, et al. The role of depletion of gut microbiota in osteoporosis and osteoarthritis: a narrative review. Front Endocrinol (Lausanne). 2022;13:847401. https://doi.org/10.3389/fendo.2022.847401
7. Silva VF, Refinetti P, Vicariotto F, Baracat EC, Soares Junior JM. Oral probiotics and vaginal microbiome in post-menopause women: an opinion for the improvement of natural therapies in gynecology. Rev Assoc Med Bras (1992). 2024;70(2):e702EDIT. https://doi.org/10.1590/1806-9282.702EDIT
8. Hao X, Shang X, Liu J, Chi R, Zhang J, Xu T. The gut microbiota in osteoarthritis: where do we stand and what can we do? Arthritis Res Ther. 2021;23(1):42. https://doi.org/10.1186/s13075-021-02427-9
9. Jiang S, Shen B. [Research progress on the relationship between gut microbiota dysbiosis and osteoarthritis]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2023;37(3):371-6. Chinese. https://doi.org/10.7507/1002-1892.202212037
10. Liu L, Tian F, Li GY, Xu W, Xia R. The effects and significance of gut microbiota and its metabolites on the regulation of osteoarthritis: close coordination of gut-bone axis. Front Nutr. 2022;9:1012087. https://doi.org/10.3389/fnut.2022.1012087
11. Dunn CM, Jeffries MA. The microbiome in osteoarthritis: a narrative review of recent human and animal model literature. Curr Rheumatol Rep. 2022;24(5):139-48. https://doi.org/10.1007/s11926-022-01066-6
12. Liu L, Tian F, Li GY, Xu W, Xia R. The effects and significance of gut microbiota and its metabolites on the regulation of osteoarthritis: close coordination of gut-bone axis. Front Nutr. 2022;9:1012087. https://doi.org/10.3389/fnut.2022.1012087
13. Chisari E, Wouthuyzen-Bakker M, Friedrich AW, Parvizi J. The relation between the gut microbiome and osteoarthritis: a systematic review of literature. PLoS One. 2021;16(12):e0261353. https://doi.org/10.1371/journal.pone.0261353
14. Sánchez Romero EA, Meléndez Oliva E, Alonso Pérez JL, Martín Pérez S, Turroni S, Marchese L, et al. Relationship between the gut microbiome and osteoarthritis pain: review of the literature. Nutrients. 2021;13(3):716. https://doi.org/10.3390/nu13030716
15. Wei J, Zhang C, Zhang Y, Zhang W, Doherty M, Yang T, et al. Association between gut microbiota and symptomatic hand osteoarthritis: data from the xiangya osteoarthritis study. Arthritis Rheumatol. 2021;73(9):1656-62. https://doi.org/10.1002/art.41729
16. Di J, Xi Y, Wu Y, Di Y, Xing X, Zhang Z, et al. Gut microbiota metabolic pathways: key players in knee osteoarthritis development. Exp Gerontol. 2024;196:112566. https://doi.org/10.1016/j.exger.2024.112566
17. Tsuchida S, Nakayama T. MALDI-based mass spectrometry in clinical testing: focus on bacterial identification. Appl Sci. 2022;12:2814. https://doi.org/10.3390/app12062814
18. Álvarez-Herms J, González A, Corbi F, Odriozola I, Odriozola A. Possible relationship between the gut leaky syndrome and musculoskeletal injuries: the important role of gut microbiota as indirect modulator. AIMS Public Health. 2023;10(3):710-38. https://doi.org/10.3934/publichealth.2023049
19. Shahbaz A, Hussain N, Saba S. Actinomycetes, cyanobacteria, and fungi: a rich source of bioactive molecules. In: Kumar A, Bilal M, Ferreira LFR, Kumari M, editors. Developments in applied microbiology and biotechnology, microbial biomolecules. Chapter 7; 2023. p. 113-33.
20. Luo S, Chen Z, Deng L, Chen Y, Zhou W, Canavese F, et al. Causal link between gut microbiota, neurophysiological states, and bone diseases: a comprehensive Mendelian randomization study. Nutrients. 2023;15(18):3934. https://doi.org/10.3390/nu15183934
21. Endicott-Yazdani TR, Dhiman N, Benavides R, Spak CW. Myroides odoratimimus bacteremia in a diabetic patient. Proc (Bayl Univ Med Cent). 2015;28(3):342-3. https://doi.org/10.1080/08998280.2015.11929268
22. Lin LY, Yang CC, Wan JY, Chang TC, Lee JY. Cutaneous infection caused by plant pathogen colletotrichum gloeosporioides. JAMA Dermatol. 2015;151(12):1383-4. https://doi.org/10.1001/jamadermatol.2015.2102
23. Madani WAM, Ramos Y, Cubillos-Ruiz JR, Morales DK. Enterococcal-host interactions in the gastrointestinal tract and beyond. FEMS Microbes. 2024;5:xtae027. https://doi.org/10.1093/femsmc/xtae027
24. Sreeja S, Babu PRS, Prathab AG. The prevalence and the characterization of the enterococcus species from various clinical samples in a tertiary care hospital. J Clin Diagn Res. 2012;6(9):1486-8. https://doi.org/10.7860/JCDR/2012/4560.2539
25. Zou SH, Zhu LY, Li Y, Zhang FG. A case of a persistent postoperative infection caused by multidrug-resistant kluyvera ascorbata in the oral and maxillofacial region. Case Rep Infect Dis. 2019;2019:2180567. https://doi.org/10.1155/2019/2180567
26. Hiippala K, Barreto G, Burrello C, Diaz-Basabe A, Suutarinen M, Kainulainen V, et al. Novel odoribacter splanchnicus strain and its outer membrane vesicles exert immunoregulatory effects in vitro. Front Microbiol. 2020;11:575455. https://doi.org/10.3389/fmicb.2020.575455
27. Xiao H, Song C, Chen Z, Jian M, Yuan C, Li Y, et al. The first case of Odoribacter splanchnicus bacteremia isolated from a patient in China. Heliyon. 2023;10(1):e23465. https://doi.org/10.1016/j.heliyon.2023.e23465
28. Jiang LZ, Shen Y, Liang F, Ye XM, Chen J, Yu YM. Intracranial Myroides odoratimimus infection after EVD successfully treated with intravenous plus intraventricular tigecycline: a case report. Infect Drug Resist. 2023;16:1955-63. https://doi.org/10.2147/IDR.S403088
29. Guo Z, Luo CX, Wu HJ, Peng B, Kang BS, Liu LM, et al. Colletotrichum species associated with anthracnose disease of watermelon (Citrullus lanatus) in China. J Fungi (Basel). 2022;8(8):790. https://doi.org/10.3390/jof8080790

ORIGINAL ARTICLE

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Independent risk factors for diversion colitis: a retrospective case-control study

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SUMMARY

OBJECTIVE: The aim of this study was to investigate independent risk factors for diversion colitis induced by the surgical interruption of fecal flow in the non-functional colon.

METHODS: We performed a retrospective study with 163 patients who underwent low anterior resections and created prophylactic ileostomies for rectal cancer between January 2014 and June 2023 at the Department of General Surgery, Air Force Medical University Tangdu Hospital. Colonoscopy results of the non-functional region of the distal colon and clinical variables were collected, including age, sex, body mass index, pathological tumor node metastasis staging, ileostomy method, diversion time, receiving radiotherapy or chemotherapy or not, suffering from preoperative inflammatory bowel disease or postoperative anastomotic leakage or not. Diagnosis of diversion colitis based on the results of the patients' colonoscopy results. Univariate analysis and multivariate analysis of diversion colitis-related risk factors were performed subsequently.

RESULTS: The morbidity of diversion colitis is 53.4% (87/163) in our study. Multivariate analysis showed that risk factors for diversion colitis included single-lumen prophylactic ileostomy (63.2 vs. 30.3%, OR 4.481, 95%CI 1.897–10.584, p<0.001), diversion time ≥90 days (79.3 vs. 40.8%, OR 4.474, 95%CI 1.849–10.826, p<0.001), inflammatory bowel disease (17.2 vs. 3.9%, OR 7.491, 95%CI 1.839–30.507, p=0.005), radiotherapy (58.6 vs. 42.1%, OR 0.515, 95%CI 0.196–1.352, p=0.178).

CONCLUSION: These findings suggest that single-lumen prophylactic ileostomy, diversion time, and inflammatory bowel disease are independent risk factors for diversion colitis.

KEYWORDS: Colitis. Colorectal surgery. Rectal cancer. Risk factor.

INTRODUCTION

With the gradual promotion of total mesorectal excision, the widespread performing of laparoscopic surgery, and stapler technology in clinical practice, the sphincter-preserving rate of patients with low rectal cancer has significantly improved[1,2]. However, the accompanying increased risk of anastomotic leakage has become an important issue that endangers safety and decreases patients' quality of life[3-5]. Prophylactic ileostomy (PI) has become an important choice for surgeons to reduce the risk of anastomotic leakage and reoperation rate after low anterior resection[6]. However, while PI plays a protective role in anastomotic leakage, its complications also need sufficient attention, such as diverting colitis (DC)[7,8]. DC is a non-specific inflammation of the non-functional region of the distal colon induced by surgical interruption of fecal flow through a stoma[7]. The pathogenesis of DC is still unclear. Endoscopic findings include edema, mucosal hemorrhage, and so on, and clinical symptoms include mucous discharge, tenesmus, bleeding, abdominal pain, and so on[7]. The report points out that the trigger for DC is the interruption of fecal flow[7].

METHODS

A total of 766 consecutive patients had surgeries for rectal cancer at the Department of General Surgery, Air Force Medical University Tangdu Hospital, between January 2014 and June 2023. This study has been approved by the Ethical Committee of Air Force Medical University Tangdu Hospital (approval number: 21-KY-14-XW-23) and was conducted in accordance with the Declaration of Helsinki after obtaining informed consent from the patients or their family members. Rectal cancer was defined as a tumor 15 cm or less from the anal verge measured with a

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rigid colonoscopy. The surgical indications included clinical T1–3 lesions based on pelvic computed tomography and magnetic resonance imaging. The eligible patients were performed PI after LAR, with a pathological tumor node metastasis staging (pTNM) class 1–3. The initial exclusion criteria included no ileostomy creation, no colonoscopy results, loss of follow-up, death, and local recurrence. For patients, the stoma closure can be performed 1–6 months after the PI. Before the stoma closure, they underwent endoscopy. A single endoscopist reviewed the colonoscopy results and diagnosed whether patients had suffered from DC or not based on the endoscopic findings such as edema and mucosal hemorrhage. Other clinical variables were collected, including age, sex, body mass index (BMI), pTNM, ileostomy method, diversion time, receiving radiotherapy or chemotherapy or not, suffering from preoperative inflammatory bowel disease (IBD) or postoperative anastomotic leakage or not. Diversion time means the time interval between PI and colonoscopy before stoma closure. PI is divided into the "single-lumen PI" group and the "double-lumen PI" group. Single-lumen PI: Cut off the ileum at a distance of 20 cm from the ileocecal region, and pull the proximal end out of the abdominal wall for ileostomy; Double-lumen PI: Take the ileum out of the abdominal wall at a distance of 20 cm from the ileocecal region for ileostomy without cutting off the ileum. Radiotherapy and chemotherapy for rectal cancer refer to the latest guidelines[9].

Statistical analysis

Kolmogorov-Smirnov tests were performed on all continuous variables. If normally distributed, described by mean±standard deviation, an independent-samples t-test was used for between-group analysis; for those not normally distributed, median and interquartile range were used, and the Mann-Whitney U test was used for between-group comparisons. The categorical variables are represented by numbers (%), and comparisons between groups were made using the Pearson χ^2 test or Fisher's exact test. The association between risk factors and DC was assessed using the chi-square test (χ^2) and unadjusted odds ratio (OR), along with the p-value that was reported for univariate analysis. Risk factors for DC were assessed using binary logistic regression analysis (entry and exit criteria of p=0.05 and p=0.20, respectively), with the adjustment of the variables including single-lumen PI, diversion time v90 days, IBD, and radiotherapy. Subsequently, multivariable logistic regression was utilized to obtain the adjusted OR and confidence intervals (CIs) for variable estimates. A two-sided p-value <0.05 was used to declare statistical significance.

RESULTS

The final retrospective study included 163 patients. The patients' baseline characteristics are listed in Table 1. Among the enrolled patients, 87 were in the DC group and 76 were in the non-DC group. There was no statistical significance between the two groups in terms of age (56.8±12.9 vs. 57.0±12.8, p=0.903), BMI (23.9±3.1 vs. 23.8±3.5, p=0.845), female (35.6 vs. 35.5%, p=0.989), chemotherapy (77.0 vs. 76.3%, p=0.917), anastomotic leakage (4.6 vs. 3.9%, p=1.000), and pTNM staging (19.5 vs. 18.4%, 39.1 vs. 39.5%, 41.4 vs. 42.1%, p=0.983).

Table 1. Baseline characteristics of patients by diversion colitis.

Baseline characteristics	Total (163)	DC (87)	Non-DC (76)	p-value
Age (years)	56.9±12.8	56.8±12.9	57.0±12.8	0.903
Female, n (%)	58 (35.6%)	31 (35.6%)	27 (35.5%)	0.989
BMI (kg/m^2)	23.8±3.3	23.9±3.1	23.8±3.5	0.845
Single-lumen PI, n (%)	78 (47.9%)	55 (63.2%)	23 (30.3%)	<0.001
Diversion time ≥90 days, n (%)	100 (61.3%)	69 (79.3%)	31 (40.8%)	<0.001
IBD, n (%)	18 (11.0%)	15 (17.2%)	3 (3.9%)	0.007
Radiotherapy, n (%)	83 (50.9%)	51 (58.6%)	32 (42.1%)	0.035
Chemotherapy, n (%)	125 (76.7%)	67 (77.0%)	58 (76.3%)	0.917
Anastomotic leakage, n (%)	7 (4.3%)	4 (4.6%)	3 (3.9%)	1.000
pTNM staging				
I	31 (19.0%)	17 (19.5%)	14 (18.4%)	0.983
II	64 (39.3%)	34 (39.1%)	30 (39.5%)	
III	68 (41.7%)	36 (41.4%)	32 (42.1%)	

DC: diversion colitis; BMI: body mass index; IBD: inflammatory bowel disease; pTNM: pathological tumor node metastasis; PI: prophylactic ileostomy.

Univariate analysis showed that DC has a higher morbidity in patients with single-lumen PI (63.2 vs. 30.3%, OR 3.961, 95%CI 2.057–7.627, p<0.001), diversion time ≥90days (79.3 vs. 40.8%, OR= 5.565, 95%CI 2.786—11.112, p<0.001), IBD (17.2 vs. 3.9%, OR 5.069, 95%CI 1.407—18.263, p=0.013), and radiotherapy (58.6 vs. 42.1%, OR 1.948, 95%CI 1.044–3.636, p=0.036) (Table 2).

The variables with p<0.20 in univariate analysis were selected for multivariable analysis. Multivariate analysis showed that risk factors for DC included single-lumen PI (63.2 vs. 30.3%, OR 4.481, 95%CI 1.897–10.584, p<0.001), diversion time ≥90days, (79.3 vs. 40.8%, OR= 4.474, 95%CI 1.849—10.826, p<0.001), IBD (17.2 vs. 3.9%, OR 7.491, 95%CI 1.839–30.507, p=0.005), and radiotherapy (58.6 vs. 42.1%, OR 0.515, 95%CI 0.196–1.352, p=0.178) (Figure 1). Finally, single-lumen PI, diversion time, and IBD are independent risk factors for DC.

Table 2. Univariate analysis of diversion colitis-related risk factors.

Source	OR	95%CI
Single-lumen PI, n (%)	3.961	(2.057–7.627)
Diversion time ≥iv days, n (%)	5.565	(2.786–11.112)
IBD, n (%)	5.069	(1.407–18.263)
Radiotherapy, n (%)	1.948	(1.044–3.636)

PI: prophylactic ileostomy; IBD: inflammatory bowel disease; OR: odds ratio; CI: confidence interval.

DISCUSSION

Stoma-induced DC can cause patients to experience a series of symptoms such as abdominal pain, mucous discharge, bleeding, tenesmus, and diarrhea after the stoma closure. A colonoscopy examination reveals edema, mucosal hemorrhage, and so on in the non-functioning region of the distal colon[7]. The occurrence and severity of DC reported in the literature are time-dependent, gradually worsening with the increase of diversion time. Literature has reported a morbidity of approximately 70–100% for DC[7,10]. In our study, the morbidity was 53.4%, which may be related to the early stoma closure and the conduction of double-lumen PI. Previous studies have shown that DC can reduce patients' quality of life[11].

The pathogenesis of DC may be as follows: prolonged fecal flow diversion leads to a decrease in anaerobic bacterial concentration and an increase in nitrate-reducing bacteria in the non-functional colon, resulting in a toxic level of nitric oxide produced by its metabolism. The toxic level of nitric oxide leads to DC[12,13]. These situations can be improved through microbiota transplantation.[14,15] Some scholars also believe that ischemia is the cause of DC[16], based on the reduction of short-chain fatty acids (SCFAs), which are produced by normal intestinal bacteria. SCFAs have the effect of relaxing vascular smooth muscle, and insufficient SCFAs may cause vasoconstriction of the pelvic artery, leading to insufficient blood supply to the colon. After local treatment with SCFAs for some time, some DC patients can improve their clinical symptoms[17]. At present,

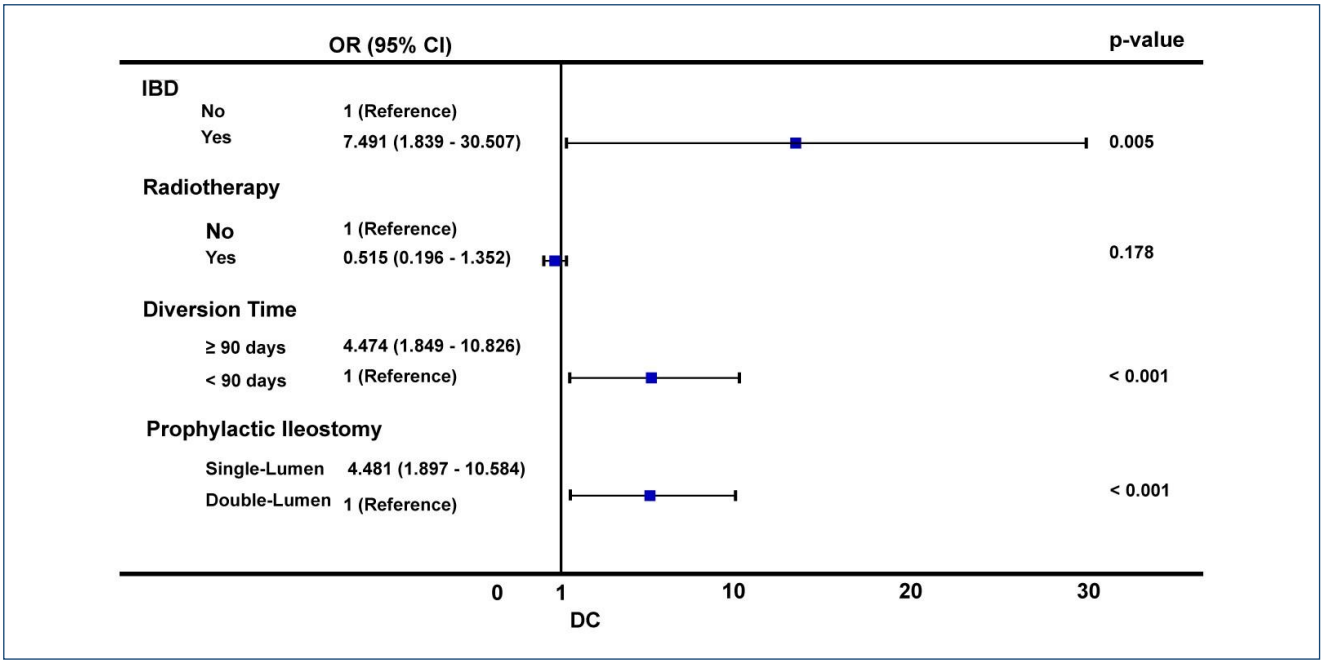

Figure 1. Multivariate analysis of diversion colitis-related risk factors.

there is no consensus on the exact pathogenesis of DC; however, there is a basic consensus that prolonged fecal flow diversion is a risk factor for DC. Traditionally, it is believed that the stoma closure should be performed 8–12 weeks after an ostomy; however, it is usual that this period extends beyond 12 months[18]. If the examination results show complete healing of the anastomosis, no local recurrence, no anastomotic stenosis, no anastomotic leakage, and no other complications, then the stoma closure should be performed immediately[18,19]. Some scholars also believe that early stoma closure can reduce the morbidity of stoma-related complications and patients' discomfort[20]. O'Sullivan et al. reported that stoma closure was feasible <14 days after the ostomy, but the morbidity of reoperations and postoperative ileus was higher[21]. Other studies have also found that there is no significant difference between early and late stoma closure in the mortality of complications[18]. The report by Nelson et al. suggested that early stoma closure did not only increase the risk of postoperative complications but also reduced the cost of ostomy care and improved patients' quality of life[22]. In short, the results of reports on whether to choose early or late stoma closure are contradictory.

The purpose of ostomy is to divert the fecal flow out of the body through the artificially established stoma, to reduce the tension of the anastomotic region in the Phase I operation, and to reduce the morbidity of anastomotic leakage and the reoperation rate[1,6]. Szczepkowski et al. reported that the morbidity of DC was not related to the ostomy method[23]. However, they only compared single-lumen PI to single-lumen colostomy, and the conclusion that DC is not related to the ostomy method is not accurate. Single-lumen PI completely interrupts intestinal continuity, thereby achieving the goal of fecal flow diversion. A double-lumen PI may not completely interrupt fecal flow, resulting in a small amount of fecal flow nourishing a portion of the distal intestine. Maybe for this reason, our study indicates that the morbidity of DC after double-lumen PI is lower than that of single-lumen PI.

IBD mainly includes ulcerative colitis and Crohn's disease. The morbidity of DC in patients without a preoperative diagnosis of IBD is 70–74%, while the morbidity in patients with a preoperative diagnosis of IBD is 91%[7]. Korelitz et al. reported that the morbidity of DC in patients who were also diagnosed with IBD before the operation was even as high as 100%[10] after fecal flow was interrupted. Our study shows that IBD is a risk factor for DC, which may be due to the rapid change in gut microbiota caused by fecal flow diversion, accelerating the destruction of the already fragile gut microbiota ecology in patients with IBD and leading to the occurrence of DC.

Radiotherapy is a very important part of the treatment for colorectal cancer[24,25]. In our study, radiotherapy had significant differences in the univariate analysis of risk factors, but it was not an independent risk factor for DC. The reason may be that 49.4% of patients with radiotherapy had a diversion time ≥ I days, and 47.0% had a single-lumen PI. We have also retrieved relevant literature, and there have been no reports that radiotherapy is an independent risk factor for DC. Due to the above results, we need to follow up on this study, increase the sample size, and continue to explore whether radiotherapy is an independent risk factor for DC. In summary, single-lumen PI, diversion time, and IBD are independent risk factors for DC. Our study indicated that for patients with high-risk factors such as IBD implementing, double-lumen PI may be beneficial, and whether single-lumen or double-lumen PI that patients undergo, stoma closure implemented within 3 months may be appropriate.

Some limitations need to be considered: (1) this study is a single-center study with a relatively small sample size, which can lead to selective bias; (2) our study is retrospective, and we cannot collect data on changes in gut microbiota and metabolic products between the two groups of patients, which limits the revelation of the pathogenesis of DC; and (3) multicenter and prospective studies are needed to confirm our findings further.

AUTHORS' CONTRIBUTIONS

DW: Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **BW:** Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **HY:** Data curation, Funding acquisition, Methodology, Resources, Software, Supervision, Writing – review & editing.

REFERENCES

1. Zhang C, Stampfl-Mattersberger M, Ruckser R, Sebesta C. [Colorectal cancer]. Wien Med Wochenschr. 2023;173(9-10):216-20. https://doi.org/10.1007/s10354-022-00975-6
2. Seow W, Dudi-Venkata NN, Bedrikovetski S, Kroon HM, Sammour T. Outcomes of open vs laparoscopic vs robotic vs transanal total mesorectal excision (TME) for rectal cancer: a network meta-analysis. Tech Coloproctol. 2023;27(5):345-60. https://doi.org/10.1007/s10151-022-02739-1
3. Chiarello MM, Fransvea P, Cariati M, Adams NJ, Bianchi V, Brisinda G. Anastomotic leakage in colorectal cancer surgery. Surg Oncol. 2022;40:101708. https://doi.org/10.1016/j.suronc.2022.101708

4. Pallan A, Dedelaite M, Mirajkar N, Newman PA, Plowright J, Ashraf S. Postoperative complications of colorectal cancer. Clin Radiol. 2021;76(12):896-907. https://doi.org/10.1016/j.crad.2021.06.002
5. Świątkowski F, Górnicki T, Bułdyś K, Chabowski M. The quality of life of patients with surgically treated colorectal cancer: a narrative review. J Clin Med. 2022;11(20):6211. https://doi.org/10.3390/jcm11206211
6. Ma H, Li X, Yang H, Qiu Y, Xiao W. The pathology and physiology of ileostomy. Front Nutr. 2022;9:842198. https://doi.org/10.3389/fnut.2022.842198
7. Tominaga K, Kamimura K, Takahashi K, Yokoyama J, Yamagiwa S, Terai S. Diversion colitis and pouchitis: a mini-review. World J Gastroenterol. 2018;24(16):1734-47. https://doi.org/10.3748/wjg.v24.i16.1734
8. Tsujinaka S, Suzuki H, Miura T, Sato Y, Murata H, Endo Y, et al. Diagnosis, treatment, and prevention of ileostomy complications: an updated review. Cureus. 2023;15(1):e34289. https://doi.org/10.7759/cureus.34289
9. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, et al. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(3):329-59. https://doi.org/10.6004/jnccn.2021.0012
10. Korelitz BI, Cheskin LJ, Sohn N, Sommers SC. The fate of the rectal segment after diversion of the fecal stream in Crohn's disease: its implications for surgical management. J Clin Gastroenterol. 1985;7(1):37-43. https://doi.org/10.1097/00004836-198502000-00005
11. Son DN, Choi DJ, Woo SU, Kim J, Keom BR, Kim CH, et al. Relationship between diversion colitis and quality of life in rectal cancer. World J Gastroenterol. 2013;19(4):542-9. https://doi.org/10.3748/wjg.v19.i4.542
12. Baek SJ, Kim SH, Lee CK, Roh KH, Keum B, Kim CH, et al. Relationship between the severity of diversion colitis and the composition of colonic bacteria: a prospective study. Gut Liver. 2014;8(2):170-6. https://doi.org/10.5009/gnl.2014.8.2.170
13. Sun Q, Shi Y, Liang X, Lu H, Huang Y, Zhu L, et al. Interaction between the intestinal flora and the severity of diversion colitis after low anterior resection of rectal cancer. Front Oncol. 2023;13:1001819. https://doi.org/10.3389/fonc.2023.1001819
14. Rodríguez-Padilla Á, Morales-Martín G, Pérez-Quintero R, Gómez-Salgado J, Rada-Morgades R, Ruiz-Frutos C. Diversion colitis: macro and microscopic findings after probiotics stimulation. Biology (Basel). 2021;10(4):303. https://doi.org/10.3390/biology10040303
15. Rodríguez-Padilla Á, Morales-Martín G, Pérez-Quintero R, Rada-Morgades R, Gómez-Salgado J, Ruiz-Frutos C. Diversion colitis and probiotic stimulation: effects of bowel stimulation prior to ileostomy closure. Front Med (Lausanne). 2021;8:654573. https://doi.org/10.3389/fmed.2021.654573
16. Villanacci V, Talbot IC, Rossi E, Bassotti G. Ischaemia: a pathogenetic clue in diversion colitis? Colorectal Dis. 2007;9(7):601-5. https://doi.org/10.1111/j.1463-1318.2006.01182.x
17. Sam SW, Hafeez B, Ong HI, Gill S, Smibert O, Lavelle A, et al. The impact of faecal diversion on the gut microbiome: a systematic review. Gut Microbiome (Camb). 2024;5:e4. https://doi.org/10.1017/gmb.2024.1
18. Vogel I, Reeves N, Tanis PJ, Bemelman WA, Torkington J, Hompes R, et al. Impact of a defunctioning ileostomy and time to stoma closure on bowel function after low anterior resection for rectal cancer: a systematic review and meta-analysis. Tech Coloproctol. 2021;25(7):751-60. https://doi.org/10.1007/s10151-021-02436-5
19. Keane C, Park J, Öberg S, Wedin A, Bock D, O'Grady G, et al. Functional outcomes from a randomized trial of early closure of temporary ileostomy after rectal excision for cancer. Br J Surg. 2019;106(5):645-52. https://doi.org/10.1002/bjs.11092
20. Clausen FB, Dohrn N, Hölmich ER, Klein M, Gögenur I. Safety of early ileostomy closure: a systematic review and meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2021;36(2):203-12. https://doi.org/10.1007/s00384-020-03761-1
21. O'Sullivan NJ, Temperley HC, Nugent TS, Low EZ, Kavanagh DO, Larkin JO, et al. Early vs. standard reversal ileostomy: a systematic review and meta-analysis. Tech Coloproctol. 2022;26(11):851-62. https://doi.org/10.1007/s10151-022-02629-6
22. Nelson T, Pranavi AR, Sureshkumar S, Sreenath GS, Kate V. Early versus conventional stoma closure following bowel surgery: a randomized controlled trial. Saudi J Gastroenterol. 2018;24(1):52-8. https://doi.org/10.4103/sjg.SJG_445_17
23. Szczepkowski M, Kobus A, Borycka K. How to treat diversion colitis?--Current state of medical knowledge, own research and experience. Acta Chir Iugosl. 2008;55(3):77-81. https://doi.org/10.2298/aci0803077s
24. Donnelly SM, Wyatt J, Powell SG, Jones N, Altaf K, Ahmed S. What is the optimal timing of surgery after short-course radiotherapy for rectal cancer? Surg Oncol. 2023;51:101992. https://doi.org/10.1016/j.suronc.2023.101992
25. Shinji S, Yamada T, Matsuda A, Sonoda H, Ohta R, Iwai T, et al. Recent advances in the treatment of colorectal cancer: a review. J Nippon Med Sch. 2022;89(3):246-54. https://doi.org/10.1272/jnms.JNMS.2022_89-310

ORIGINAL ARTICLE

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The effect of sexually transmitted disease education via instagram on the knowledge and attitudes of university students: a pilot study

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the effects of sexually transmitted disease education provided via Instagram on university students' knowledge and attitudes about sexually transmitted diseases.

METHODS: This pretest-posttest control group experimental study was conducted on 69 participants (Instagram group: 30, control group: 39). Participants in the Instagram group followed the @sexualinfectmarmara Instagram account prepared by the researchers. Five modules about sexually transmitted diseases prepared by the researchers were shared on this account.

RESULTS: When the pre-training STD scores of the Instagram and control groups were compared with the analysis of covariance (ANCOVA) analysis, it was found that the scores of the Instagram group were statistically significantly higher than those of the control group. No significant difference was found between the sexually transmitted disease scores. After the training, the participants in the Instagram group responded significantly more with disagreement to the statement "sexually transmitted disease patients are easily recognized in society."

CONCLUSION: Instagram can be a new and alternative educational tool for increasing the sexually transmitted disease knowledge and attitude levels of university students.

KEYWORDS: Social media. Training. STDs.

INTRODUCTION

Sexually transmitted diseases (STDs) are increasing globally and are a problem that particularly affects young adults[1]. Due to social and biological factors and engaging in risky sexual behaviors due to peer and social media influences, young adults are at a high risk of acquiring STDs. In this regard, the most important problem is that young people do not have sufficient knowledge about STDs[2]. With the development of technology, websites, mobile applications, and social media tools are used to provide information about STDs. It has been reported that these methods can be effective in reducing STDs[3,4]. A large proportion of young people are Internet and social media users, which provides an important opportunity for them to learn about STDs[5].

Today, various technological tools such as websites and mobile applications are used to provide STD education to young people. However, there are no studies on STD education via Instagram. Instagram has 1 billion users worldwide and is a popular social media platform where photos and videos are shared. It has been stated in the literature that Instagram is used as a low-cost and effective tool for providing education on various diseases[6,7].

This study was conducted to evaluate the effect of education provided via Instagram on the knowledge and attitude levels of university students about some of the common STDs, namely chlamydia, human papillomavirus (HPV), human immunodeficiency virus (HIV), and syphilis.

RESEARCH HYPOTHESES

H1: After the training, the Instagram group will have higher STD Knowledge Test (STDKT) scores than the control group.

H2: After the training, the Instagram group will have higher STD (chlamydia, HPV, HIV, and syphilis)-Specific Knowledge Test (STDSKT) scores than the control group.

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METHODS

Study design and setting

The present study is an experimental study conducted with a pretest-posttest control group. The study was conducted at the Faculty of Health Sciences, Marmara University, between January 2022 and February 2023.

Participants

The study included students between the ages of 18 and 25 years, studying in the Physiotherapy and Rehabilitation, Health Management, and Nutrition-Dietetics departments, who were in their second year, used Instagram, had not received training on STDs, had not been diagnosed with STDs, and agreed to participate in the study. Students studying in the Physiotherapy and Rehabilitation (n=8) and Nutrition-Dietetics departments formed the Instagram group (n=22), and students studying in the Health Management department (n=39) formed the control group. The allocation of students to the two groups based on departments was decided by drawing lots.

Sample size calculation

The sample size was calculated using OpenEpi, version 3. With a confidence interval of 95% and a power of 80%, the Instagram group post-education STDKT score was found to be 28.50±2.01 and the control group post-education STDKT score was found to be 26±4.1. Based on the calculation made, it was decided that at least 27 people should be included in each group. Considering that there may be a loss of cases in each group, 90 participants (Instagram group: 45, control group: 45) were included in the study. Twenty-one participants withdrew from the study/were excluded from the study. Finally, the study was conducted on 69 participants (Instagram group: 30, control group: 39).

Data collection tools and data acquisition

Data were obtained using the Demographic Information Form (DIF), sexually transmitted disease Knowledge Test (STDKT), sexually transmitted disease Specific Knowledge Test (STDSKT), and STD Attitude Survey (STDAS), before and after the training.

- DIF: This form consists of a total of seven questions that evaluate the sociodemographic characteristics of the participants (age, gender, education level of mother and father, source from where they get information about health problems, etc.).
- STDKT: This test aims to evaluate the general knowledge level of individuals about STDs[8]. In our study, this knowledge test was employed with a total of 20 questions (items that were not compatible with the educational content were removed), and each correct answer was awarded 5 points. A maximum score of 5–100 can be rated for the knowledge level of individuals about STDs.. The Kuder–Richardson (KR)-21 reliability coefficient, which was reported as 0.82 in the study of Siyez and Siyez[8], was found to be 0.80 in our study.
- STDSKT: This test includes 10 questions on chlamydia, HPV, HIV, and syphilis. The purpose of the test is to measure the level of knowledge about the agents, symptoms, findings, treatment methods, and possible situations that may occur if these diseases are not treated[9]. Each correct answer is worth 10 points. According to the difficulty index evaluation of the test, four questions were classified as easy (40%), two questions as medium (20%), and four questions as difficult (30%). As a result of the discrimination index of the test, six items were found to be excellent, two items were acceptable, and two items were found to be weak. The KR-20 reliability coefficient of the test was determined as 0.60 in our study.
- STDAS: This three-question survey, prepared in line with the relevant literature, aims to measure the basic attitudes of the participants about STDs[10,11].

Sexually transmitted disease education program

Five modules about STDs prepared by the researchers were used in the education program, of which the general information module about STDs includes general information about the frequency of STDs and their types, signs and symptoms, treatment options, complications, and protection methods. The other four modules provide information about the causative agents, transmission routes, diagnostic tests, treatment modalities, and protection methods of HPV, syphilis, HIV/AIDS, and chlamydia diseases. The information in the modules was prepared in the form of descriptive posts and animation shows (a total of 28 contents) and was shared on an Instagram account called @sexualinfectmarmara (https://www.instagram.com/sexualinfectmarmara?utm_source=qr&igsh=YXJwODVyNTU1cmln).

Data collection

The researchers invited second-year students for participation from the departments where they would conduct the study by explaining the purpose of the study. Students who were willing to participate were asked to sign an informed consent form, and their contact information was obtained.

Instagram group

A pre-test data collection link, which was transferred to Google Drive, was sent to the participants via WhatsApp. Participants who filled out the pre-test forms were asked to follow the @sexualinfectmarmara Instagram account. After a sufficient number of participants were attained, the STD training modules were shared on Instagram every day for 4 weeks. Two weeks after the final content was shared, a post-test data collection link was sent to the participants via WhatsApp.

Analysis of data

Categorical data were analyzed using the χ^2 test and Bonferroni correction test. The Kolmogorov-Smirnov test was used to check the data for normal distribution. Parametric data were evaluated using the independent samples t-test and paired sample t-test. The analysis of covariance (ANCOVA) test was applied, assuming the pre-education scores as covariates and the post-education scores as dependent variables. It was evaluated at a $p<0.05$ significance level.

Ethical aspects of the research

Ethics committee approval was obtained from the Non-Interventional Clinical Research Ethics Committee, Faculty of Health Sciences, Marmara University (date: 30.12.2021/protocol no. 124). Permission for the use of STDKT was received from Siyez via e-mail.

RESULTS

Data on the characteristics of the participants in the study are presented in Table 1. There was no statistically significant difference between the groups in terms of age, gender, and maternal education level ($p>0.05$) (Table 1). It was determined that 90.00% (n=27) of the participants in the Instagram group had used social media/Internet to obtain information about STDs in the past, and there was a statistically significant difference between the groups ($p<0.05$).

It was found that both the pre-training STDKT scores ($p<0.05$ and $p<0.001$, respectively) and the post-training

Table 1. Comparison of the distribution of characteristics of participants in the groups.

Characteristics	Instagram group (n=30)		Control group (n=39)		t	p
	X+SD		X+SD			
Age (years)	20.50±0.97		20.07±0.89		1.86	0.06
	N	%	N	%	χ^2	p
Gender						
Female	25	83.3	29	74.4	0.80	0.37
Male	5	16.7	10	25.6		
Mother's education level						
Primary school	12	40.00	5	12.80	7.63	0.054
Secondary school	7	23.30	12	30.80		
High school	10	33.30	17	43.60		
University	1	3.30	5	12.80		
Father's education level						
Primary school	8	26.70	1	2.60	11.80	**0.008***
Secondary school	8	26.70	6	15.40		
High school	8	26.70	18	46.20		
University	6	20.00	14	35.90		
Total	30	100.00	39	100.00		
From where they have learned about STDs in the past**						
Social media—internet	27	90.00	22	56.40	9.29	**0.002***
Friends—peers	14	46.70	26	66.70	2.78	0.09
Family	5	16.70	17	43.60	5.65	**0.01***

*p<0.05. **Row percentage is used. STD: sexually transmitted disease. Statistically significant values are denoted in bold. X+SD: represents mean±standard deviation.

STDSKT scores (p<0.001 and p<0.001, respectively) of the participants in the Instagram and control groups were statistically significantly different (Table 2).

It was also found that the post-training STDKT score of the Instagram group increased statistically significantly compared to the pre-training level (p<0.001), while the pre-training STDSKT scores did not change after the training (p=0.05) (Table 2).

When the post-training STDKT scores of the Instagram and control groups were compared with the ANCOVA analysis, assuming the pre-training scores as covariates, it was found that the scores of the Instagram group increased statistically significantly compared to the control group (p<0.001). When the post-training STDSKT scores of the Instagram and control groups were compared with the ANCOVA test, it was determined that the scores of both groups were similar (p>0.05) (Table 2).

While the responses to the statement "patients with STDs are easily recognized in society" were similar between the groups before the training, it was found that there was a statistically significant difference between the groups after the training, and this difference was due to those who disagreed (p<0.05) (Table 3).

DISCUSSION

This study was conducted to evaluate the effect of education provided via Instagram on the knowledge and attitude levels of

Table 2. Comparison of the scores of the participants in the groups from the sexually transmitted disease Knowledge Test and the sexually transmitted disease-specific Knowledge Test.

"Results for knowledge tests	Pre-Training			Post-training					
	Group	X±SD	t; p^1	X±SD	t; p^2	t; p^3	F	ηp^2	p^4
STDKT	Instagram group (n=30)	56.16±25.14	2.65; 0.01*	68.83±19.50	6.08; 0.00**	−2.77; 0.01*	25.63	0.28	0.00*
	Control group (n=39)	42.23 ±15.84		42.69±16.17		−0.19; 0.84			
STDSKT	Instagram group (n=30) Control group (n=39)	46.66±16.88 25.12±11.89	6.21; 0.00**	52.66±23.6230.00±16.54	4.47; 0.00**	−1.96; 0.05 −1.65; 0.10	1.97	0.029	1.65

p^1: Comparison of pre-training knowledge test scores between groups (independent samples t-test). p^2: Comparison of post-training knowledge test scores between groups (independent samples t-test). p^3: Comparison of pre-training and post-training knowledge test scores within the group (paired sample t-test). p^4: ANCOVA. *p<0.05; **p<0.001. STDKT: sexually transmitted disease Knowledge Test; STDSKT: sexually transmitted disease Specific Knowledge Test.

Table 3. Comparison of the distribution of responses to sexually transmitted diseases given by participants in the groups before and after the training.

Expressions	Before training						After training					
	Experimental group (n=30)		Control group (n=39)				Experimental group (n=30)		Control group (n=39)			
	n	%	N	%	χ^2	p	N	%	n	%	χ^2	P
Teenagers are more vulnerable to STDs												
Agree	23	76.7	31	79.5	0.77	0.5	24	80	29	74.4	2.41	0.29
Disagree	–	–	–	–			6	20	7	17.9		
Undecided	7	23.3	8	20.5			–	–	3	7.7		
Patients with STDs are easily recognized in society												
Agree	9	30	18	46.2	3.41	0.18	7	23.30	16	41.00	8.62	0.01*
Disagree	13	43.3	9	23.1			12	40.00	4	10.30		
Undecided	8	26.7	12	30.8			11	36.70	19	48.70		
Protecting against STDs is difficult and costly												
Agree	11	36.7	21	53.8	5.31	0.07	11	36.7	22	56.4	2.79	0.24
Disagree	13	43.3	7	17.9			10	33.3	10	25.6		
Undecided	6	20	11	28.2			9	30	7	17.9		
Total	30	100	39	100			30	100	39	100		

Chi-square test; Bonferroni correction test. *p<0.05. STD: sexually transmitted disease.

university students about some common STDs. The findings show that hypothesis H1 is supported. It was determined that the STD scores of the Instagram group increased significantly after the education compared to the control group. This situation emphasizes the potential of social media-based education to increase the general knowledge level of the participants. It is thought that platforms such as Instagram can be an effective educational tool, especially for young people and individuals with high digital media usage[10].

However, the results of hypothesis H2 did not occur as expected. No statistically significant difference was found between the STDSKT scores of the Instagram and control groups after the training ($p>0.05$). This result shows that the potential of education provided through social media to increase knowledge on certain topics may be limited. It supports the idea that topics requiring special knowledge such as chlamydia, HPV, HIV, and syphilis should be addressed with a more in-depth and interactive training method. It is understood that social media training can be effective on basic information, but more comprehensive methods should be adopted for special information[12]. A similar 2022 study assessed the knowledge of students in public high schools in poor communities about HPV and STDs, their attitudes toward these diseases, and their attitudes toward the prevention of these diseases and concluded that adolescents had very limited knowledge about HPV and cervical cancer[13].

The significant difference in the responses to the statement "STD patients are easily recognized in society" after the training reveals the potential of social media training to change the social perceptions of the participants. It was observed that the participants had a more critical perspective after the training. This indicates the potential of training conducted via social media to provide participants with a thought-provoking perspective on issues, such as stigmatization and social perception.

Limitations of the study

The study findings cannot be generalized to all university students. Since there are no STDSKT and STDAS that have been examined for validity and reliability in our country, forms prepared by the researchers were used. Another limitation is the use of objectively analyzed quantitative questionnaires, which relied on the self-report of students on their knowledge about the subjects without any confirmation. As a result, the knowledge assessed is subjective or perceived. Moreover, these questionnaires do not provide an opportunity to explore socioeconomic factors such as religious beliefs or to assess the prevalence of sexually transmitted infections/HPV and vaccination status. Therefore, further studies are required.

CONCLUSION AND RECOMMENDATIONS

This study highlights the role of social media and the Internet in education and shows that platforms such as Instagram can be an important tool for acquiring knowledge. However, it should be noted that traditional education methods are also effective for gaining more in-depth knowledge on certain topics. Future research should examine the long-term effects of social media-based education programs and how they affect participants' social perceptions in more detail. It is also thought that the content and presentation of social media education should be carefully designed to maximize their potential to increase participants' knowledge.

AUTHORS' CONTRIBUTIONS

ÖCG: Conceptualization, Formal Analysis, Supervision. **BK:** Data curation, Writing – review & editing. **YE:** Data curation, Writing – review & editing. **NM:** Data curation, Writing – review & editing. **EA:** Data curation, Writing – review & editing. **FD:** Data curation, Writing – review & editing.

REFERENCES

1. WHO. Child and adolescent health and development progress report 2006. WHO publication. Volume 4; 2007. p. 28. Available from: https://doi.org/10.1177/156482650702800414
2. Sieving RE, Gewirtz O'Brien JR, Saftner MA, Argo TA. Sexually transmitted diseases among US adolescents and young adults: patterns, clinical considerations, and prevention. Nurs Clin North Am. 2019;54(2):207-25. https://doi.org/10.1016/j.cnur.2019.02.002
3. Kachur R, Hall W, Coor A, Kinsey J, Collins D, Strona FV. The use of technology for sexually transmitted disease partner services in the United States: a structured review. Sex Transm Dis. 2018;45(11):707-12. https://doi.org/10.1097/OLQ.0000000000000864
4. Vermund SH, Geller AB, Crowley JS. Sexually transmitted infections: adopting a sexual health paradigm. In: Sexually transmitted infections. Washington (DC): National Academies of Sciences, Engineering, and Medicine; 2021. Available from: https://doi.org/10.17226/25955
5. Baran B, Kaptano?lu ?N, Esen E, Siyez DM. Reproductive system augmented reality application for sexual health classes. Int J Sex Heal. 2020;32(4):408-20. https://doi.org/10.1080/19317611.2020.1825028
6. Blunck D, Kastner L, Nissen M, Winkler J. The effectiveness of patient training in inflammatory bowel disease knowledge via Instagram: randomized controlled trial. J Med Internet Res. 2022;24(10):e36767. https://doi.org/10.2196/36767

7. Curtis RG, Ryan JC, Edney SM, Maher CA. Can Instagram be used to deliver an evidence-based exercise program for young women? A process evaluation. BMC Public Health. 2020;20(1):1-9. https://doi.org/10.1186/s12889-020-09563-y
8. Siyez DM, Siyez E. Üniversite ö□rencilerinin cinsel yolla bula□an hastalıklara ili□kin bilgi düzeylerinin incelenmesi. Türk Üroloji Dergisi. 2009;35(1):49-55.
9. Kalaycı, □. SPSS uygulamalı çok de□i□kenli istatistik teknikleri. Ankara: Asil Yayın Da□ıtım; 2009.
10. Kassie AA, Gudayu TW, Araya BM. Knowledge, attitude, and preventive practices towards sexually transmitted infections among preparatory school students in West Gojjam Zone, Ethiopia. Advances in Public Health; 2020. Available from: https://doi.org/10.1155/2020/6894394
11. Ardelia V, Jaroah S. Exploring social media use integration based on educational level among emerging adults. Int J Curr Educ Res. 2023;2(2):106-14. https://doi.org/10.53621/ijocer.v2i2.249
12. Jiang G, Liu F, Liu W, Liu S, Chen Y, Xu D. Effects of information quality on information adoption on social media review platforms: moderating role of perceived risk. Data Sci Manag. 2021;1(1):13-22. https://doi.org/10.1016/j.dsm.2021.02.004
13. Soares Junior JM, Oliveira HMC, Luquetti CM, Zuchelo LTS, Arruda Veiga EC, Raimundo JZ, et al. Adolescents' knowledge of HPV and sexually transmitted infections at public high schools in São Paulo: a cross-sectional study. Clinics (Sao Paulo). 2022;77:100138. https://doi.org/10.1016/j.clinsp.2022.100138

ORIGINAL ARTICLE

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The effect of eight different gene polymorphisms on osteopenia and osteoporosis in the Turkish population

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SUMMARY

OBJECTIVE: Bone mineral density is affected by many gene regions. Osteoporosis is a disease that occurs due to decreased bone mineral density and has a polygenetic multifactorial pathogenesis. The aim of this study was to examine the effect of gene variants in eight gene regions related to bone mineral density in patients diagnosed with osteopenia or osteoporosis.

METHODS: A total of 60 patients diagnosed with osteoporosis, 50 patients diagnosed with osteopenia, and 40 healthy volunteers (control group) were included in the study. Collagen type I alpha 1 1997G/T, estrogen receptor α PvuII, estrogen receptor α XbaI, vitamin D receptor BsmI, lactase gene, osteoprotegerin G209A, osteoprotegerin T245G, and interleukin-6 G174C gene variants were analyzed.

RESULTS: No important difference was found in the distribution of collagen type I alpha 1 1997G/T, estrogen receptor α PvuII, estrogen receptor α XbaI, vitamin D receptor BsmI, lactase gene T13910C, osteoprotegerin T245G, and interleukin-6 G174C gene variants between groups. A significant difference was detected between the distribution of osteoprotegerin G209A gene variants in the patient groups and the distribution of osteoprotegerin G209A gene variants in the control group. On the other hand, no important difference was detected in the distribution of osteoprotegerin G209A gene variants between patient groups.

CONCLUSION: The osteoprotegerin G209A gene variant may be associated with the risk of osteopenia and osteoporosis in the Turkish population. Other gene variants analyzed that affect bone mineral density were not associated with the risk of osteopenia and osteoporosis.

KEYWORDS: Gene polymorphism. Osteoprotegerin. Osteoporosis. Vitamin D receptor. Osteopenia.

INTRODUCTION

Osteoporosis, characterized by skeletal fragility associated with reduced bone mass, is a well-identified and expanding public health issue. According to a report by a foundation based on osteoporosis disease, it is estimated that there are 10.2 million people with osteoporosis in America and an additional 43.4 million people have low bone mass. It is also predicted that the number of individuals with low bone mass or osteoporosis will exceed 71 million by 2030[1]. Osteoporosis, in which fractures cause significant morbidity and mortality, occurs most frequently in postmenopausal women, but cases of osteoporosis also occur in premenopausal women and men. While the treatment of cases of osteoporosis often focuses on the underlying condition, a variety of secondary causes, from endocrine diseases to genetic conditions, are often neglected[2].

Many genes affect bone mineral density, a polygenetic skeletal trait[3]. Osteoporosis, which occurs due to decreased bone mineral density, has a polygenetic and multifactorial pathogenesis, and therefore it cannot be adequately diagnosed clinically and hence inadequately treated[4]. Therefore, it is very important to identify people at a high risk of osteoporotic fractures in a timely manner. Accordingly, screening for polygenic risk scores and similar risk factors is one of the developments in case finding[5].

Collagen type I alpha 1 (COL1A1) is one of the two genes encoding collagen type I. Collagen type I, the most plentiful protein in people, also contributes 90% of the entire organic portion of the matrix of bones[6]. Estrogen receptor α (ESR1) stimulates the gene transcription of sialoprotein, an acidic glycoprotein specific to bone mineralized tissues that is expressed in the early stages of bone tissue development[7]. Vitamin D receptor (VDR) gene variants are known as the main risk factor for low bone mineral density[8].

Osteoprotegerin (OPG) is a soluble nuclear factor-kappa B ligand (RANKL) decoy receptor produced predominantly by osteoblasts. It prevents osteoclastic bone resorption and osteoclast formation by inhibiting the RANKL–RANKL receptor interaction. The mass loss of bone tissues depends on the

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RANK–RANKL–OPG system, which is the main regulatory system of the survival, activation, and induction of osteoclast differentiation[9]. Lactase gene (LCT) variants may affect calcium intake and therefore bone health[10]. Interleukin 6 (IL-6) promotes osteoclast formation and bone resorption. Polymorphisms in the IL-6 promoter region have been associated with plasma IL-6 levels. Furthermore, variation at the IL-6 locus may contribute to genetic susceptibility to bone fragility.[11].

Many genetic factors affect bone mineral density in different ways. This study was planned to investigate the relationship between variants observed in eight different gene regions and the pathogenesis of osteoporosis and osteopenia.

METHODS

Study design

Ethics committee approval for this study was received from the Non-Interventional Clinical Research Ethics Committee, Faculty of Medicine, Ataturk University (Ethics Committee approval number: 26.04.07/01/07). Sixty patients diagnosed with osteoporosis and fifty patients diagnosed with osteopenia at the Department of Physical Therapy and Rehabilitation, Faculty of Medicine Research Hospital, Ataturk University, were included in the study. In addition, 40 healthy volunteers with normal bone mineral density were included in the study. Approximately 10 mL of blood sample was taken from the participants' left brachial vein.

Biochemical processes

DNAs were isolated from the whole blood samples taken from all participants in the Molecular Analysis Laboratory of the Department of Medical Biochemistry, Faculty of Medicine, Atatürk University. The isolated DNAs were amplified by the polymerase chain reaction multiplex method using specific primers. Microchip hybridization using oligonucleotide probes was applied to amplicons. COL1A1 1997G/T, ESR1 PvuII, ESR1 XbaI, VDR BsmI, LCT T13910C, IL-6 G174C, OPG G209A, and OPG T245G gene regions were analyzed for variants.

Statistical analysis

The Statistical Package for the Social Sciences for Windows 22.0 (IBM, NY, USA) program was used in the statistical analysis of evaluating the data in the study. Categorical data were expressed as percentage and frequency. Continuous data were expressed as mean±standard deviation. In group comparisons, the chi-square test was used for categorical data and the independent samples t-test was used for continuous data.

RESULTS

The mean age of the osteoporosis patient group included in the study was 60.12±9.74 years, the mean age of the osteopenia patient group was 51.98±11.63 years, and the mean age of the control group was 43.50±12.09 years. Notably 93.33% (n=56) of the osteoporosis patient group, 90.00% (n=45) of the osteopenia patient group, and 77.50% (n=31) of the control group were women. There was a statistically significant difference in mean ages between the groups ($p<0.001$). Additionally, the ratio of female individuals in the osteoporosis patient group was higher than the ratio of female individuals in the control group ($p=0.021$). The genotype distribution of the groups is presented in Table 1.

No significant difference was found between the groups in terms of the genotype distributions of COL1A1 1997G/T, ESR1 PvuII, ESR1 XbaI, VDR BsmI, LCT T13910C, OPG T245G, and IL-6 G174C. In terms of the OPG G209A genotype distribution, no individual with an AA genotype was found in all three groups. Additionally, a significant difference was detected between the OPG G209A genotype distribution of both osteoporosis and osteopenia patient groups and the OPG G209A genotype distribution of the control group (Table 1).

DISCUSSION

Osteoporosis, which occurs as a result of decreased bone mineral density and bone microarchitecture deterioration, is a chronic skeletal disease common all over the world. The most common form is the form that occurs due to aging and causes serious mortality and morbidity. Rare forms are monogenic; they usually begin in childhood or young adulthood. The most common of these monogenic forms is related to mutations in COL1A2 and COL1A1, two genes encoding type I collagen[12]. A systematic review on osteoporosis in postmenopausal women reported no significant relation between the COL1A1 gene variant and osteoporosis risk in Asian or Caucasian women[13]. Another systematic review based on the clinical studies of osteoporosis reported that women with the COL1A1 1997G/T GG genotype had higher hip bone mineral density than women with the GT genotype, but COL1A1 gene variants alone are unlikely to play a role in the association with osteoporosis and fractures[14].

In this study conducted on the Turkish adult population, no difference was found in the distribution of the COL1A1 1997G/T gene variant between osteoporosis and osteopenia patients and healthy individuals.

The association between ESR1 gene variants and postmenopausal osteoporosis has been widely studied, but findings are

Table 1. The genotype distribution of the groups.

Genotype	Osteoporosis patient group (1) n=60, n (%)	Osteopenia patient group (2) n=50, n (%)	Control group (3) n=40, n (%)	p		
				(1–2)	(1–3)	(2–3)
Collagen type I alpha 1 (COL1A1) 1997G/T						
GG	40 (66.67)	30 (60.00)	25 (62.50)	>0.05	>0.05	>0.05
GT	14 (23.33)	13 (26.00)	9 (22.50)			
TT	6 (10.00)	7 (14.00)	6 (15.00)			
Estrogen receptor α (ESR1) PvuII						
TT	12 (20.00)	16 (32.00)	13 (32.50)	>0.05	>0.05	>0.05
TC	31 (51.67)	20 (40.00)	19 (47.50)			
CC	17 (28.33)	14 (28.00)	8 (20.00)			
Estrogen receptor α (ESR1) XbaI						
AA	22 (36.67)	23 (46.00)	22 (55.00)	>0.05	>0.05	>0.05
AG	25 (41.67)	17 (34.00)	11 (27.50)			
GG	13 (21.67)	10 (20.00)	7 (17.50)			
Vitamin D receptor (VDR) BsmI						
BB	9 (15.00)	8 (16.00)	4 (10.00)	>0.05	>0.05	>0.05
Bb	29 (48.33)	25 (50.00)	24 (60.00)			
Bb	22 (36.67)	17 (34.00)	12 (30.00)			
Lactase gene (LCT)						
TT	1 (01.67)	2 (04.00)	0 (00.00)	>0.05	>0.05	>0.05
TC	2 (03.33)	0 (00.00)	1 (02.50)			
CC	57 (95.00)	48 (96.00)	39 (97.50)			
Osteoprotegerin (OPG) G209A						
GG	54 (90.00)	45 (90.00)	40 (100.00)	>0.05	**0.042***	**0.048***
GA	6 (10.00)	5 (10.00)	0 (00.00)			
AA	0 (00.00)	0 (00.00)	0 (00.00)			
Osteoprotegerin (OPG) T245G						
TT	54 (90.00)	46 (92.00)	39 (97.50)	>0.05	>0.05	>0.05
TG	6 (10.00)	4 (08.00)	1 (02,50)			
GG	0 (00.00)	0 (00.00)	0 (00.00)			
Interleukin-6 (IL-6) G174C						
GG	33 (55.00)	26 (52.00)	20 (50.00)	>0.05	>0.05	>0.05
GC	21 (35.00)	22 (44.00)	19 (47.50)			
CC	6 (10.00)	2 (04.00)	1 (02.50)			

COL1A1: collagen type I alpha 1; ESR1: estrogen receptor α; VDR: vitamin D receptor; LCT: lactase gene; OPG: osteoprotegerin; IL-6: interleukin-6. *Statistically significant values (p<0.05) are denoted in bold.

conflicting. In a study examining the relationship between ESR1 gene variants and postmenopausal osteoporosis in the Chinese population, it was reported that only the ESR1 rs9340799 (XbaI) variant was related to postmenopausal osteoporosis[15]. On the other side, a systematic review on 36 observational studies involving five ESR-related gene variants, including 18,487 controls and 12,507 cases, stated that there was no relation between ESR1 gene variants and osteoporosis risk[16].

In this study, where two gene regions of the ESR1 gene were examined, no difference was determined in the distribution of ESR1 gene variants between osteoporosis and osteopenia patients and healthy individuals.

A recent systematic review indicates that VDR BsmI and TaqI gene variants may affect the risk of osteoporosis in Asians and Caucasians[17]. In another systematic review on VDR gene variants, it was stated that the VDR FokI variant in women and Indians and the VDR BsmI variant in West Asians may affect the risk of osteoporosis[18]. A study conducted on White British men associated the VDR TaqI variant with an increased risk of osteoporosis, but not the VDR BsmI and ApaI variants[19].

In this study, which included both male and female Turkish participants, no difference was found in the distribution of the VDR BSM gene variant between osteoporotic and osteopenic patients and healthy individuals.

Intravenous administration of adipose tissue-derived stem cells reduces bone loss in mice with osteoporosis. OPG, a natural inhibitor of RANKL receptor activator, is rich in adipose tissue-derived stem cells. Therefore, OPG inhibits osteoclast differentiation and reduces gene expression related to bone resorption[20]. In a systematic review, conducted on 14 studies including 2280 healthy controls and 2383 osteoporotic patients, it was reported that the G allele of the OPG A163G variant may increase the risk of osteoporosis in Caucasians, while the C allele of the OPG G1181C variant may reduce the risk of osteoporosis in Asians. Both these effects have been reported to be observed in postmenopausal women[21]. A study on Croatian postmenopausal women reported that the OPG A163G variant may have an impact on higher bone loss[22].

In this study, where two gene regions of the OPG gene were examined, no difference was found in the distribution of the OPG T245G gene variant between osteoporosis and osteopenia patients and healthy people. On the other hand, a difference was detected in the distribution of the OPG G209A gene variant between osteoporosis and osteopenia patients and healthy individuals.

In this study, also no difference was found in the distribution of LCT T13910C and IL-6 G174C gene variants between osteoporosis and osteopenia patients and healthy individuals.

CONCLUSION

In this study including both male and female Turkish adult participants, COL1A1 1997G/T, ESR1 PvuII, ESR1 XbaI, VDR BsmI, LCT T13910C, OPG T245G, and IL-6 G174C gene variants were not associated with the risk of osteoporosis and osteopenia. On the other hand, the OPG G209A gene variant may be related to the risk of osteoporosis and osteopenia.

AUTHORS' CONTRIBUTIONS

NU: Conceptualization, Project administration, Resources, Validation, Writing – original draft. **AhK:** Conceptualization, Project administration, Resources, Validation, Writing – original draft. **AdK:** Formal Analysis, Resources, Software, Visualization, Writing – review & editing.

REFERENCES

1. Arceo-Mendoza RM, Camacho PM. Postmenopausal osteoporosis: latest guidelines. Endocrinol Metab Clin North Am. 2021;50(2):167-78. https://doi.org/10.1016/j.ecl.2021.03.009
2. Ebeling PR, Nguyen HH, Aleksova J, Vincent AJ, Wong P, Milat F. Secondary osteoporosis. Endocr Rev. 2022;43(2):240-313. https://doi.org/10.1210/endrev/bnab028
3. McDonald MM, Khoo WH, Ng PY, Xiao Y, Zamerli J, Thatcher P, et al. Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption. Cell. 2021;184(5):1330-47.e13. https://doi.org/10.1016/j.cell.2021.02.002
4. Thomasius F, Hadji P. [Update on fracture prevention after menopause]. Ther Umsch. 2021;78(8):435-9. https://doi.org/10.1024/0040-5930/a001294
5. Lorentzon M, Abrahamsen B. Osteoporosis epidemiology using international cohorts. Curr Opin Rheumatol. 2022;34(5):280-8. https://doi.org/10.1097/BOR.0000000000000885
6. Chen Y, Yang S, Lovisa S, Ambrose CG, McAndrews KM, Sugimoto H, et al. Type-I collagen produced by distinct fibroblast lineages reveals specific function during embryogenesis and Osteogenesis Imperfecta. Nat Commun. 2021;12(1):7199. https://doi.org/10.1038/s41467-021-27563-3
7. Takai H, Matsumura H, Matsui S, Kim KM, Mezawa M, Nakayama Y, et al. Unliganded estrogen receptor α stimulates bone sialoprotein gene expression. Gene. 2014;539(1):50-7. https://doi.org/10.1016/j.gene.2014.01.063
8. Montazeri-Najafabady N, Dabbaghmanesh MH, Mohammadian Amiri R, Akbarzadeh M. Association of vitamin D receptor BsmI gene polymorphism with BMD Z-score in Iranian children and adolescents (9 - 18 years old). Int J Endocrinol Metab. 2019;17(2):e82677. https://doi.org/10.5812/ijem.82677
9. Udagawa N, Koide M, Nakamura M, Nakamichi Y, Yamashita T, Uehara S, et al. Osteoclast differentiation by RANKL and OPG signaling pathways. J Bone Miner Metab. 2021;39(1):19-26. https://doi.org/10.1007/s00774-020-01162-6
10. Tolonen S, Laaksonen M, Mikkilä V, Sievänen H, Mononen N, Räsänen L, et al. Lactase gene c/t(-13910) polymorphism, calcium intake, and pQCT bone traits in Finnish adults. Calcif Tissue Int. 2011;88(2):153-61. https://doi.org/10.1007/s00223-010-9440-6
11. Moffett SP, Zmuda JM, Cauley JA, Stone KL, Nevitt MC, Ensrud KE, et al. Association of the G-174C variant in the interleukin-6 promoter region with bone loss and fracture risk in older women. J Bone Miner Res. 2004;19(10):1612-8. https://doi.org/10.1359/JBMR.040707
12. Mäkitie RE, Costantini A, Kämpe A, Alm JJ, Mäkitie O. New insights into monogenic causes of osteoporosis. Front Endocrinol (Lausanne). 2019;10:70. https://doi.org/10.3389/fendo.2019.00070

13. Yu KH, Tang J, Dai CQ, Yu Y, Hong JJ. COL1A1 gene -1997G/T polymorphism and risk of osteoporosis in postmenopausal women: a meta-analysis. Genet Mol Res. 2015;14(3):10991-8. https://doi.org/10.4238/2015.September.21.11

14. Xie P, Liu B, Zhang L, Chen R, Yang B, Dong J, et al. Association of COL1A1 polymorphisms with osteoporosis: a meta-analysis of clinical studies. Int J Clin Exp Med. 2015;8(9):14764-81. PMID: 26628959

15. Shu J, Li J, Fu Y, Hui X, Jin Y, Chen M, et al. Association of ESR1 polymorphism rs2234693 and rs9340799 with postmenopausal osteoporosis in a Chinese population. BMC Musculoskelet Disord. 2020;21(1):346. https://doi.org/10.1186/s12891-020-03359-2

16. Ren H, Liu H, Huang L, Xie W, Lin D, Luo D. Association of ESR1 and ESR2 polymorphisms with osteoporosis: a meta-analysis from 36 studies. J Clin Densitom. 2022;25(4):699-711. https://doi.org/10.1016/j.jocd.2022.08.007

17. Jiang LL, Zhang C, Zhang Y, Ma F, Guan Y. Associations between polymorphisms in VDR gene and the risk of osteoporosis: a meta-analysis. Arch Physiol Biochem. 2022;128(6):1637-44. https://doi.org/10.1080/13813455.2020.1787457

18. Chen B, Zhu WF, Mu YY, Liu B, Li HZ, He XF. Association between vitamin D receptor BsmI, FokI, and Cdx2 polymorphisms and osteoporosis risk: an updated meta-analysis. Biosci Rep. 2020;40(7):BSR20201200.https://doi.org/10.1042/BSR20201200

19. Kow M, Akam E, Singh P, Singh M, Cox N, Bhatti JS, et al. Vitamin D receptor (VDR) gene polymorphism and osteoporosis risk in White British men. Ann Hum Biol. 2019;46(5):430-3. https://doi.org/10.1080/03014460.2019.1659851

20. Lee KS, Lee J, Kim HK, Yeom SH, Woo CH, Jung YJ, et al. Extracellular vesicles from adipose tissue-derived stem cells alleviate osteoporosis through osteoprotegerin and miR-21-5p. J Extracell Vesicles. 2021;10(12):e12152. https://doi.org/10.1002/jev2.12152

21. Guo L, Tang K, Quan Z, Zhao Z, Jiang D. Association between seven common OPG genetic polymorphisms and osteoporosis risk: a meta-analysis. DNA Cell Biol. 2014;33(1):29-39. https://doi.org/10.1089/dna.2013.2206

22. Cvijetic S, Grazio S, Kosovic P, Uremovic M, Nemcic T, Bobic J. Osteoporosis and polymorphisms of osteoprotegerin gene in postmenopausal women - a pilot study. Reumatologia. 2016;54(1):10-3. https://doi.org/10.5114/reum.2016.58755

ORIGINAL ARTICLE

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Evaluation of cinitapride's efficacy and safety in treating functional dyspepsia with overlapping symptoms: a real-world study in Chinese healthcare settings

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SUMMARY

OBJECTIVE: Cinitapride, a gastrointestinal prokinetic, is commonly used for treating functional dyspepsia. However, large-scale, real-world data on its efficacy, especially in patients with overlapping symptoms, are limited. The aim of this study was to evaluate the clinical effectiveness and safety of cinitapride in Chinese patients with functional dyspepsia, including those with overlapping symptoms, in a real-world setting.

METHODS: In this single-arm, prospective, multicentric study, 1,012 Chinese outpatients with functional dyspepsia and functional dyspepsia overlapping with gastroesophageal reflux disease, irritable bowel syndrome, and/or functional constipation were treated with cinitapride (1 mg t.i.d.) from May 2019 to March 2021. Symptom improvement was assessed at weeks 2 and 4, with adverse events recorded.

RESULTS: At weeks 2 and 4, the overall symptom improvement rate was 62.4 and 90.9%, respectively. Subgroup improvement rates were as follows: functional dyspepsia-gastroesophageal reflux disease, 86.8%; functional dyspepsia-irritable bowel syndrome, 96.2%; functional dyspepsia-functional constipation, 91.7%; and functional dyspepsia-gastroesophageal reflux disease-irritable bowel syndrome, 67.6%. functional dyspepsia patients showed statistically significantly higher improvement than those with overlapping symptoms at weeks 2 ($p=0.018$) and 4 ($p=0.009$). The dyspepsia symptom score decreased by 51.0% at week 2 and 74.4% at week 4 ($p<0.001$). The most common adverse event was asymptomatic electrocardiogram abnormalities (n=8).

CONCLUSION: Cinitapride is effective and well-tolerated in treating functional dyspepsia and functional dyspepsia-overlapping gastroesophageal reflux disease, irritable bowel syndrome, and functional constipation in Chinese patients.

KEYWORDS: Real-world. Cinitapride. Effectiveness. Safety. Dyspepsia. Comorbidity.

INTRODUCTION

Functional dyspepsia (FD), a common gastrointestinal disorder affecting around 20% of the population, is characterized by recurrent epigastric pain, postprandial fullness, and early satiety. Approximately 80% of patients with FD show no structural or biochemical abnormalities. The pathogenesis of FD is thought to involve disordered brain–gut signaling, leading to issues, such as disturbed gastroduodenal motility, visceral hypersensitivity, and altered gut microbiota and immune responses[1]. FD frequently overlaps with other gastrointestinal disorders, including gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), and/or functional constipation (FC). Studies report a 7.41% GERD-FD overlap, with 41.15% of GERD patients experiencing FD symptoms, and a 64% FD-IBS overlap in functional gastrointestinal disorder (FGID) patients[2,3]. Overlapping FD generally results in more severe symptoms, higher depression rates, impaired quality of life, and a greater economic and societal burden.

Prokinetics are a key component of FD pharmacotherapy and are recommended for symptom control in clinical guidelines[4].

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Traditional effective gastrointestinal tract promotility agents such as domperidone and cisapride were restricted for usage or withdrawn due to life-threatening cardiac arrhythmias. Considering the prevalence of FD and FD with overlapping symptoms worldwide, novel alternative gastrointestinal prokinetic drugs with good safety and efficacy are urgently needed.

Cinitapride, a benzamide-derived molecule, which exhibits agonistic activity at 5-hydroxytryptamine1 (HT1) and 5-hydroxytryptamine4 (5HT4) receptors and antagonistic activity at 5HT2 and D2 dopaminergic receptors[5], has been widely used in mild-to-moderate FD and GERD[6-8]. It has been proved that it is also effective for IBS and FC symptoms[9,10]. Cinitapride is of great benefit in accelerating gastrointestinal motility among preclinical studies and phase III and phase IV clinical trials[11-13]. Nevertheless, there is a lack of real-world data evaluating its effect on FD-overlapping symptoms.

Therefore, we investigated the clinical effectiveness and tolerability of cinitapride in Chinese patients with FD alone and FD with overlapping symptoms in a real-world setting, thus providing evidence for the treatment.

METHODS

Patients

From May 2019 to March 2021, 1,012 consecutive gastroenterology outpatients with FD were recruited across 12 sites in China. All patients met Rome IV diagnostic criteria, having experienced postprandial fullness, early satiety, or mid-upper abdominal discomfort for at least 6 months. Exclusion criteria included structural gastrointestinal diseases, mental impairments, allergies to cinitapride, or conditions likely to result in a follow-up loss.

Written informed consent was obtained from all patients prior to study participation. This study adhered to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Ethical approval was obtained from the Ruijin Hospital's Ethics Committee and all engaged centers. The study was registered with ChiCTR (www.chictr.org.cn, ChiCTR2000030949).

Study design

This was a multicentric, prospective, observational study conducted in a real-world setting. A face-to-face questionnaire survey at baseline was conducted for eligible patients. The questionnaire was designed based on Rome IV criteria, which mainly included patient's general information, relevant gastroscopy, barium meal (gastric emptying) test results, FD-related symptoms, and quality of life assessment. All enrolled patients were instructed to take cinitapride (1 mg, t.i.d.) for 4 weeks. Follow-ups were performed through on-site questionnaires or telephone questionnaires at the second and fourth weeks of the treatment.

Effectiveness evaluation

A questionnaire was used to assess dyspeptic symptoms, including postprandial fullness, early satiety, mid-upper abdominal pain, and burning discomfort. Symptom severity was self-assessed on a 5-point Likert scale: none (0), mild (1), moderate (2), severe (3), and extreme (4). Symptom frequency was also rated on a 5-point scale: none (0), <1 day/week (1), 1 day/week (2), >1 day/week (3), and every day (4)[14]. The total symptom score was calculated by multiplying each symptom's severity by its frequency, with a maximum score of 64. Treatment was deemed effective if the symptom improvement rate exceeded 50%. Primary endpoints were improvement rates at weeks 2 and 4.

Safety assessment

The occurrence of adverse events (AEs) was evaluated and recorded during the whole study. AE severity was categorized into mild, moderate, or severe, and the extent of severity refers that it led to hospitalization or death. Patients recruited in Shanghai Ruijin Hospital and Qingyuan People's Hospital were selected to take laboratory examinations including surface electrocardiogram (ECG), liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and renal function (creatinine) examinations at baseline and at week 4, thus actively monitoring the safety of the heart, liver, and kidney.

Statistical analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc.) on full analysis set (FAS) and safety analysis set (SS). Paired t-test or Wilcoxon signed-rank test was used for within-group comparisons and t-test or analysis of variance for between-group comparisons. Chi-square or Fisher's exact test was applied to categorical data. Statistical significance was set at $p<0.05$ with a 95% confidence interval.

RESULTS

Basline characteristics

In total, 1,012 patients receiving cinitapride treatment and at least one post-treatment safety evaluation were included in the SS, while 983 patients with post-baseline efficacy data were included in the FAS. Of the FAS, 68.9% (677/983) had FD alone and 31.1%

(306/983) had overlapping symptoms, including FD-GERD (49.7%), FD-IBS (35.3%), FD-FC (3.6%), FD-GERD-IBS (11.1%), and FD-IBS-FC (0.3%). A majority of the patients were aged 31–50 years (50.6%), with a balanced gender distribution (51.8% of females). The body mass index of 74.3% was within the normal range. Disease duration varied, with 50.7% having FD for 1–12 months and 38.1% for over 1 year. Most patients (66.9%) were treated with cinitapride monotherapy, while others received additional prokinetics, gastric mucosal protectors, antacids, or anti-*Helicobacter pylori* (Hp) drugs (Table 1).

Primary endpoint: effective rate of total symptom score improvement

Till March 2021, 983 patients with FD completed 4 weeks of treatment with cinitapride. As shown in Table 2, after 2 and 4 weeks of cinitapride treatment, the effective rate of total symptom score improvement of the total FD population had reached 62.4 and 90.9%, respectively. After 2 weeks of cinitapride treatment, the effective rate in the FD-alone group and FD combined with overlapping symptoms group was 65.8 and 55.0%, respectively. While after 4 weeks, the effective

Table 1. Demographic information and baseline characteristics of the enrolled patients.

	Patients (n=983) (n [%])		Patients (n=983) (n [%])
Age, years		Hp (+)	99 (10.1)
18–30	109 (11.1)	drugs	
31–50	497 (50.6)	Cinitapride alone	658 (66.9)
51–60	212 (21.6)	Prokinetics	196 (19.9)
>60	163 (16.6)	Mucosal protective drugs	112 (11.4)
Gender (female)	509 (51.8)	Antacids	178 (18.1)
BMI (18.5–23.9, kg/m^2)	730 (74.3)	Anti-Hp treatment	41 (4.2)
Course of disease		**Diagnosis**	
New diagnosis	9 (0.9)	FD	677 (68.9)
1 week–1 month	85 (8.6)	FD-overlapping symptoms	306 (31.1)
1 month–1 year	498 (50.7)	FD-GERD	152 (49.7)
>1 year	375 (38.1)	FD-IBS	108 (35.3)
Never smoke	696 (70.8)	FD-FC	11 (3.6)
Never drink	517 (52.6)	FD-GERD-IBS	34 (11.1)
Had Hp check	72 (7.3)	FD-IBS-FC	1 (0.3)

BMI: body mass index; Hp: ***Helicobacter pylori***; FD: functional dyspepsia; FD-GERD: functional dyspepsia-gastroesophageal reflux disease; FD-IBS: functional dyspepsia-irritable bowel syndrome; FD-FC: functional dyspepsia-functional constipation; FD-GERD-IBS: functional dyspepsia-gastroesophageal reflux disease-irritable bowel syndrome; FD-IBS-FC: functional dyspepsia-irritable bowel syndrome-functional constipation.

Table 2. Effective rate of total symptom score improvement among overall and subgroups.

	2 weeks	p-value	4 weeks	p-value
Overall samples	62.4% (598/958)		90.9% (871/958)	
FD alone	65.8% (434/660)	0.018*	92.2% (604/655)	0.009*
FD-overlapping symptoms	55.0% (164/298)		88.1% (267/303)	
FD-GERD	56.1% (83/148)	0.422#	86.8% (131/151)	0.001#
FD-IBS	58.7% (61/104)		96.2% (102/106)	
FD-GERD-IBS	35.3% (12/34)		67.6% (23/34)	
FD-FC and FD-IBS-FC	66.7% (8/12)		91.7% (11/12)	

*FD-alone group compared with the FD-overlapping symptom group; #comparisons between FD-overlapping symptom subgroups. p-value was obtained by Pearson's chi-square test. FD: functional dyspepsia; FD-GERD: functional dyspepsia-gastroesophageal reflux disease; FD-IBS: functional dyspepsia-irritable bowel syndrome; FD-GERD-IBS: functional dyspepsia-gastroesophageal reflux disease-irritable bowel syndrome; FD-FC: functional dyspepsia-functional constipation; FD-IBS-FC: functional dyspepsia-irritable bowel syndrome-functional constipation.

rate of these two groups had reached 92.2 and 88.1%, respectively. The FD group exhibited statistically significantly higher improvement rates in total symptom score compared to the FD with overlapping symptoms group, with a 9.2% difference at 2 weeks (p=0.018) and a 4.1% difference at 4 weeks (p=0.009).

Improvement rates in the total symptom score were not statistically significantly different between the subgroups of FD-overlapping symptoms at week 2 (p=0.422). However, with prolonged drug administration until 4 weeks, the effective rate of subgroups was statistically significantly different (p=0.001), while it was 86.8, 96.2, 67.6, and 91.7% in the FD-GERD, FD-IBS, FD-GERD-IBS, and FD-FC and FD-IBS-FC subgroups, respectively.

Secondary endpoints: dyspepsia symptom improvement rate

After 2 and 4 weeks of cinitapride treatment, the average dyspepsia symptom score in the total population decreased by 51.0 and 74.4%, respectively. At 4 weeks, all four main symptoms of dyspepsia improved by over 70%, with early satiety showing the highest improvement (80.6%). Improvement rates at 4 weeks were statistically significantly higher compared to 2 weeks (p<0.001). Patients with FD alone showed higher symptom improvement rates than those with overlapping symptoms, with total score differences at 2 weeks (53.77 vs. 46.68%, p=0.001) and 4 weeks (77.15 vs. 69.34%, p<0.001). Early satiety improved the most in the FD-IBS group, with an 87.2% decrease (p=0.002), while postprandial fullness showed the greatest improvement in the FD-GERD group (71.8%, p=0.073). Epigastric pain/burning improved significantly in the FD-IBS group, with symptom relief rates of 83.8 and 92.8% (p=0.001 and p=0.004, respectively). Additionally, the FD-IBS group had the largest decrease in the total symptom score, showing a reduction of 73.18% (p=0.002).

Safety analysis

All patients who received cinitapride therapy and underwent at least one post-treatment safety evaluation were enrolled in the SS. Of the 1,012 patients, 3 cases of AE were observed during follow-up at week 2, including gastric distention (n=1), dizziness (n=1), and nausea (n=1), with an incidence rate of 0.29%, of which no cases of serious adverse events (SAEs) were reported. All these symptoms were mild and recovered soon after drug discontinuation.

Considering the safety of cinitapride on the heart, liver, and kidney, patients at Ruijin Hospital and Qingyuan People's Hospital (n=94) were actively monitored by laboratory examination at baseline and 4 weeks after initial treatment. In these 94 samples, 8 people experienced mild ECG abnormalities including alteration in ST-T waves (n=4), sinus arrhythmia (n=3), and high left ventricular voltage (n=1), while no cases of prolonged QT interval were found. One patient showed slight elevations in AST (42 IU/L, normal level 8–40 IU/L) (Table 3). Cinitapride treatment resulted in an 8.1% incidence of AEs after 4 weeks.

DISCUSSION

Cinitapride, a benzamide derivative, stimulates 5-HT4 and 5-HT1 and blocks the 5-HT2 and D2 receptors. The gastrointestinal motility effect of cinitapride is mainly achieved by enhancing acetylcholine release via stimulating 5-HT4 receptors and antagonizing the dopamine D2 receptor. Cinitapride demonstrates greater in vitro stimulatory activity on guinea pig intestinal smooth muscle than metoclopramide, suggesting a mechanism involving enhanced acetylcholine release from intramural cholinergic neurons. Previous studies have also demonstrated that cinitapride has gastroprotective effects to improve gastric ulceration and secretion in rats, which could be partly explained through 5-HT-dependent mechanisms via 5-HT_2R antagonism and 5-HT_1R agonism.

Although results on the effectiveness of cinitapride have been inconsistent, clinical guidelines recommend prokinetic agents as first-line treatment for FD[15]. Several randomized

Table 3. Adverse events and laboratory abnormalities during treatment.

AEs	2 weeks (n [%])	4 weeks (n [%])
Any AE	3 (0.29)	9 (8.1)
Serious adverse reactions	0	0
Gastric distention	1	0
Dizziness	1	0
Nausea	1	0
Abnormal laboratory examination		
ECG abnormalities		8 (7.2)
Alteration in ST-T waves		4
High left ventricular voltage		1
Sinus arrhythmia (tachycardia/bradycardia)		3
Prolonged QT interval		0
Elevations in ALT		0
Elevations in AST		1 (0.9)
Elevated serum creatinine		0

ECG: electrocardiogram; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AE: adverse event; ST-T: ST segment and T wave abnormalities; QT: corrected QT interval (Bazett formula).

controlled trials have investigated cinitapride's efficacy in FD patients. Phase I studies showed similar therapeutic efficacy between metoclopramide and cinitapride, with good tolerability in healthy Chinese subjects at doses of 1–4 mg. Phase II studies demonstrated better efficacy and tolerability of cinitapride compared to metoclopramide and placebo for gastrointestinal transit disorders. A Phase III trial confirmed cinitapride's non-inferiority to domperidone in patients with mild-to-moderate postprandial distress syndrome-predominant FD. Additionally, a Phase IV study in Pakistan showed that cinitapride effectively controlled dyspepsia symptoms and improved patients' quality of life. However, real-world data on cinitapride's effectiveness, especially in patients with overlapping symptoms, remain limited. This study is the first real-world evaluation of cinitapride's efficacy and safety in FD and FD with overlapping symptoms.

In the current study, cinitapride proved effective in treating both FD and FD with overlapping symptoms. Following 2 and 4 weeks of treatment, the effective rate of total symptom score improvement reached 62.4 and 90.9%, respectively. Dyspepsia symptom scores decreased by 51.0% at week 2 and 74.4% at week 4. Significant improvements were seen in the four main dyspeptic symptoms—postprandial fullness, early satiety, epigastric pain, and epigastric burning—at both time points, with the improvement rate for early satiety reaching 80.6% by week 4. A statistically significant improvement in dyspepsia symptom scores was observed between weeks 2 and 4 ($p<0.001$), highlighting the benefits of continued cinitapride use for at least 4 weeks.

In real-world settings, FD is often complicated by overlapping symptoms, which can worsen patient outcomes and reduce quality of life. This study, the first of its kind, evaluated cinitapride's efficacy in patients with overlapping symptoms. After 4 weeks, the FD-IBS subgroup showed the highest effective rate of total symptom score improvement (96.2%), while the FD-GERD, FD-GERD-IBS, and FD-FC and FD-IBS-FC subgroups had effective rates of 86.8, 67.6, and 91.7%, respectively. In the FD-IBS subgroup, early satiety showed the largest symptom score reduction, decreasing by 87.2% at week 4. The FD-GERD subgroup showed the most improvement in postprandial fullness (71.8%), while the FD-IBS subgroup demonstrated the most improvement in epigastric pain and burning, with symptom reductions of 83.8 and 92.8%, respectively. The FD-IBS subgroup also had the largest decrease in the total symptom score (73.2%). These results suggest that cinitapride's effectiveness varies depending on the specific overlapping symptoms, with the best outcomes seen in FD patients who also have IBS. Epidemiological studies have shown high rates of overlap between FD, GERD, and IBS, indicating potential shared pathophysiological mechanisms. This study's findings further support the theory that cinitapride may target common mechanisms underlying these overlapping conditions.

When comparing the efficacy of cinitapride in patients with FD alone versus those with overlapping symptoms, the results indicated that patients with FD alone responded better, with higher rates of total symptom score improvement and dyspepsia symptom improvement. The reduced efficacy in patients with overlapping symptoms may be due to the increased complexity and severity of their conditions. The precise mechanism by which cinitapride affects FD with overlapping symptoms is still unclear but may involve shared pathophysiological mechanisms, such as delayed gastric emptying, impaired gastric accommodation, and possibly the peripheral opioid system.

Adverse reactions to cinitapride, such as exanthema, sore throat, extrapyramidal symptoms, and unexplained increases in globulin levels, have been reported in previous studies[12,13,16]. However, no severe adverse events were noted in this study. Traditional prokinetic agents such as domperidone, mosapride, and cisapride were withdrawn due to cardiac safety concerns[17-19], making cinitapride's safety profile particularly important. In this real-world study, cinitapride was well tolerated, with no signs of hepatorenal or cardiac toxicity. Mild ECG abnormalities were reported in eight cases, but none were symptomatic, and no QT interval prolongation was observed, consistent with prior studies[20]. A mild, asymptomatic increase in AST was noted in one patient, but no serious adverse reactions occurred throughout the study. Cinitapride is rapidly absorbed and primarily metabolized by CYP3A4 and CYP2C8, which may reduce the risk of drug interactions.

This is the first study to analyze the efficacy and safety of cinitapride on FD with overlapping symptoms and also the first study to be conducted in a real-world setting. This real-world, multicentric, prospective, non-interventional study with a large sample size is relatively persuasive. However, patient compliance management is usually regarded as a difficult part in real-world studies. Of the 1012 enrolled cases, 29 were excluded due to missing follow-up data, which might be due to that, after the treatment, a satisfactory effect has been achieved and the patient's willingness to return to hospital has decreased. Patient compliance is an important factor affecting the outcome of clinical studies, especially in real-world settings. In our study, we have taken a number of measures to improve patient compliance, such as patient education, medication guidance, and regular follow-ups. In future studies, incentives could be developed to encourage patients to follow up on time, such as providing transportation subsidies, and electronic reminders,

regular follow-up phone calls, or text reminders could be used to further improve patient compliance.

CONCLUSION

To sum up, in this first real-world study on the clinical effectiveness and safety of cinitapride among Chinese FD and FD-overlapping GERD, IBS, and FC population, our findings demonstrate that cinitapride is efficacious and well tolerated.

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AUTHORS' CONTRIBUTIONS

BY: Conceptualization, Data curation, Writing – original draft. **SW:** Formal Analysis, Investigation. **JC:** Methodology, Project administration. **XZ:** Resources, Software. **BW:** Validation, Visualization. **YW:** Formal Analysis, Methodology. **JW:** Investigation, Project administration. **NZ:** Resources, Visualization. **JS:** Funding acquisition, Supervision, Writing – review & editing. **DZ:** Funding acquisition, Supervision, Writing – review & editing.

REFERENCES

1. Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. Lancet. 2020;396(10263):1689-702. https://doi.org/10.1016/S0140-6736(20)30469-4
2. Geeraerts A, Houtte B, Clevers E, Geysen H, Vanuytsel T, Tack J, et al. Gastroesophageal reflux disease-functional dyspepsia overlap: do birds of a feather flock together? Am J Gastroenterol. 2020;115(8):1167-82. https://doi.org/10.14309/ajg.0000000000000619
3. Wulffen M, Talley NJ, Hammer J, McMaster J, Rich G, Shah A, et al. Overlap of irritable bowel syndrome and functional dyspepsia in the clinical setting: prevalence and risk factors. Dig Dis Sci. 2019;64(2):480-6. https://doi.org/10.1007/s10620-018-5343-6
4. Moayyedi P, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017;112(7):988-1013. https://doi.org/10.1038/ajg.2017.154
5. Zhang X, Wang Y, Cheng J, Hu Y, Liu J, Chen J, et al. Pharmacokinetics and tolerability of cinitapride in healthy Chinese volunteers: a randomized, open-label, single- and multiple-dose study. Xenobiotica. 2019;49(3):313-21. https://doi.org/10.1080/00498254.2018.1447710
6. Marcelín-Jiménez G, Contreras L, Esquivel J, Ávila Ó, Batista D, Ángeles AP, et al. Development of an UPLC-MS/MS micromethod for quantitation of cinitapride in plasma and its application in a pharmacokinetic interaction trial. Bioanalysis. 2017;9(6):569-79. https://doi.org/10.4155/bio-2016-0210
7. Qi Q, Wang N, Liu H, Li Y. Prokinetics for the treatment of functional dyspepsia: an updated systematic review and network meta-analysis. BMC Gastroenterol. 2023;23(1):370. https://doi.org/10.1186/s12876-023-03014-9
8. Surós A, Adell F, Novoa V, Castellarnau J, Diosdado D, Carrasquer J, et al. [Cinitapride in the treatment of gastroesophageal reflux. Comparative study with metoclopramide and placebo]. Rev Med Univ Navarra. 1992;37(1):18-23. PMID: 1626164
9. Herrerias JM, Garcia MM. [Non-ulcerative dyspepsia with primary functional constipation. Evaluation of its treatment with cinitapride combined or not with methylcellulose]. Rev Med Univ Navarra. 1993;38(1):30-5.
10. Patelg H. Development and validation of HPLC method for simultaneous estimation of cinitapride and pantoprazole in pharmaceutical dosage form; 2012.
11. Massingham R, Bou J, Roberts DJ. A comparison of the stimulatory effects of metoclopramide and cinitapride in the guinea-pig isolated ileum. J Auton Pharmacol. 1985;5(1):41-53. https://doi.org/10.1111/j.1474-8673.1985.tb00564.x
12. Du Y, Su T, Song X, Gao J, Zou D, Zuo C, et al. Efficacy and safety of cinitapride in the treatment of mild to moderate postprandial distress syndrome-predominant functional dyspepsia. J Clin Gastroenterol. 2014;48(4):328-35. https://doi.org/10.1097/MCG.0000000000000033
13. Baqai MT, Malik MN, Ziauddin F. Efficacy and safety of cinitapride in functional dyspepsia. J Pak Med Assoc. 2013;63(6):747-51. PMID: 23901678
14. Melchior C, Desprez C, Wuestenberghs F, Leroi AM, Lemaire A, Goucerol G. Impact of opioid consumption in patients with functional gastrointestinal disorders. Front Pharmacol. 2020;11:596467. https://doi.org/10.3389/fphar.2020.596467
15. Oh JH, Kwon JG, Jung HK, Tae CH, Song KH, Kang SJ, et al. Clinical practice guidelines for functional dyspepsia in Korea. J Neurogastroenterol Motil. 2020;26(1):29-50. https://doi.org/10.5056/jnm19209
16. González Gutiérrez ML, Rubio Pérez M, Vázquez Cortés S, Martínez González Lema B. Cinitapride-induced exanthema. J Investig Allergol Clin Immunol. 2010;20(2):174. PMID: 20461977
17. Doggrell SA, Hancox JC. Cardiac safety concerns for domperidone, an antiemetic and prokinetic, and galactogogue medicine. Expert

Opin Drug Saf. 2014;13(1):131-8. https://doi.org/10.1517/14740338.2014.851193

18. Benatar A, Feenstra A, Decraene T, Vandenplas Y. Effects of cisapride on corrected QT interval, heart rate, and rhythm in infants undergoing polysomnography. Pediatrics. 2000;106(6):E85. https://doi.org/10.1542/peds.106.6.e85

19. Endo J, Nomura M, Morishita S, Uemura N, Inoue S, Kishi S, et al. Influence of mosapride citrate on gastric motility and autonomic nervous function: evaluation by spectral analyses of heart rate and blood pressure variabilities, and by electrogastrography. J Gastroenterol. 2002;37(11):888-95. https://doi.org/10.1007/s005350200150

20. Robert M, Salvà M, Segarra R, Pavesi M, Esbri R, Roberts D, et al. The prokinetic cinitapride has no clinically relevant pharmacokinetic interaction and effect on QT during coadministration with ketoconazole. Drug Metab Dispos. 2007;35(7):1149-56. https://doi.org/10.1124/dmd.106.010835

ORIGINAL ARTICLE

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"Organ transplantation was a second chance given to me": a qualitative study of the experiences of solid organ transplantation patients

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SUMMARY

OBJECTIVE: The aim of this study was to qualitatively examine the needs of patients undergoing organ transplantation.
METHODS: The sample of the study consisted of 17 patients. Data were evaluated using Colaizzi's seven-stage content analysis method.
RESULTS: Two themes such as returning to daily life after organ transplantation and difficulties experienced after organ transplantation were determined.
CONCLUSION: Individuals experienced physiological problems and fear of rejection after organ transplantation. Moreover, patients who experienced rejection fell into despair. However, their quality of life increases in the long term. Besides, individuals could not receive social support during transplantation.
KEYWORDS: Organ grafting. Requirements. Transplantation. Qualitative research.

INTRODUCTION

Currently, there is no treatment option available other than organ transplantation for resuscitation of patients[1,2]. Organ transplants vary from country to country around the world but are obtained from cadaver donors. However, there are not enough organs to meet the need, and the number of patients waiting for transplantation is increasing day by day[3-5]. Turkey ranks first in the world among the countries that receive organ transplants from living donors[6].

In the transplantation process, providing the best conditions for the donor and the recipient, improving the quality of life in the later period, and meeting the information needs are as important as the successful transplantation of the organ[2,4]. Although the health-related quality of life increases after transplantation, the level of the quality of life of healthy people cannot be reached[4,7]. After transplantation, individuals experience many problems, including pain because of surgery, nausea, vomiting, susceptibility to infections, loss of concentration, hair loss, loss of sexual desire, and depressive feelings because of immunosuppressive drugs. These symptoms can negatively affect the individual's quality of life and impair their adherence to treatment[7,8]. All these may cause feelings such as hopelessness, anxiety, and fear after transplantation, which may negatively affect the patients' compliance with treatment.

Transplantation is quite challenging for patients. Hence, this qualitative study was conducted to examine the needs of patients who underwent solid organ transplantation.

METHODS

Type of research

This research is a phenomenological qualitative study carried out to examine the needs of patients who underwent solid organ transplantation.

Qualitative research is especially recommended when complex issues need to be explored in depth. Phenomenology is a qualitative research method used in the in-depth investigation of experiences, enabling individuals to express their perspectives and perceptions[9].

Participants

Social media increases communication and interactions about health. Today, people seek answers to issues related to their health by using social media tools, and health professionals answer the questions of individuals using these tools[10]. Facebook is one of the most popular social media platforms[11].

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The universe of the research consisted of patients in groups created about organ transplantation on Facebook. The purposive sampling method was used in the study. The sample of the study consisted of patients who had stated in these Facebook groups that they had undergone transplantation, had posts to search for post-transplant information, and met the inclusion criteria of the study.

The inclusion criteria for the study were as follows: (1) Patients who are included in groups about organ transplantation on Facebook; (2) solid organ transplant patients; and (3) those aged 18 years and older and agreed to participate in the study.

Qualitative studies do not have a fixed sample size and interviews should continue until data saturation is reached[12,13]. The present study was completed with 17 patients whose data started to repeat, and data saturation was reached.

Data collection

The data were collected via mobile phone by the researcher (EAG), who is a psychiatric nurse specialist and experienced in qualitative research, between April 15 and June 15, 2022, using an introductory information form and a semi-structured interview form.

Introductory information form: In this form, there are 12 questions regarding introductory information.

Semi-structured interview form: This form consists of four open-ended questions developed by the authors after reviewing the relevant literature[8] (Table 1).

First, a private message was sent to individuals who stated that they had undergone transplantation and had been seeking information in the aforementioned Facebook groups. The purpose of the study was explained to these individuals and they were invited to the study. The interviews were audio recorded with the consent of the participants. The interviews lasted an average of 30–35 min. Incomprehensible questions and answers were repeated. A single interview was conducted with each participant.

Rigor and trustworthiness

The reliability of the data was obtained based on the strategies determined by Jiggins Colorafi and Evans[14]. These strategies are consistency, confirmability, reliability, and transferability. For consistency, all interviews were conducted by the same researcher. For confirmability, the data were transferred to a computer, stored, and analyzed independently by two researchers (YS and EAG). For the reliability of the study, the participants were encouraged to freely express their views at the beginning of the interview. An expert opinion was taken for the suitability of the interview forms. In addition, two experts experienced in qualitative research were consulted in order to confirm whether the sub-themes given under the conceptual theme reached in the research represent the mentioned conceptual category. Experts agreed that the sub-themes represent the themes. Participant confirmation was obtained to ensure reliability. The study is transferrable since data saturation is ensured. In this study, sample selection, participant characteristics, and how the study was conducted were explained in detail to ensure transferability.

Research team

The research team consisted of three researchers who are academicians. The first researcher has a doctorate in surgical nursing and has performed studies on organ transplantation. The second researcher has a doctorate in psychiatric nursing, and the third researcher who conducted the interviews was a psychiatric nurse who ensured the sustainability of effective communication and interviews with the participants. All the researchers have scientific research experience in qualitative research.

Data analysis

Data were evaluated using Colaizzi's seven-stage content analysis method[15]. The interviews were transcribed word for word. All data were read multiple times by two researchers, and important statements were underlined. Meanings were formed from important expressions. Important statements were decided based on their frequent repetition by the patients and their occurrence in the literature. Frequently repeated common statements were grouped and categorized, and themes and sub-themes were created by revealing the relationships between the categories. The created themes and sub-themes were integrated with the patients' experiences. The basic framework of the experiences of the patients who had undergone transplant surgery was established. Finally, the data obtained from the interviews were summarized and the patients were asked whether they wanted

Table 1. Semi-structured interview questions.

What has changed in your life after organ transplantation?
What are the difficulties/problems you experience after organ transplantation?
How did the pandemic period affect your disease process as a transplanted individual?
What are the problems you encountered as an organ transplant individual during the pandemic period?

to add any statements regarding the accuracy of the data, but they did not make any additions.

The themes were supported by direct quotations[12]. The Consolidated Criteria for Reporting Qualitative Research checklist was followed during the study[16].

Ethical consideration

Ethics committee approval (2022-122) was obtained from Erciyes University Social and Human Sciences, and verbal informed consent was obtained from the patients.

RESULTS

In this study, 76.5% of the patients were male, 70.5% were married, and their mean age was 45.52±11.97 years. Notably, 70.5% of the patients had a liver transplant, all patients received transplants from a living donor, and 64.7% of them received organs from their relatives (Table 2).

Three main themes and five sub-themes were determined and are summarized in Table 3.

Theme 1. Return to daily life after organ transplantation

Some of the patients stated that they regained their old health and life after transplantation. Some of the patients stated that they changed their environment after transplantation.

Sub-theme 1.1. Restoring health

Some of the patients stated that they regained their old health, their appetite had increased, and they paid more attention to their health than before.

> "*I started living healthy. I cut out everything unhealthy from my life. The transplant was a second chance given to me*" *(P-8, F, 42 years)*.

Sub-theme 1.2. Change of environment

Some of the patients mentioned that they kept a distance from their relatives, who stayed away from them in order not to donate organs.

> "*My environment has changed. When I was in such trouble, my relatives were not with me. When you are in trouble, you expect support from your relatives*" *(P-7, M, 58 years)*.

Theme 2. Difficulties experienced after organ transplantation

Some of the patients stated that they had some physical problems after transplantation, most of them experienced fear of rejection, and some of them stated that they experienced rejection. Most of the patients stated that they were worried about the health of their donor.

Table 2. Demographic variables of the patients (n=17).

Demographic variables	n	%
Gender		
Female	4	23.5
Male	13	76.5
Age (mean±SD [min–max])	45.52±11.97 (30–67)	
Waiting time for transplantation	1.76±2.18 (0–6 years)	
Average time after transplantation	7.52±6.04 (2–19 years)	
Marital status		
Married	12	70.5
Single	5	29.5
Occupation		
Worker	7	41.1
Retired	6	35.2
Officer	2	11.8
Not working	2	11.8
Transplanted organ		
Kidney	5	29.5
Liver	12	70.5
Donor type*		
Relatives	11	64.7
Unknown person	6	36.3

*All donors were living donors. SD: standard deviation.

Table 3. Themes and sub-themes.

Themes	Sub-themes
Return to daily life after organ transplantation	• Restoring health • Change of environment
Difficulties experienced after organ transplantation	• Physiological problems • Rejection and fear of rejection • Fear that something will happen to the donor

Sub-theme 2.1. Physiological problems

Some of the patients stated that they experienced physiological problems, such as edema, stenosis, and long-term drains after the transplant surgery.

> "*The complications of the surgery made me very exhausted. My drains were left too long. There have been strictures. It forced me for 9 months*" *(P-11, M, 59 years)*.

Sub-theme 2.2. Rejection and fear of rejection

Some of the patients stated that rejection developed after the organ transplant surgery and they needed to be transplanted again, while some of them stated that they experienced fear because of the risk of rejection after the transplant.

> "*There was a protein leak in 2015. I had COVID-19 and a lung infection twice. This caused my kidney to fail and reject. I had the second COVID-19 very hard. I need to be transplanted again*" *(P-16, M, 41 years)*.

Most of the patients stated that they were afraid of experiencing rejection.

Sub-theme 2.3. Fear that something will happen to the donor

Some of the patients stated that they were worried about the health of their relatives who donated organs for organ transplantation, and they felt responsible.

> "*I had a very stressful surgery. I was terrified. I was anxious that something would happen to the donor of the liver. I have established close relations with the donor*" *(P-7, M, 58 years)*.

DISCUSSION

Although significant progress has been made in recent years with the development of technology, drugs, and surgical techniques, organ supply remains the primary problem[17]. In this study, it was found that 17 participants had similar experiences in the post-transplantation period, such as paying attention to a healthy life, fear of something happening to donors, and environmental changes.

The period with the highest incidence of infection in the post-transplantation period is between the first and sixth months[17,18]. In this study, individuals experienced physiological problems, such as edema and stenosis, in the early post-transplantation period, but their quality of life increased afterward, and individuals saw transplantation as a second chance and tried to lead a more regular life. Studies have shown that individuals experience problems, such as infection, especially in the first months after transplantation[2,19]. In the study conducted by Dinkçi et al., individuals experienced problems, especially in the first month, and their condition improved toward the sixth month[18].

Organ transplantation is a process where hard experiences are experienced by the individuals before, during, and after transplantation. Individuals can be more sensitive during this period and seek more support from their relatives[6]. In this study, patients kept a distance from their relatives, who stayed away from them in order not to donate organs.

Fear of organ rejection, acceptance of the new organ, and psychosocial support systems are very important in coping with the disease[20]. Individuals may have concerns about loss of function, medical care costs, and organ rejection[2,19,20]. In this study, some of the patients stated that rejection developed after the organ transplant surgery and they needed to be transplanted again, while others stated that they had a fear of and hopelessness because of rejection after transplantation. The results are in line with the literature[2,19,20].

In a qualitative study, it has been stated that individuals experience feelings of gratitude and guilt toward the organ donor[21]. Similarly, in this study, some of the patients stated that they were worried about the health of their relatives, who donated organs for organ transplantation, and that they felt responsible.

CONCLUSION

After organ transplantation, individuals experienced physiological problems, such as edema, stenosis, and long drains, and some symptoms such as rejection and fear of rejection appeared, but their health was regained in the long term. Some individuals could not get support from their relatives during transplantation.

AUTHORS' CONTRIBUTIONS

YS: Conceptualization, Writing – review & editing. **EAG:** Data curation, Formal Analysis, Writing – review & editing. **HT:** Data curation, Formal Analysis, Writing – review & editing.

REFERENCES

1. Gülen H, Karaca A. Donor education and nursing care in the organ transplantation process. J Duzce Univ Institute Health Sci. 2018;8:83-8.
2. Soylu D, Tuna A. Nursing care in cadaver organ transplantation processes. Turkiye Klinikleri J Intern Med. 2020;5:62-9.
3. Black CK, Termanini KM, Aguirre O, Hawksworth JS, Sosin M. Solid organ transplantation in the 21st century. Ann Transl Med. 2018;6(20):409. https://doi.org/10.21037/atm.2018.09.68
4. Öden TN, Korkmaz FD. Responsibilities of the nurse in increasing the rate of organ transplantation from cadaver donor: what can we do in the field? J Celal Bayar Univ Health Sci Institute. 2021;8:558-65.
5. Gruessner RWG, Gruessner AC. Solid-organ transplants from living donors: cumulative United States experience on 140,156 living donor transplants over 28 years. Transplant Proc. 2018;50(10):3025-35. https://doi.org/10.1016/j.transproceed.2018.07.024
6. Andacoglu O, Aki FT. Global perspective on kidney transplantation: Turkey. Kidney360. 2021;2(7):1160-2.
7. Çelik Ö, Ürer E, Bayram EC, Kılıç BG. The importance of psychiatric support and treatment in a child with heart transplant. J Clin Psychiatry. 2019;22:487-92.
8. Ordin YS, Karayurt Ö. Effects of a support group intervention on physical, psychological, and social adaptation of liver transplant recipients. Exp Clin Transplant. 2016;14(3):329-37. https://doi.org/10.6002/ect.2014.0220
9. Hossain MS, Alam MK, Ali MS. Phenomenological approach in the qualitative study: data collection and saturation. ICRRD Qual Index Res J. 2024;5(2):147-72. https://doi.org/10.53272/icrrd.v5i2.4
10. Chen J, Wang Y. Social media use for health purposes: systematic review. J Med Int Res. 2021;23(5):e17917.
11. Sindermann C, Duke É, Montag C. Personality associations with Facebook use and tendencies towards Facebook use disorder. Addict Behav Rep. 2020;11:100264.
12. Kyngäs H, Mikkonen K, Kääriäinen M. The application of content analysis in nursing science research. Springer Nat. 2019;3:13-21. https://doi.org/10.1007/978-3-030-30199-6
13. Mwita K. Factors influencing data saturation in qualitative studies. Int J Res Bus Soc Sci. 2022;11(4):414-20.
14. Colorafi KJ, Evans B. Qualitative descriptive methods in health science research. HERD. 2016;9(4):16-25. https://doi.org/10.1177/1937586715614171
15. Colaizzi P.F. Psychological research as the phenomenologist views it. In: Valle R, King M, editors, Existential phenomenological alterations for psychology, Oxford University Press; 1978. p. 48-71.
16. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349-57. https://doi.org/10.1093/intqhc/mzm042
17. Svobodová I, Honsová E. [Infections after kidney transplantation]. Cesk Patol. 2015;51(3):120-2. PMID: 26421952
18. Dinkçi S, Kibar F, Demir E, Paydas S, Erdoğan S, Yaman A. Böbrek nakli yapılan hastalarda nakil öncesi ve nakil sonrası enfeksiyon etkenlerinin sıklığı. Cukurova Med J. 2022;47:1050-8.
19. Demir Korkmaz F, Öden TN. Intensive care process of liver transplant patient. Turkiye Klinikleri J Nurs Sci. 2021;13(1):139-51. https://doi.org/10.5336/nurses.2020-75828
20. Çelik Ö, Ürer E, Bayram E.C, Kılıç BG. The importance of psychiatric support and treatment in a child with heart transplantation. J Clin Psy. 2019;22(4):487-92. https://doi.org/10.5505/kpd.2019.98704
21. Gündüz ES, Akyolcu N. The effect of end-stage renal disease on psychosocial life, coping methods and patients' organ transplant perception: a qualitative research. Gevher Nesibe J Med Health Sci. 2020;5:67-79. https://doi.org/10.46648/gnj.106

ORIGINAL ARTICLE

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The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography SUV_{Max} in deciding on a computed tomography-guided lung biopsy in solid solitary pulmonary nodules

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SUMMARY

OBJECTIVE: The aim of this study was to calculate a useful cut-off point of the ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography SUV_{Max} value to decide on a computed tomography-guided percutaneous transthoracic needle biopsy for solitary pulmonary nodules of sizes between 11 and 20 mm.

METHODS: Between January 2015 and April 2020, patients with solitary pulmonary nodules who underwent computed tomography-guided percutaneous transthoracic needle biopsy were retrospectively reviewed, and those with solitary pulmonary nodules of 11–20 mm in diameter, who had undergone an ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography examination before computed tomography-guided percutaneous transthoracic needle biopsy, were included in the study. A total of 76 patients who met the inclusion criteria were evaluated.

RESULTS: There was no distinguishing finding on the computed tomography examination ($p>0.05$). The SUV_{Max} values of the malignant solid solitary pulmonary nodules were higher than the benign solitary pulmonary nodules ($p<0.05$).

CONCLUSION: The benign and malignant solid solitary pulmonary nodules between 11 and 20 mm have similar computed tomography features. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography is a useful imaging technique for distinguishing benign and malignant solitary pulmonary nodules. Notably, 4.85 SUV_{Max} value can be used to decide on a computed tomography-guided percutaneous transthoracic needle biopsy procedure in solid solitary pulmonary nodules between 11 and 20 mm with excellent sensitivity and moderate specificity rates.

KEYWORDS: Solitary pulmonary nodule. Biopsy. Needle. CT scans. Fluorodeoxyglucose F18.

INTRODUCTION

A solitary pulmonary nodule (SPN) is a single, spherical, or oval-shaped radiopaque lesion smaller than 30 mm in diameter, which is completely surrounded by pulmonary parenchyma[1]. It was reported that changes in the diagnostic yield of computed tomography biopsy significantly altered preferences when the probability of malignancy was 10 or 30% of current smokers or ex-smokers[2]. The malignancy rate is approximately 30% for SPNs with a diameter of 21–30 mm and approximately 12% for those with a diameter of 11–20 mm[3]. The 5-year survival rate for lung cancer is approximately 15.6% since it is diagnosed in an advanced stage in most patients[4]. Therefore, the early diagnosis of malignant SPNs is critical to increase the survival of lung cancer patients.

CT-PTNB is a safe and effective minimally invasive procedure with high diagnostic accuracy[5]. Nodule size is one of the major risk factors for increased complication rates[6]. The smaller size of SPNs increases the failure rate of accessing the target lesion, the rate of insufficient tissue sampling, and the rate of false-negative results, and it is also linked to a higher complication rate[7,8]. Therefore, it may be difficult to decide on a CT-PTNB procedure due to the higher risk of complications and inadequate biopsy results, especially in SPNs under 20 mm. As an alternative to tissue sampling in managing solid SPNs larger than 8 mm, regardless of risk group, a 3-month thorax CT and/or PET/CT follow-up is recommended by the Fleischner Society guidelines[9].

^{18}F-FDG PET/CT is a metabolic imaging method routinely performed in oncology practice[10]. ^{18}F-FDG PET/CT has been successfully used to investigate SPNs since 2000s[11]. In literature, although many publications have reported the role of ^{18}F-FDG PET/CT, there is no consensus on the cut-off value of SUV_{Max} in different size pulmonary nodules.

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The aim of this study was to calculate a useful cut-off point of the ^{18}F-FDG PET/CT SUV_{Max} value to decide on a CT-PTNB for solid SPNs of sizes between 11 and 20 mm.

METHODS

This study conformed in accordance with the 2013 Declaration of Helsinki. The study was approved by the Ethics Committee of Gaziantep University (No: 2020/326). Written informed consent was obtained from all individual participants included in the study.

Patients

All biopsy procedures were decided considering the Fleischner Society 2013 and 2017 criteria[9]. Between January 2015 and April 2020, patients with SPNs who underwent CT-PTNB in the interventional radiology department of our hospital were retrospectively reviewed. A total of 112 patients with SPNs who had complete CT-PTNB reports were found in our interventional radiology database. In total, 36 of these patients were excluded from the study due to having SPNs larger than 20 mm in size (n=17), having subsolid nodules (n=13), or not undergoing an ^{18}F-FDG PET/CT examination despite having SNPs of 11–20 mm in diameter (n=6). Finally, a total of 76 patients (53 males and 23 females, mean age 62.21±12.69 years), who met the inclusion criteria were evaluated.

Biopsy procedure

Biopsies were performed on patients with INR <1.5 and platelet count >50,000 K/μL. Positioning (supine, prone, or lateral) was adjusted based on SPN location for safe needle access. Using a Siemens CT (SOMATOM) with 20 mAs, 120 kV, 8×1.25 mm collimation, and 2.5 mm slice thickness, each procedure employed an 18-G cutting needle and a 17-G coaxial needle. At least three cuts were taken for adequate tissue sampling, and a post-procedural CT was conducted to check for complications such as pneumothorax or hemorrhage.

Diagnostic evaluation

CT-PTNB diagnoses were categorized as malignant, benign, unspecified (atypical cells), and non-diagnostic (insufficient tissue). Final diagnoses were confirmed via surgical resection, follow-up CT, or lab/pathology exams. A ≥20% reduction in nodule size on follow-up CT signified a benign SPN.

Computed tomography images

Diagnostic contrast-enhanced or non-contrast thorax CT images were reviewed by two radiologists, each with 5 years of experience, who were blinded to the pathologic diagnosis. The CT morphological features of the solid SPNs, nodule diameter (mm), nodule contour (smooth, lobulated, spiculated), localization, hilar lymphadenopathy (LAP), and emphysema were determined based on consensus.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography images

All ^{18}F-FDG PET/CT images were routinely obtained after at least 6 h of fasting. The ^{18}F-FDG PET/CT images from the skull base to the middle of the thigh were obtained approximately 1 h later in patients who received ^{18}F-FDG once their serum glucose levels were <110 mg/dL. All collected data were transferred to dedicated workstations for post-processing, and the SUV_{Max} values of the SPNs were calculated and noted separately.

Statistical analysis

Data were analyzed using SPSS 21.0 (IBM Corp., Armonk, NY, USA). Frequency distributions were provided for categorical variables, and means, standard deviations, medians, and IQRs for numerical variables. The Mann-Whitney U test, t-test, and chi-square test assessed differences between groups, while ROC analysis determined the SUV_{Max} cut-off value. A p-value <0.05 indicated statistical significance.

RESULTS

Biopsy-based diagnosis and final diagnosis

Sufficient tissue was obtained for pathological examination in all patients except one with a 12 mm solid SPN in the right lower lobe. The coaxial CT-PTNB diagnoses were malignant (81.5%), benign (14.5%), unspecified (2.7%), and non-diagnostic (1.3%). Final diagnoses were malignant (81.5%), benign (17.2%), and missing (1.3%). Malignant diagnoses were confirmed by surgical resection, while benign findings were accepted as final (Table 1).

There was a statistically significant relationship between pathological diagnosis and gender. The malignancy rate was higher in males than in females (p=0.037). A statistically significant difference was also observed between the pathological diagnosis and the ^{18}F-FDG PET/CT SUV_{Max} median values. The median SUV_{Max} value of the malignant SPNs was significantly higher than that of the benign SPNs (med-IQR 11.2–7 vs. 6.9–13.5, p=0.006). The patient age and the CT features of the SPNs (size, contour, and presence of hilar LAP and emphysema) were similar in benign and malign cases (p>0.05) (Table 2).

Table 1. Coaxial computed tomography-guided percutaneous transthoracic needle biopsy and final diagnoses of the 76 solid solitary pulmonary nodules of 11–20 mm in diameter.

Diagnoses	CT-PTNB diagnoses		Final diagnoses	
	n	%	n	%
Adenocarcinoma	31	40.8	31	40.8
Squamous cell carcinoma	14	18.4	14	18.4
Small cell carcinoma	7	9.2	7	9.2
Metastasis	10	13.2	10	13.2
Granulomatous inflammation	5	6.5	5	6.5
Benign cytology	5	6.5	7	9.2
Hydatid cyst remnant	1	1.3	1	1.3
Unspecified atypical cells*	2	2.7	None	None
Non-diagnostic[?]	1	1.3	Missing	Missing

*Final diagnoses were benign; [?]missing. CT-PTNB: computed tomography-guided percutaneous transthoracic needle biopsy.

Table 2. Comparison of the computed tomography and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography findings of the benign and malignant solid solitary pulmonary nodules.

	Benign vs. malignant SPN	
	Test value	p-value
Sex	4.748[c]	0.037**
Age	1.308[mw]	0.191
Nodule size	1.043[mw]	0.297
Contour	0.332[c]	0.564
Hilar LAP	1.359[c]	0.244
Emphysema	0.646[c]	0.421
^{18}F-FDG PET/CT SUV_{Max}	2.734[mw]	0.006**

[mw]Mann-Whitney U test; [c]Chi-square test; **statistically significant. SPN: solitary pulmonary nodule; LAP: lymphadenopathy; ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; PET/CT: positron emission tomography/computed tomography.

The ROC curve analysis was performed to obtain a cut-off value for ^{18}F-FDG PET/CT SUV_{Max} indicating the malignancy risk of solid SPNs. According to the ROC analysis, two cut-off values were identified for SUV_{Max} indicating malignancy risk: 7.05 and 4.85. At the cut-off value of 7.05, SUV_{Max} had a sensitivity of 93.1% and specificity of 83.3%. At the cut-off value of 4.85, the sensitivity and specificity of SUV_{Max} were calculated as 100 and 66.7%, respectively.

DISCUSSION

Although the diagnostic accuracy of CT-PTNB is very high in large nodules, in SPNs smaller than 20 mm, the diagnostic accuracy rates decrease, and reaching the target lesion with a needle can be challenging[8,12]. Another disadvantage of CT-guided biopsy in SPNs smaller than 20 mm is increased complication rates[13]. The likelihood of malignancy increases in large nodules, but nodule size does not exclude malignancy[9]. However, lipoid pneumonia, focal atelectasis, granulomatous inflammation, and progressive massive fibrosis, which are benign conditions, can also exhibit spiculated contours[14]. Although well-defined margins and a smooth contour may be a sign of benignity, pulmonary metastasis and 20% of primary lung malignancies have smooth contours[15]. Therefore, it becomes more challenging to decide on a biopsy procedure for SPNs smaller than 20 mm.

The role of ^{18}F-FDG PET/CT is clearer in SPNs with a 20–30 mm size compared to SPNs of 11–20 mm in diameter due to the very low specificity, low spatial resolution, and partial volume effect[16]. Malignant nodules have higher ^{18}F-FDG uptake values than benign nodules[17,18]. In other studies, the sensitivity and specificity of SUV_{Max} ≥2.5 were reported as 77 and 85%, respectively, for>8 mm nodules, and as 95 and 46%, respectively, for those smaller than 30 mm[19,20]. While the efficiency of ^{18}F-FDG PET/CT is rather limited in lung nodules with pure ground-glass opacity, the reliability of ^{18}F-FDG PET/CT increases in nodules with a solid component larger than 5 mm[21]. Another factor may be related to the necrosis content of the nodule. Due to the smaller necrosis area in small nodules, the ^{18}F-FDG uptake increases, and PET/CT gives a higher SUV_{Max} value[16]. Therefore, a wide necrotic component of larger nodules may mislead the physicians based on low SUV_{Max} values. Furthermore, this heterogeneity of lung nodules may make it difficult to determine a cut-off value for SUV_{Max} to distinguish benign and malignant nodules at high sensitivity and specificity rates.

Chronic granulomatous inflammation may exhibit spiculated contours on CT similar to malignant SPNs, and this decreases the specificity of ^{18}F-FDG PET/CT[20,22]. The sensitivity and specificity rates of ^{18}F-FDG PET/CT decrease in pure GGNs and subsolid nodules that have a solid component smaller than 10 mm due to the low ^{18}F-FDG uptake[23]. Dabrowska et al.[18] investigated a cut-off value of ^{18}F-FDG PET/CT to identify malignant SPNs in 71 patients. They determined that at a cut-off value of 2.1, SUV_{Max} had 77% sensitivity and 92% specificity[18]. The SUV_{Max} value may decrease to 1.25 in subsolid nodules, and the low SUV_{Max} value of benign nodules creates an overlap zone for the SUV_{Max} value in distinguishing benign and malignant SPNs[16]. This overlap zone reduces the specificity rates of ^{18}F-FDG PET/CT.

The rates of major and overall complications of CT-PTNB are reported as 5.7% and 38.8%, respectively[24]. In addition, emphysema and needle path length are mentioned as the risk factors of pneumothorax[13,25].

This study has certain limitations that should be noted. First, the small sample size of the study makes it difficult to interpret the data. Furthermore, due to the retrospective nature and single-center design of the study, the data may be subject to bias. Multicenter, prospective, randomized studies with larger samples are needed.

CONCLUSION

Solid pulmonary nodules of 11–20 mm often have similar CT features, complicating benign versus malignant differentiation. The ^{18}F-FDG PET/CT, with an SUV_{Max} threshold of 4.85, improves diagnostic accuracy and helps guide CT-guided biopsies. This threshold ensures high sensitivity and balanced specificity, supporting precise biopsy decisions and enhancing patient-centered care for small SPNs.

ETHICS APPROVAL

The study was approved by the Ethics Committee of Gaziantep University (No: 2020/326).

AUTHORS' CONTRIBUTIONS

BSSU: Conceptualization, Methodology, Software, Supervision, Writing – original draft. **ABB:** Data curation, Methodology, Software, Validation. **MO:** Data curation, Investigation, Supervision, Visualization, Writing – review & editing. **CMA:** Conceptualization, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. **SE**: Conceptualization, Software, Supervision, Validation. **MFA:** Data curation, Software, Supervision. **ABK:** Data curation, Methodology, Software, Validation. **MCT:** Conceptualization, Methodology, Software, Supervision, Writing – original draft.

REFERENCES

1. He R, Ming C, Lei Y, Chen W, Ye L, Li G, et al. Preoperative pulmonary nodule localization: a comparison of hook wire and Lung-pro-guided surgical markers. Clin Respir J. 2024;18(1):e13726. https://doi.org/10.1111/crj.13726
2. Smith Z, Barnett SA, Gorelik A, Pascoe DM, Manser RL. Strategies for the management of solitary pulmonary nodules: a survey of patient preferences. Ann Thorac Surg. 2022;113(5):1670-5. https://doi.org/10.1016/j.athoracsur.2021.04.094
3. Harzheim D, Eberhardt R, Hoffmann H, Herth FJ. The solitary pulmonary nodule. Respiration. 2015;90(2):160-72. https://doi.org/10.1159/000430996
4. Wood DE, Eapen GA, Ettinger DS, Hou L, Jackman D, Kazerooni E, et al. Lung cancer screening. J Natl Compr Canc Netw. 2012;10(2):240-65. https://doi.org/10.6004/jnccn.2012.0022
5. Hong T, Ji G, Sun T, Gui X, Ma T, Zhang H. CT-guided percutaneous transthoracic needle biopsy (PTNB): a thoracic surgeon's learning curve and experience summary. Thorac Cancer. 2023;14(7):673-82. https://doi.org/10.1111/1759-7714.14793
6. Goto M, Fukumoto K, Ichikawa Y, Tsubouchi H, Uchiyama M, Mori S. Pathologically confirmed spontaneous regression of small cell lung cancer after computed tomography-guided percutaneous transthoracic needle biopsy followed by surgery. Surg Case Rep. 2023;9(1):187. https://doi.org/10.1186/s40792-023-01759-9
7. Mazzone PJ, Lam L. Evaluating the patient with a pulmonary nodule: a review. JAMA. 2022;327(3):264-73. https://doi.org/10.1001/jama.2021.24287
8. Tian Y, Wang C, Yue W, Lu M, Tian H. Comparison of computed tomographic imaging-guided hook wire localization and electromagnetic navigation bronchoscope localization in the resection of pulmonary nodules: a retrospective cohort study. Sci Rep. 2020;10(1):21459. https://doi.org/10.1038/s41598-020-78146-z
9. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the fleischner society 2017. Radiology. 2017;284(1):228-43. https://doi.org/10.1148/radiol.2017161659
10. Wei Y, Ma L, Li P, Lu J, Ren J, Yan S, et al. FAPI compared with FDG PET/CT for diagnosis of primary and metastatic lung cancer. Radiology. 2023;308(2):e222785. https://doi.org/10.1148/radiol.222785
11. Zaman MU, Fatima N. 18FDG PET/CT and lung cancer: beaconhouse for treating oncologists. J Coll Physicians Surg Pak. 2023;33(12):1341-3. https://doi.org/10.29271/jcpsp.2023.12.1341
12. Huang MD, Weng HH, Hsu SL, Hsu LS, Lin WM, Chen CW, et al. Accuracy and complications of CT-guided pulmonary core biopsy in small nodules: a single-center experience. Cancer Imaging. 2019;19(1):51. https://doi.org/10.1186/s40644-019-0240-6
13. Li X, Jin F, Zhou T, Ru Y, Gu F, Wang L, et al. Diagnostic accuracy of CT-guided percutaneous pulmonary biopsy for distinguishing

benign and malignant solitary pulmonary nodules. Altern Ther Health Med. 2023;29(8):918-23. PMID: 37773650

14. Wu W, Gu L, Zhang Y, Huang X, Zhou W. Pulmonary nodule clinical trial data collection and intelligent differential diagnosis for medical internet of things. Contrast Media Mol Imaging. 2022;2022:2058284. https://doi.org/10.1155/2022/2058284
15. Kim TJ, Kim CH, Lee HY, Chung MJ, Shin SH, Lee KJ, et al. Management of incidental pulmonary nodules: current strategies and future perspectives. Expert Rev Respir Med. 2020;14(2):173-94. https://doi.org/10.1080/17476348.2020.1697853
16. Tang K, Wang L, Lin J, Zheng X, Wu Y. The value of 18F-FDG PET/CT in the diagnosis of different size of solitary pulmonary nodules. Medicine (Baltimore). 2019;98(11):e14813. https://doi.org/10.1097/MD.0000000000014813
17. Koster EJ, Engen-van Grunsven ACH, Bussink J, Frielink C, Geus-Oei LF, Kusters B, et al. [18F]FDG Uptake and expression of immunohistochemical markers related to glycolysis, hypoxia, and proliferation in indeterminate thyroid nodules. Mol Imaging Biol. 2023;25(3):483-94. https://doi.org/10.1007/s11307-022-01776-4
18. Dabrowska M, Krenke R, Korczynski P, Maskey-Warzechowska M, Zukowska M, Kunikowska J, et al. Diagnostic accuracy of contrast-enhanced computed tomography and positron emission tomography with 18-FDG in identifying malignant solitary pulmonary nodules. Medicine (Baltimore). 2015;94(15):e666. https://doi.org/10.1097/MD.0000000000000666
19. Evangelista L, Panunzio A, Cervino AR, Vinante L, Al-Nahhas A, Rubello D, et al. Indeterminate pulmonary nodules on CT images in breast cancer patient: the additional value of 18F-FDG PET/CT. J Med Imaging Radiat Oncol. 2012;56(4):417-24. https://doi.org/10.1111/j.1754-9485.2012.02408.x
20. Sebro R, Aparici CM, Hernandez-Pampaloni M. FDG PET/CT evaluation of pathologically proven pulmonary lesions in an area of high endemic granulomatous disease. Ann Nucl Med. 2013;27(4):400-5. https://doi.org/10.1007/s12149-013-0695-7
21. Evangelista L, Panunzio A, Scagliori E, Sartori P. Ground glass pulmonary nodules: their significance in oncology patients and the role of computer tomography and 18F-fluorodeoxyglucose positron emission tomography. Eur J Hybrid Imaging. 2018;2(1):2. https://doi.org/10.1186/s41824-017-0021-z
22. Yan N, Sugihara F, Hayashi N, Sasaki T, Ishii Y, Hayashi H, et al. Pulmonary mediastinal actinomycosis with "pound cake sign" on magnetic resonance imaging mimicking an infiltrative malignant tumor: a case report. Radiol Case Rep. 2024;19(8):3334-8. https://doi.org/10.1016/j.radcr.2024.05.001
23. Tsunezuka Y, Shimizu Y, Tanaka N, Takayanagi T, Kawano M. Positron emission tomography in relation to Noguchi's classification for diagnosis of peripheral non-small-cell lung cancer 2 cm or less in size. World J Surg. 2007;31(2):314-7. https://doi.org/10.1007/s00268-006-0475-9
24. Heerink WJ, Bock GH, Jonge GJ, Groen HJ, Vliegenthart R, Oudkerk M. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. Eur Radiol. 2017;27(1):138-48. https://doi.org/10.1007/s00330-016-4357-8
25. Shin B, Kim SB, Kim CW, Park IH, Lee WY, Byun CS. Risk factors related to the recurrence of pneumothorax in patients with emphysema. J Thorac Dis. 2020;12(10):5802-10. https://doi.org/10.21037/jtd-20-1557B

ORIGINAL ARTICLE

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Assessment of adulthood immunization knowledge, attitudes, and behavior

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SUMMARY

OBJECTIVE: Adulthood vaccination has not reached adequate levels, both in Turkey and around the world. The aim of this study was to identify the knowledge, attitude, and behavior of vaccination in those aged 18 years.

METHODS: This is a cross-sectional study. Questionnaires were applied to 686 participants attending Family Health Centers. For the analysis of data, the statistical significance used was $p<0.05$.

RESULTS: Notably, 72.4% of people had at least one vaccination in adulthood. The most frequent vaccinations were tetanus (55.1%), influenza (26.8%), and hepatitis B (8.2%). PATH analysis found that the effect of variables with direct effects on vaccination (apart from the situation of thinking that vaccinations are necessary in adulthood) disappeared in the model in which adult vaccine recommendations were used as mediators.

CONCLUSION: The adult vaccination situation is inadequate. It is necessary to inform society about adult vaccinations and recommend vaccination. Tools such as information given during health services and implementations such as social education and brochures, posters, media, and public information spots may be used with this aim.

KEYWORDS: Adult. Vaccine. Immunization.

INTRODUCTION

Immunization acquired by vaccination is one of the most effective strategies to protect public health. Within the framework of the Expanded Programme on Immunization recommended by the World Health Organization, significant progress has been made for vaccinations in the newborn and childhood periods on a global level. But it is not possible to say the success of neonatal and childhood vaccinations in the world in general is reflected in vaccination in the adult[1-3]. Whereas, especially due to reasons such as pregnancy, chronic diseases, travel, and intravenous drug use, susceptible groups emerge and require vaccination in adulthood[4]. Mortality and morbidity due to diseases preventable with vaccinations in the adult are still observed. For example, every year nearly 50,000 adults die due to diseases preventable with vaccination in America[5].

In Turkey, there is no systematic program about vaccination in the adult period, apart from some vaccinations administered to women of reproductive age and the elderly. Studies have shown that the public does not have sufficient information about this topic[6]. This research was completed with the aim of investigating the knowledge, attitude, and behavior of adult individuals about the topic.

METHODS

This study was a cross-sectional study. The research was completed in Canakkale province located in the Southern Marmara region of Turkey.

The population comprised individuals aged 18 years and older residing in neighborhoods in Kepez town located in Canakkale central county and linked to the central county. The sample size formula was used to estimate the sample size population rate. This formula used a value of p: 0.05 in situations where the rate is not known for the incidence of an event ($Z\alpha/2$:1.96, alpha value 0.05, deviation 5%). The population value was taken as the population aged 18 years and older residing in neighborhoods in Canakkale central county and Kepez town (126,893), and the minimal sample number to be reached was determined as 384 people. The minimal sample number that must be reached was weighted for the population aged 18 years and older in neighborhoods in the research region with the layered sample selection method. Notably, six family health centers (FHC) representing all neighborhoods in the research region were chosen. People attending the FHC were reached on a voluntary basis with the non-probability sampling method. The research was completed in six FHC in August 2019. In the period of the

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study, 686 people from a total of 1,311 aged 18 years and older attending the FHC (52.3%) were reached (more people were reached in each neighborhood than the minimal sample number). With the face-to-face interview method, participants completed a survey lasting 10–15 min. The survey included questions about sociodemographic features, questions about current health status and information, and attitudes and behavior about adult immunization.

Ethics committee approval

Written permission for the study was granted by Canakkale Provincial Directorate of Health for the FHC in the study (number: 18231034-604.99) and by Canakkale Onsekiz Mart University clinical research ethics committee (decision date: 20.02.2019, decision no: 2019-04).

Statistical analysis

Analysis of research data used the SPSS version 20.0, STATA 14, and SPSS AMOS programs. Analyses accepted $p<0.05$ as statistically significant.

PATH analysis (adulthood vaccination recommendations as a mediator variable) was applied to investigate factors that may affect the situation of having any vaccination in adulthood. PATH analysis is a form of multiple regression describing the indirect, direct, and total effects of independent variables on a dependent variable. To assess the fit of the model, acceptable limits were $0.05<RMSEA£0.08$, $0.05<RMR£0.08$, $0.90£FI£0.94$, $0.90£CFI£0.94$, $2<X^2/sd£5$, while limits of perfect fit were $0£RMSEA£ 0.05$, $0£RMR£0.05$, $GFI≥0.90$, $AGFI≥0.90$, $NFI≥0.95$, $IFI≥0.95$, $CFI≥0.95$, $0£X^2/sd£2$. The applied PATH analysis model abided by these criteria.

RESULTS

The study group comprised 686 people. Mean age was 48.1±16.5 years (median: 49, minimum–maximum: 18–90). Other descriptive features of participants are presented in Table 1.

Of the study group, 77% saw vaccination in the adult as required and 72.4% had done any vaccination in the adult (Table 2). Of vaccinations done, the most common were tetanus (55.1%), influenza (26.8%), and hepatitis B (8.2%).

Among participants, 58.9% were recommended vaccinations in the adult and 9.4% of these people had not done the recommended vaccines (Table 2). When the reasons for rejection were asked of these 38 people who had not done the recommended vaccines, the most common responses were not thinking the vaccines were protective against disease (26.3%), not thinking the vaccination was necessary/thinking vaccines are harmful (23.7%), thinking that they would acquire immunity by catching the disease rather than from vaccination (21.1%), fear of vaccine side effects (10.5%), and not having time to get the vaccine (10.5%).

Table 1. Characteristics of the study group.

Variables	Mean (median)
Age (year) (n: 686)	48.1±16.5 (49.0)
Gender (n: 686)	n (%)
Female	358 (52.2)
Male	328 (47.8)
Occupation (n: 686)	
Healthcare professionals/healthcare workers	41 (6.0)
Other occupational groups	645 (94.0)
Marital status (n: 686)	
Married	505 (73.6)
Single	119 (17.3)
Widow/divorced	62 (9.1)
Education status (n: 686)	
Primary education	271 (39.5)
High school and higher education	415 (60.5)
Chronic illness (n: 686)	
Yes	376 (54.8)
No	310 (45.2)
Allergy to any factor (n: 686)	
Yes	152 (22.2)
No	534 (77.8)

n: number; %: percentage.

When people were asked about their thoughts on adulthood vaccinations, the most frequent responses were, "I know about adulthood vaccinations; however, I don't know what these vaccinations are" (51.2%) and "only adults with some diseases should be vaccinated, there is no need to vaccinate all adults" (38.3%). Among participants, 63.3% had received vaccines in the childhood period and 73.2% stated that they or their family did not have their childhood vaccine card (Table 2). When people were asked, "whose opinion and recommendation is important to you in your decision to be vaccines?," the most common answer was health employees at 92%.

Factors that may affect vaccination in the adult were investigated with PATH analysis. Variables explaining direct effects were reduced age, being male, being married, having chronic disease, having allergies, thinking vaccination in adults will protect infants, children, and pregnant people around them from disease, they or their families not having their childhood vaccine card, seeing vaccinations as necessary in the adult, and receiving vaccinations recommended to them in the adult

(p<0.05). In the model where being recommended vaccination in the adult was used as the mediator variable (indirect effects), explanatory variables were identified as being a health employee/working in the health area and seeing vaccination as necessary in the adult (p<0.05) (Table 3).

DISCUSSION

The majority of participants (77%) saw vaccination in the adult as necessary. A study performed in FHC in Ankara found this frequency was 50.5%, while a study in a family clinician clinic in an education-research hospital identified this rate was 84.3%[7,8]. Different results obtained about this topic lead to consideration that there are attitude variations in geographies with different sociocultural features. The incidence of receiving any vaccine in the adult is 72.4%. The most common vaccinations were tetanus (55.1%), influenza (26.8%), and hepatitis B (8.2%). A study in the Istanbul region reported that 57.9% had done vaccinations in the adult and the most common vaccinations were tetanus (42.1%), influenza (23.9%), and hepatitis B (18.2%)[9]. A study by Bolatkale et al. identified that the most common vaccinations were tetanus (59%), influenza (35.1%), and hepatitis B (28.1%)[8]. In Turkey, tetanus vaccinations are administered in emergency services as a result of injury, within the framework of the maternal and neonatal tetanus elimination program and during military duty. The high identification of the influenza vaccine administration frequency may be explained by the occasional deadly influenza epidemics observed and the awareness of this situation in society. However, the vaccination frequencies obtained in studies are not at the desired levels.

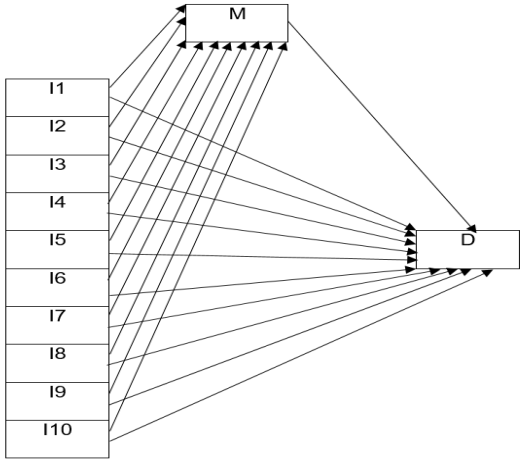
In this study, 58.9% of people had been recommended vaccinations in adulthood. Of those recommended vaccinations, 9.4% had not done vaccines for a variety of reasons. The most common reasons were not thinking vaccines were protective against the disease; not seeing vaccination as required/thinking

Table 2. Vaccination in adulthood, recommendation to vaccination, opinions about vaccination, and childhood vaccination status.

Variables	n (%)
Thinking that vaccination is necessary in adulthood (n: 686)	
Yes	528 (77.0)
No	80 (11.7)
Undecided	78 (11.3)
To be vaccinated in adulthood (n: 686)	
Yes	497 (72.4)
No	189 (27.6)
Recommendation for vaccination in adulthood (n: 686)	
Yes	404 (58.9)
No	282 (41.1)
Being of proposed adulthood vaccination (n: 404)*	
Yes	366 (90.6)
No	38 (9.4)
Ideas on adulthood vaccination (n: 686)**	
I know about adulthood vaccinations; however, I don't know what these vaccinations are	351 (51.2)
Only adults with some diseases should be vaccinated, there is no need to vaccinate all adults	263 (38.3)
I know exactly of adulthood vaccinations	41 (6.0)
There isn't need for vaccination in adulthood	24 (3.5)
Vaccinations are required for only children	19 (2.8)
All adults should be vaccinated	27 (3.9)
Required only in case of epidemic	3 (0.4)
I have no idea	30 (4.4)

n: number; %: percentage; *Participants who were recommended to be vaccinated in adulthood answered this question; **More than one answer could be obtained for this question and the percentage was calculated from the study group of 686 people.

Table 3. Affecting factors of vaccination in adulthood, PATH analysis.



Direct effect		EC	p-value	Indirect effect		EC	p-value
	M->D	0.5231	**<0.001**				
	I1->D	-0.0031	**0.005**		I1->M->D	-0.0014	0.085
	I2->D	0.0704	**0.010**		I2->M->D	-0.0071	0.719
	I3->D	0.0618	0.275		I3->M->D	0.0894	**0.030**
	I4->D	0.0458	**0.014**		I4->M->D	0.0116	0.394
	I5->D	0.0648	**0.043**		I5->M->D	-0.0072	0.755
	I6->D	0.1088	**0.001**		I6->M->D	-0.0011	0.961
	I7->D	0.0562	**0.003**		I7->M->D	0.0194	0.165
	I8->D	0.0647	0.050		I8->M->D	-0.0449	0.061
	I9->D	0.0552	**0.008**		I9->M->D	0.0005	0.974
	I10->D	0.0491	**0.014**		I10->M>D	0.0564	**<0.001**

I: Independent variable; I1: Age (continuous variable); I2: Gender (female: 0, male: 1); I3: Occupation (other occupational groups: 0, healthcare professionals/healthcare workers: 1); I4: Marital status (single: 0, widow/divorced: 1, married: 2); I5: Chronic illness (no: 0, yes: 1); I6: Allergy (no: 0, yes: 1); I7: Thinking that vaccination in adults will protect infants, children, and pregnant people around them from disease (undecided: 0, no: 1, yes: 2); I8: Childhood immunization status (All childhood vaccinations have been/have been done, but doesn't know whether all of them have been done: 0, Doesn't know/remember any one, no: 2); I9: Having the their childhood vaccination card in themselves or their family (yes: 0, doesn't know/remember: 1, no: 2); I10: Thinking that vaccinations are necessary in the adulthood (no: 0, undecided: 1, yes: 2); M (Mediator variable): Recommendation to vaccination in adulthood (no: 0, yes: 1); D (Dependent variable): To be vaccinated in adulthood (no: 0, yes: 1); EC: effect coefficient; p: statistical significance level.
In statistical analysis, $p<0.05$ is statistically significant. $p<0.05$ values are bold.

vaccines are harmful; thinking they would acquire immunity by catching the disease rather than from vaccination; and fear of vaccine side effects. A study by Uzuner et al. found the most common responses to the question "if you did not have the vaccinations, what was the reason?" were not being informed about the topic (47.1%), not seeing vaccination as required (43.2%), and thinking of vaccine side effects (3.1%)[9]. Non-scientific misinformation has an important place in vaccine rejection. Positive policies should be developed to inform the public.

Half of our study group had information about adulthood vaccinations; however, they did not know what these vaccinations were, with 38.3% stating vaccinations were only required for those with some illnesses, 2.8% thinking vaccinations were only required by children, and 4.4% having no idea about the topic. A study in Antalya stated that 37% of people thought only those with certain diseases required vaccination, 36% knew about adulthood immunization but did not fully know what, 4% thought vaccinations could only be administered to children, and another 4% stated that vaccination was not required in the adult[10]. Studies show that society does not have sufficient information about adult vaccines, and there is common misinformation that vaccines are only required for some diseases. In our study, when people were asked, "whose opinion and recommendations are most important to you when deciding on vaccination?" the most common response was health employees (92%). In the study by Karabay et al., 93.8% of the participants answered that the guidance of healthcare professionals was effective in getting vaccinated[6]. A study conducted in Ankara revealed that when participants were asked about their preferred sources for informed on adulthood vaccinations, the most common responses were doctors (88.0%) and midwives/nurses (25.4%)[7]. The frequent misinformation in society and seeing health employees as a reliable source about the topic indicate just how important it is for health employees to give information about adulthood vaccination in every situation of contact with patients. Another study found that only 20.5% of clinicians had done information about adulthood vaccination after graduation and the majority (88.5%) stated they required practical refreshment[11]. We believe that education for health personnel before and after graduation will be effective in communicating accurate information to society. Informing health employees, the most important source of information in society, with frequent in-service education and about making vaccination recommendations to patients may contribute to developing positive attitudes. Social media may be used with this aim. However, it is important for society to reach information about evidence-based medical practices through the use of social media. Otherwise, there may be information pollution about the topic on social media. For this reason, we think it is important that scientific organizations or scientists use social media more frequently with the aim of transferring information to society.

In the literature, the factors affecting vaccination in adults display variability. For example, the study by Asık et al. identified that being a woman was a factor increasing vaccination, while age was ineffective[10]. Similarly, a study in Ankara stated that the gender and age variables did not affect vaccination in the adult[7]. In our study, factors affecting vaccination in the adult were investigated with PATH analysis (direct and indirect effect). Indirect effects appeared to remove the effects of a variety of sociodemographic factors (like age, gender, and presence of chronic disease) as a result of vaccine recommendations to people. This situation may indicate that people tend to get vaccinated when recommended, regardless of sociodemographic factors. When examined from this aspect, one of the most important variables affecting vaccination behavior is recommending vaccines to people. In studies in the literature, one of the most important reasons for the lack of sufficient levels of adulthood vaccination is the lack of vaccine recommendations[12]. A study conducted at Akdeniz University Faculty of Medicine Hospital involving over 2,000 individuals found that 68.2% of those vaccinated received their vaccines based on recommendations from their doctor[13]. Additionally, a separate study at Yozgat Bozok University, which included 3,000 participants, revealed that 73.7% of individuals who were recommended pneumococcal vaccinations and 68.4% of those who were recommended influenza vaccinations went on to receive those vaccinations[14].

People can be offered vaccines through healthcare professionals. Social media, television, public information spots, and public education studies may be used to recommend vaccinations to the public.

CONCLUSION

The frequency of vaccination in adults, as well as their awareness and attitudes toward this issue, is currently insufficient. One of the key factors that can increase vaccination rates is the recommendation of vaccines for individuals. To address this, it is essential to continuously provide information during health service implementations and public education initiatives. Additionally, enhancing the importance of vaccination in the training of healthcare personnel is crucial. Tools such as brochures, posters, and public information campaigns can be effectively utilized for this purpose.

AUTHORS' CONTRIBUTIONS

ÖÖ: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SO:** Methodology, Project administration, Writing – review & editing. **CB:** Methodology, Project administration, Writing – review & editing.

REFERENCES

1. Doherty TM, Ecarnot F, Gaillat J, Privor-Dumm L. Nonstructural barriers to adult vaccination. Hum Vaccin Immunother. 2024;20(1):2334475. https://doi.org/10.1080/21645515.2024.2334475
2. Kolobova I, Nyaku MK, Karakusevic A, Bridge D, Fotheringham I, O'Brien M. Vaccine uptake and barriers to vaccination among at-risk adult populations in the US. Hum Vaccin Immunother. 2022;18(5):2055422. https://doi.org/10.1080/21645515.2022.2055422
3. Greenberg GM, Koshy PA, Hanson MJS. Adult vaccination. Am Fam Physician. 2022;106(5):534-42. PMID: 36379499
4. Bonanni P, Steffen R, Schelling J, Balaisyte-Jazone L, Posiuniene I, Zatoński M, et al. Vaccine co-administration in adults: an effective way to improve vaccination coverage. Hum Vaccin Immunother. 2023;19(1):2195786. https://doi.org/10.1080/21645515.2023.2195786
5. National Foundation for Infectious Diseases. We the people have the right to be vaccine–preventable disease free. [cited on 2024 Nov 13]. Available from: https://www.nfid.org/we-the-people-have-the-right-to-be-vaccine-preventable-disease-free/
6. Karabay O, Yigit Y, Aydın E, Tok FM, Karaca I, Boz B, et al. Factors affecting attitudes and behaviors towards vaccination. Sakarya Med J. 2021;11(2):353-9.
7. Baran Aksakal FN, Kocak C, Uğras Dikmen A, Altun B, Buyukdemirci E. Investigation of knowledge, attitudes and behaviors related to adult vaccination of people over 18 years old who apply to family health centers in Ankara. Flora. 2018;23(3):124-34. https://doi.org/10.5578/flora.66953
8. Bolatkale MK, Kutlu R, Eryılmaz MA. The adult immunization knowledges and vaccination status of individuals who applied to family medicine polyclinic. Konuralp Med J. 2019;11(3):362-8.
9. Uzuner A, Arabacı S, Yüceel AI, Kocaturk AC, Kaynar E, Khan A. Knowledge, attitude and behaviors of adults about adulthood immunization. TJFMPC. 2018;12(3):215-25.
10. Asık Z, Cakmak T, Bilgili P. Knowledges, attitudes and behaviours of adults about adult vaccines. Turk J Fam Pract. 2013;17(3):113-8.
11. Yuruyen G, Toprak ID, Kutlu Y. Adult vaccination awareness in physicians. Bosphorus Med J. 2019;6(3):89-93.
12. Johnson DR, Nichol KL, Lipczynski K. Barriers to adult immunization. Am J Med. 2008;121(Suppl 2):S28-35. https://doi.org/10.1016/j.amjmed.2008.05.005
13. Turhan O, Polat HH, Oncel S, Akcan A, Eravsar K, Yalcın AN. Pneumococcal vaccination status in adults sixty-five years and older. Kuwait Med J. 2010;42(2):135-8.
14. Erbay A, Kader C, Ede H, Süher M, Akyol L, Intepe YS, et al. Influenza and pneumococcal vaccination uptake in adults aged ≥65 years and high risk groups admitted to Yozgat Bozok University Research and Application Hospital. Klimik J. 2018;31(3):205-9.

ORIGINAL ARTICLE

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Comparison of myocardial perfusion scintigraphy and strain echocardiography in patients undergoing coronary angiography

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SUMMARY

OBJECTIVE: Myocardial perfusion scintigraphy is a common non-invasive method for assessing ischemic burden, though artifacts can affect accuracy. Speckle-tracking strain echocardiography improves left ventricular function assessment, and global longitudinal strain correlates well with coronary artery disease. The aim of this study was to compare myocardial perfusion scintigraphy with global longitudinal strain in stable angina pectoris patients.

METHODS: A total of 133 suspected coronary artery disease patients who underwent myocardial perfusion scintigraphy and coronary angiography were prospectively enrolled and classified as myocardial perfusion scintigraphy true positives or false positives based on coronary angiography results. Global longitudinal strain values for the epicardium, endocardium, and myocardium (avg) were calculated.

RESULTS: Ischemic percentages of myocardial perfusion scintigraphy>12% and mid-wall global longitudinal strain<-18.4% correlated with true positive coronary angiography results. Left ventricular ejection fraction/global longitudinal strain mid ratio positively correlated with coronary artery disease presence and severity. Higher ischemic percentages of myocardial perfusion scintigraphy showed a negative correlation (r: −0.2606, p: 0.002) with global longitudinal strain, indicating a greater likelihood of coronary artery disease (OR 0.25, 95%CI 0.08–0.73, p: 0.012). Female sex was linked to fewer true positive myocardial perfusion scintigraphy results.

CONCLUSION: The GLS value of the Left Ventricle obtained by two-dimentional strain echocardiography offers sensitivity and specificity similar to myocardial perfusion scintigraphy in the detection of coronary artery disease.. An elevated left ventricular ejection fraction/global longitudinal strain ratio is a significant predictor of the presence and severity of coronary artery disease.

KEYWORDS: Two-dimensional echocardiography. Global longitudinal strain. Myocardial perfusion imaging.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of global mortality. Stable angina pectoris (SAP), or chronic coronary syndrome, is a specific form of CAD. Non-invasive diagnostic methods are preferred for evaluating patients with SAP[1].

Myocardial perfusion scintigraphy (MPS) is a non-invasive imaging technique with high accuracy for evaluating ischemic burden in SAP. It identifies ischemic and infarcted areas after radiopharmaceutical injection. However, MPS is susceptible to artifacts and challenges that can lead to false-positive (FP) or false-negative CAD assessments.

Two-dimensional (2D) transthoracic echocardiography is a common non-invasive method for detecting SAP, providing important information on left ventricular ejection fraction (LVEF) and wall motion. Adding speckle tracking to echocardiography enhances the detection of CAD by allowing precise assessments of segmental myocardial deformation[2]. Longitudinal myocardial fibers are the most sensitive to ischemia and are predominantly located in the subendocardial layer. According to the literature, there is a strong correlation between myocardial deformation values obtained by global longitudinal strain (GLS) analysis and the presence of CAD.

This study aimed to compare MPS findings with GLS values derived from strain echocardiography (S-ECHO) in patients with SAP who underwent coronary angiography (CAG).

METHODS

Between July 2023 and August 2024, 133 patients who underwent MPS and CAG with suspected CAD were prospectively included in the study. Patients with acute coronary syndrome, a history of revascularization (stent and bypass), heart failure with low ejection fraction (EF), and moderate-to-advanced valvular diseases were excluded. The patients were divided into two main groups according to the results of CAG: MPS true positives (MPS-TPs) and MPS -FPs. Percentages and regions in MPS were also recorded. Patients who underwent CAG due to MPS positivity were included. The study was conducted in compliance with the Declaration of Helsinki. The study protocol was approved by the Institutional Committee on Human Research

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and Ethics. All patients provided a written informed consent. The Trakya University's Ethics Committee approved this study (clinical trial approval number: TÜTF-GOBAEK-2023/398).

Data assessments

Echocardiographic images were obtained using Vivid S70 systems (GE Healthcare, Horton, Norway) and were analyzed on the Echo-PAC workstation. Conventional echocardiographic measurements followed standard guidelines, with the software automatically calculating GLS values for epicardial, endocardial, and myocardial layers (GLS-epi, GLS-endo, and GLS-mid [avg], respectively), with GLS-mid recorded as GLS Avg. Severe CAD was defined by CAG ≥70% stenosis, and SYNTAX scores were calculated for these cases using the online tool (version 2.28)[3]. After the SYNTAX scores were calculated, the patients were divided into three groups as described in the literature[4]. This grouping was made as SYNTAX scores 0–22, 23–32, and 33 and higher. Patients with severe CAD were placed in the MPS TP group.

Statistical analysis

Statistical analyses were conducted using SPSS version 25.0 (SPSS, Chicago, IL, USA). Continuous variables were presented as means and standard deviations, while categorical variables were reported as counts and percentages. The Shapiro-Wilk test assessed normality. An independent samples t-test compared continuous variables between two groups, and the Pearson's chi-square test evaluated relationships among categorical variables. Receiver operating characteristic curve analysis determined curve areas and cutoff points. Logistic regression analysis identified independent variables. All tests were two-tailed, with $p<0.05$ deemed statistically significant.

RESULTS

In this study, a total of 133 patients were enrolled and divided into two groups: 58 (43.60%) in the MPS-FP group and 75 (56.40%) in the MPS-TP group. The MPS-FP group showed a female predominance (60.35%, p=0.002). The mean age of all patients was 59 years, with the MPS-TP group being older. Higher rates of diabetes, hypertension, and smoking were observed in the MPS-TP group, as expected. Conventional echocardiographic parameters, including LVEF, left ventricular (LV) diameter, and LV mass index, did not differ significantly. The MPS percentages were 14.88±5.28 for the MPS-TP group and 11.10±2.79 for the MPS-FP group. Table 1 presents the clinical characteristics and echocardiographic parameters of the study population comparing the MPS-TP and MPS-FP groups.

Vascular disease distributions were analyzed by the vessel count and lesion location: 27 patients (36.0%) had single-vessel disease, 18 (24%) had two-vessel disease, and 30 (40%) had three-vessel disease. Left anterior descending (LAD) lesions were most common (81.33%), with circumflex artery (CX) and right coronary artery (RCA) lesions showing similar rates (60 and 61.33%, respectively). All GLS values were statistically significantly lower in the MPS-TP group ($p<0.001$) (Table 1). Ischemia was mainly in the anterior (68%) and lateral (52%) regions, followed by inferior (47%), septal (26%), and apical (14%) regions. In the MPS-TP group, Pearson's correlation coefficient revealed a negative correlation between MPS ischemic percentages and GLS values (Table 2).

While the diagnostic performance of MPS percentages and GLS parameters in the MPS-TP group was evaluated, the GLS mid (avg) cutoff value for predicting CAD in the MPS-TP group was <-18.4. Sensitivities and specificities were estimated to be in the range of 84–86% (area under the curve [AUC]: 0.91, $p<0.001$). When the cutoff values for MPS were analyzed, a value of 12% was found (Table 2).

Correlation analysis showed a statistically significant increase in the LVEF/GLS ratio with higher SYNTAX scores ($r=0.3164$, $p=0.006$). While GLS values did not differ statistically significantly by the number of affected vessels ($p=0.315$), the LVEF/GLS ratio was statistically significantly higher in three-vessel disease than in single-vessel disease (3.69±0.56 vs. 4.07±0.45, $p=0.042$). By SYNTAX grouping, a decrease in GLS values and an increase in the LVEF/GLS ratio were observed ($p=0.038$). The SYNTAX scores showed a statistically significant negative correlation with all GLS values (GLS Avg: $r=-0.3361$, $p=0.003$). Regression analysis identified age, male sex, and GLS mid (mean) as independent variables (Table 3). In a multivariate model, the LVEF/GLS ratio was also found as an independent risk factor (OR 231, $p<0.001$).

In the analyses performed for lesion prediction, a decrease in regional longitudinal strain (RLS) values related to the lesion site was found for LAD and RCA lesions. In patients with CX lesions, there was a statistically significant decrease in RLS values related to both the LAD and CX territories ($p<0.001$).

DISCUSSION

The main findings of the study can be summarized as follows: (1) In patients with SAP, there was a correlation between MPS results above 12% (sensitivity: 0.77, specificity: 0.81) and mid-wall GLS (avg) values below -18.4% (sensitivity: 0.74, specificity: 0.96) with TP CAG outcomes. (2) Within the MPS-TP group, there was a positive correlation between the LVEF/GLS

Table 1. The clinical characteristics of patients and some conventional echocardiographic and two-dimensional global longitudinal strain parameters of the study population in comparison with myocardial perfusion scintigraphy true positives and myocardial perfusion scintigraphy false positives.

Variables	MPS false positives (NS-CAD) (n=58) (mean±SD)	MPS true positives (CAD, yes) (n=75) (mean±SD)	p
Age (years)	55.94±9.99	61.70±9.61	<0.001
Gender			
Male, n (%)	23 (39.65)	50 (66.67)	
Female, n (%)	35 (60.35)	25 (33.33)	0.002
BMI, kg/m^2	29.47±3.84	29.21±4.64	0.728
DM, n (%)	12 (20.68)	32 (42.66)	0.008
HT, n (%)	48 (82.75)	63 (84)	0.848
Smoking, n (%)	23 (39.65)	43 (57.33)	0.036
HL, n (%)	24 (41.37)	49 (65.33)	0.006
LVEF (%)	65.75±4.47	64.73±5.37	0.251
E/e'	8.36±2.27	9.11±2.23	0.029
LVEDD (mm)	46.98±3.88	47.12±4.18	0.847
LVESD (mm)	29.53±3.43	30.24±3.82	0.272
LV mass index (g/m^2)	97.02±16.41	101.81±22.45	0.175
LA volume index (mL/m^2)	21.64±4.58	21.83±5.33	0.761
Percentage of ischemia in MPS	11.10±2.79	14.88±5.28	<0.001
GLS mid-myo (avg), %	-22.04±2.14	-15.48±2.37	<0.001
GLS endocardial, %	-24.99±2.48	-18.43±2.95	<0.001
GLS epicardial, %	-19.53±1.80	-14.92±2.60	<0.001
LVEF/GLS Avg ratio	3.05±0.32	3.86±0.61	<0.001

BMI: body mass index; CAD: coronary artery disease; Cx: circumflex artery; DM: diabetes mellitus; HL: hyperlipidemia; HT: hypertension; EDD: end-diastolic diameter; EF: ejection fraction; ESD: end-systolic diameter; LA: left atrial; LV: left ventricular; MPS: myocardial perfusion scintigraphy; NS: non-significant; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; Avg: average.

Table 2. Diagnostic performance of myocardial perfusion scintigraphy percentage: Global longitudinal strain parameters and the correlation between ischemic percentages of myocardial perfusion scintigraphy and global longitudinal strain values in the myocardial perfusion scintigraphy true-positive group.

Diagnostic performance of GLS parameters in the true-positive group					
	Cutoff	AUC (95%CI)	Sensitivity	Specificity	p
GLS (Avg)	-18.4	0.90 (0.84–0.95)	0.74 (0.63–0.83)	0.96 (0.88–0.99)	<0.001
GLS endocardial	-22.3	0.91 (0.84–0.95)	0.84 (0.74–0.90)	0.86 (0.75–0.92)	<0.001
GLS epicardial	-16.4	0.90 (0.83–0.94)	0.77 (0.66–0.85)	0.96 (0.88–0.99)	<0.001
Diagnostic performance of MPS percentages in the true-positive group					
	Cutoff	AUC (95%CI)	p		
Percentage of ischemia in MPS	>12	0.76 (0.68–0.86)	<0.001		
Sensitivity: 0.77 (0.66–0.85)		Specificity: 0.81 (0.69–0.89)			
Correlation between ischemic percentages of MPS and GLS values in the true-positive group					
	Correlation (r)	p			
GLS (Avg)	-0.2606	0.002			
GLS endocardium	-0.2716	0.002			
GLS epicardium	-0.2636	0.002			

GLS: global longitudinal strain; Avg: average; MPS: myocardial perfusion scintigraphy; AUC: area under the curve; CI: confidence interval.

Table 3. Uni-multivariate and stepwise binary logistic regression analyses for myocardial perfusion scintigraphy-TPs.

Log reg	Univariate model-1			Multivariate model-1		
	OR	95%CI	p	OR	95%CI	p
Age	1.062	1.02–1.10	0.002	1.12	1.02–1.23	0.018
Sex (male)	3.043	1.49–6.20	0.002	12.9	1.60–104.9	0.016
DM	2.853	1.30–6.24	0.009	2.00	0.33–12.07	0.446
Smoking	2.045	1.01–1.10	0.044	0.97	0.18–5.17	0.977
LVEF/GLS	103.0	20–514	<0.001	2.34	0.01–1836	0.802
GLS-endo	0.441	0.34–0.58	<0.001	0.67	0.30–1.51	0.345
GLS-avg	0.381	0.27–0.53	<0.001	0.25	0.08–0.73	0.012
GLS-epi	0.339	0.23–0.49	<0.001	1.79	0.57–5.67	0.217
EF	0.961	0.89–1.02	0.250	1.22	0.98–1.51	0.067

Multivariate model-2			
	OR	95%CI	p
Age	1.17	1.06–1.29	0.002
Sex (male)	5.57	1.06–29.2	0.042
DM	0.89	0.19–4.08	0.886
Smoking	0.95	0.19–4.65	0.956
LVEF/GLS	231	24–2222	<0.001

Log Reg: logistic regression; GLS: global longitudinal strain; Avg: average; Epi: epicardium; Endo: endocardium; EF: ejection fraction; DM: diabetes mellitus; CI: confidence interval; OR: odds ratio.

mid ratio and both the presence and severity of CAD. (3) A negative correlation was identified between increasing ischemic percentages of MPS and GLS values, indicating that this correlation is associated with an increased likelihood of TP CAD. (4) Additionally, it was found that female sex was associated with a reduced rate of TP results in MPS.

Risk stratification in SAP is essential for optimal management. The recent European Society of Cardiology guidelines recommend direct invasive CAG for patients with a pre-test probability of CAD over 85%. For those with a pre-test probability between 15 and 85%, non-invasive stress testing, preferably with imaging, is advised to reduce costs and complications following invasive procedures[1]. Although treadmill or bicycle exercise testing is cost-effective, safe, and widely available, it has been used less frequently in recent years because of its low sensitivity[5]. MPS is recommended by clinical guidelines for assessing ischemic burden in patients with suspected angina pectoris and a moderate-to-high pre-test probability (15–85%). Additionally, it is essential for risk stratification and treatment planning in patients diagnosed with CAD[1]. In patients with angina symptoms, the MPS method has a sensitivity of 86–88% and a specificity of 74–76% for detecting coronary stenosis[6]. While this method is valuable for diagnosing CAD, its main limitation is the radiation exposure from thallium-201 radiopharmaceuticals. Additionally, limited availability in various health-care settings and the need for skilled specialists to interpret results pose further challenges[6]. MPS has a significant rate of false-negative and FP results[7]. It may not accurately reflect CAD severity in patients with multivessel disease. Factors contributing to FPs, especially in obese individuals and women, include attenuation artifacts, technical limitations, coronary vasospasm, circulation abnormalities, cardiomyopathy, and conduction issues like left bundle branch block[8]. The guidelines recommend that CAG should be considered if MPS reveals ischemia of 10% or more[1]. In our study, we found an ischemic burden of 12% as a cutoff value for MPS in the detection of CAD in the MPS-TP group. Therefore, additional imaging techniques are required to guide the invasive strategy in distinguishing between these closely related values.

Echocardiography is a widely used, radiation-free technique. However, suboptimal image quality in some patients can hinder the assessment of segmental motion in CAD, and an accurate visual analysis requires an experienced operator[9]. Conventional echocardiographic measurements can obscure regional wall motion abnormalities, but studies show that 2D speckle-tracking strain analysis can reveal subtle myocardial changes indicative of CAD[10]. In our study, we identified a threshold of <-18.4% for LV/GLS (avg) to detect CAD in the

MPS-TP group using S-ECHO. The literature suggests that S-ECHO provides valuable information not only in the detection of CAD but also in the assessment of wall motion abnormalities[11]. In the literature, a study examining 268 patients with negative cardiac biomarkers and non-specific electrocardiographic (ECG) findings but with a suspicion of CAD identified a cutoff value of -18.8% for LV/GLS. In their study, the sensitivity of GLS was found to be 72%, while the specificity was 82%[12]. In our study, the cutoff value for LV/GLS (avg) was determined to be -18.4%, with a sensitivity of 74% and a specificity of 96% for GLS. Furthermore, a decrease in LV/GLS values was confirmed to be an independent predictor of stable CAD in patients without wall motion abnormalities[10]. On the other hand, the literature suggests that negative results for LV/GLS obtained by S-ECHO may provide an acceptable negative predictive value for CAD[9]. In our study, we similarly found that GLS (avg) measurements serve as a negative predictor of CAD for patients with TP results in MPS. It has been determined that S-ECHO can guide the discharge of patients with suspected CAD who have normal GLS values from emergency departments or cardiology clinics.

S-ECHO has several advantages over MPS, including enhanced accessibility, greater repeatability, and shorter procedure times[13]. The literature shows that patients with CAD have lower left ventricular GLS values than those with normal coronary arteries. Additionally, patients with significant stenosis in a specific artery exhibit a greater reduction in RLS from that segment. Thus, S-ECHO is useful for diagnosing CAD and identifying the responsible lesions in affected coronary arteries[14]. However, in our study, while the subgroup analysis of patients with MPS-TPs revealed that the endo-mid-epi values of LAD-RLS from the same segment were lower compared to other regions (with LAD-lesion –16.51; without –20.64, p<0.001), regression analysis indicated that no RLS value served as an independent predictor for predicting LAD lesions (OR 3.35, 95%CI 0.16–67.23, p:0.408). Similarly, the literature demonstrates that studies utilizing speckle-tracking echocardiography in patients with total and subtotal stenosis in different coronary arteries have successfully distinguished between the degrees of stenosis[15]. In our study, although a greater reduction was observed in RLS values applied for lesion-specific evaluation, we determined that none of the RLS parameters could be utilized as predictors for lesions (p>0.05). The most likely reasons for this finding may include the fact that coronary arteries do not solely supply specific segments, variations during the coronary arteries, the presence of collateral circulation, and microvascular circulation disturbances.

A remarkable finding of our study was the increase in the LVEF/GLS ratio in MPS-TP patients, independent of EF. We observed that as the SYNTAX score increased, GLS values decreased and the LVEF/GLS ratio rose, indicating a negative correlation. This suggests that the LVEF/GLS ratio may indicate disease prevalence beyond just CAD presence. In a study conducted on acute coronary syndrome patients in the literature, GRACE score, SYNTAX score, and GLS values were used. In this study, it was found that the LV/GLS ratio could be used in patients with high GRACE scores[16]. Therefore, we believe that the increase in the LVEF/GLS ratio in patients with stable CAD as seen in our study can be used to predict subclinical LV dysfunction. It is known that the specificity and sensitivity of MPS are lower, and its diagnostic value is reduced in women. Possible reasons for this are attenuation artifacts or anterior chest wall morphologies[8]. Breast tissue most commonly causes artifacts on the anterior wall. In other regions, the diaphragm in the inferior wall and adipose tissue in the lateral wall may cause artifacts. In our study, we observed a female predominance in the MPS-FP group. LVEF/GLS examination may be an important alternative to MPS in female patients with SAP and CAD.

CONCLUSION

In SAP patients, LV/GLS from 2D speckle-tracking echocardiography shows sensitivity and specificity similar to MPS for detecting CAD. A higher LVEF/GLS ratio is a strong indicator of CAD severity. LV/GLS is a useful non-invasive option, especially for female patients prone to MPS FPs due to artifacts.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS COMMITTEE APPROVAL

The Trakya University's Ethics Committee approved this study (clinical trial approval number: TUTF-GOBAEK-2023/398).

AUTHORS' CONTRIBUTIONS

ÇK: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **MG:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2024;45(36):3415-537. https://doi.org/10.1093/eurheartj/ehae177
2. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr. 2004;17(10):1021-9. https://doi.org/10.1016/j.echo.2004.06.019
3. Collet C, Onuma Y, Miyazaki Y, Morel MA, Serruys PW. Integration of non-invasive functional assessments with anatomical risk stratification in complex coronary artery disease: the non-invasive functional SYNTAX score. Cardiovasc Diagn Ther. 2017;7(2):151-8. https://doi.org/10.21037/cdt.2017.03.19
4. ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur J Cardio-Thoracic Surg. 2018;55:4-90.
5. Froelicher VF, Lehmann KG, Thomas R, Goldman S, Morrison D, Edson R, et al. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative Exercise Testing and Angiography. Ann Intern Med. 1998;128(12 Pt 1):965-74. https://doi.org/10.7326/0003-4819-128-12_part_1-199806150-00001
6. Semirgin SU, Algül Gİ, Tosun FC, editors. Miyokart perfüzyon sintigrafisi: tuzak ve artefaktlar. Nucl Med Semin; 2024;10(1):62-80. https://doi.org/10.4274/nts.galenos.2024.0006
7. Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. J Nucl Cardiol. 2006;13(1):24-33. https://doi.org/10.1016/j.nuclcard.2005.12.004
8. Semirgin SU, Algül Gİ, Tosun FC. Myocardial perfusion imaging: pitfalls and artifacts. Nucl Med Semin. 2024;10(1):62-80. https://doi.org/10.4274/nts.galenos.2024.0006
9. Ng AC, Sitges M, Pham PN, Tran T, Delgado V, Bertini M, et al. Incremental value of 2-dimensional speckle tracking strain imaging to wall motion analysis for detection of coronary artery disease in patients undergoing dobutamine stress echocardiography. Am Heart J. 2009;158(5):836-44. https://doi.org/10.1016/j.ahj.2009.09.010
10. Choi JO, Cho SW, Song YB, Cho SJ, Song BG, Lee SC, et al. Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality. Eur J Echocardiogr. 2009;10(5):695-701. https://doi.org/10.1093/ejechocard/jep041
11. Sun L, Zhu W, Xu Y, Gao M, Sun S, Li J. Clinical study of two-dimensional speckle tracking to evaluate abnormal myocardial motion due to coronary lesions. Echocardiography. 2024;41(1):e15744. https://doi.org/10.1111/echo.15744
12. Schroeder J, Hamada S, Gründlinger N, Rubeau T, Altiok E, Ulbrich K, et al. Myocardial deformation by strain echocardiography identifies patients with acute coronary syndrome and non-diagnostic ECG presenting in a chest pain unit: a prospective study of diagnostic accuracy. Clin Res Cardiol. 2016;105(3):248-56. https://doi.org/10.1007/s00392-015-0916-2
13. Götte MJ, Germans T, Rüssel IK, Zwanenburg JJ, Marcus JT, Rossum AC, et al. Myocardial strain and torsion quantified by cardiovascular magnetic resonance tissue tagging: studies in normal and impaired left ventricular function. J Am Coll Cardiol. 2006;48(10):2002-11. https://doi.org/10.1016/j.jacc.2006.07.048
14. Akiash N, Mohammadi M, Mombeini H, Nikpajouh A. Myocardial strain analysis as a non-invasive screening test in the diagnosis of stable coronary artery disease. Egypt Heart J. 2021;73(1):49. https://doi.org/10.1186/s43044-021-00173-6
15. Kalay N, Celik A, Inanc T, Dogan A, Ozdogru I, Kaya MG, et al. Left ventricular strain and strain rate echocardiography analysis in patients with total and subtotal occlusion in the infarct-related left anterior descending artery. Echocardiography. 2011;28(2):203-9. https://doi.org/10.1111/j.1540-8175.2010.01298.x
16. Fouad A, Farag EM, Roshdy HS, Gad MM, Almaashani S, Sayed A. The possible utility of global longitudinal strain in the risk-stratifying process of non-ST elevation-acute coronary syndrome. Echocardiography. 2024;41(2):e15769. https://doi.org/10.1111/echo.15769

ORIGINAL ARTICLE

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Comparison of high- and low-dose radial extracorporeal shock wave therapy in carpal tunnel syndrome

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SUMMARY

OBJECTIVE: The aim of this study was to compare the efficacy of radial extracorporeal shock wave therapy administered at low vs. high pressures in patients with carpal tunnel syndrome.

METHODS: Patients with carpal tunnel syndrome were randomized into two groups: low-dose group and high-dose group. Each patient underwent a total of four sessions of radial extracorporeal shock wave therapy, administered once a week. The radial extracorporeal shock wave therapy was delivered at 4.0 bars for the high-dose group and 1.5 bars for the low-dose group. Both groups received conventional physical therapy program consisting of transcutaneous electrical nerve stimulation, paraffin wax, orthoses, and tendon gliding exercises, three times per week over a 4-week duration. Outcome measures included pain levels, hand grip strength, pinch strength, the Boston Carpal Tunnel Syndrome Questionnaire, and nerve conduction studies.

RESULTS: Both groups exhibited improvements across all measures, except for the nerve conduction studies parameters. In the intragroup analysis, statistically significant differences were observed with small-to-moderate effect sizes for median motor distal latency, median sensory nerve conduction velocity, median sensory distal latency, and the Boston functional status subscale, all favoring the high-dose group ($p<0.05$). In the low-dose group, a statistically significant difference with a moderate effect size was noted solely for hand grip strength ($p<0.05$).

CONCLUSION: High-dose radial extracorporeal shock wave therapy was significantly better than low-dose radial extracorporeal shock wave therapy with small-to-moderate effect sizes in the recovery of the function and nerve conduction studies parameters of patients with carpal tunnel syndrome.

Clinical Trials Registry: The study was registered on the Clinical Trials Registry (registration number: NCT05681663).

KEYWORDS: Carpal tunnel syndrome. Extracorporeal shock wave therapy. Pain. Electromyography. Treatment.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a prevalent form of neuropraxia affecting the upper extremity[1]. Non-steroidal anti-inflammatory drugs, local corticosteroid injections, diuretics, vitamin B supplements, rest splints, manual therapy techniques, and physical therapy modalities are utilized in the management of CTS[2].

Extracorporeal shock wave therapy (ESWT) operates on the principle of directing high-amplitude sound waves toward the injured area of the body. Experimental studies indicated that ESWT enhanced nitric oxide production, repaired damaged axons, and promoted axonal regeneration[3,4]. Therefore, using the ESWT in patients with CTS could be a useful treatment option, especially for nerve healing.

In the literature, studies investigating the effect of radial ESWT (rESWT) on CTS used different pressure applications, and they reported that rESWT reduces the symptoms of CTS[5-7]. However, there is no consensus on which pressure value is more effective. Therefore, the aim of this study was to compare the effects of low (1.5 bars)- and high (4.0 bars)-pressure doses on CTS symptoms.

METHODS

The study employed a randomized, single-blind, 1:1 parallel-group design and was conducted at Kırşehir Ahi Evran University from December 2022 to April 2023. Approval was granted by the local ethics committee on November 22, 2022 (2022-21/185). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Participants

Inclusion criteria consisted of individuals aged 18–65 years, experiencing paresthesia, pain, and vasomotor symptoms in the region associated with the median nerve for more than 6 weeks, a positive provocative test, and a neurophysiological assessment indicating mild-to-moderate median nerve lesion severity. Patients were excluded if they had undergone previous injections or surgery within the last 3 months, had severe CTS, exhibited any sensory and/or motor deficits in the ulnar or radial nerve, or had systemic conditions contributing to CTS.

Randomization

A randomization process was conducted to assign 36 patients with CTS to two study groups: high-dose group (HDG, n=18) and low-dose group (LDG, n=18), utilizing matched-pairs randomization based on age and sex (Figure 1).

Blinding

All evaluations were conducted by the investigator, who remained blinded to the group assignments throughout the study. The patients and clinicians were not blinded.

Interventions

The conventional physiotherapy program included transcutaneous electrical nerve stimulation (TENS), tendon gliding exercises, wrist resting splint, and paraffin wax treatment. This physiotherapy regimen was identical for both groups and was administered three times per week over a 4-week duration.

Transcutaneous electrical nerve stimulation

Conventional TENS was administered, with the pulse duration adjusted to 50–100 μs, and was delivered at a frequency of 100 Hz for a duration of 20 min, at an amplitude that did not induce muscle contractions[6].

Tendon gliding exercises

The patients were directed to perform tendon gliding exercises as recommended by Totten and Hunter[8].

Orthosis

The use of a night orthosis to keep the wrist in a neutral position was advised for each patient[5].

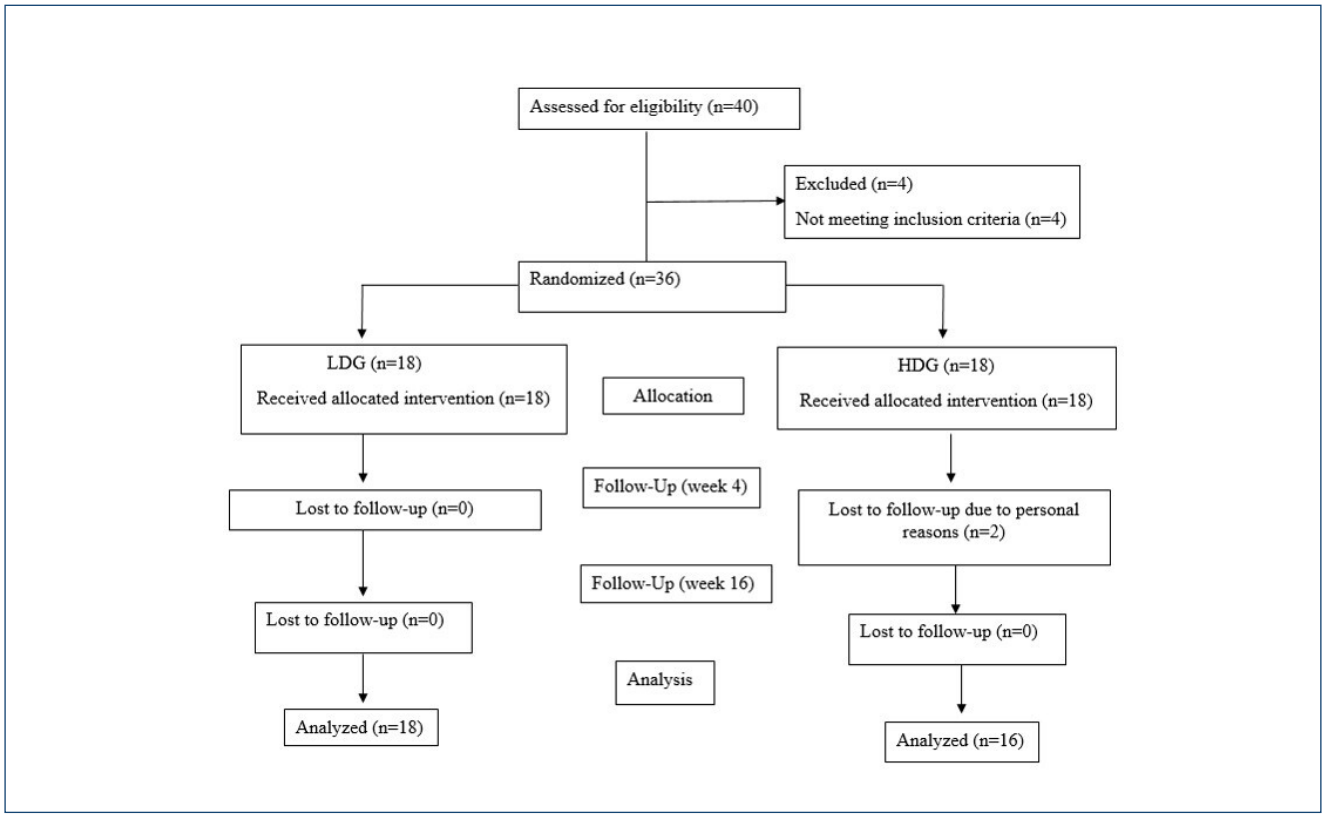

Figure 1. Study flowchart.

Paraffin wax

Patients were asked to dip their hands up to their wrists in a paraffin cauldron. After each immersion, the patient's hand was removed from the paraffin cauldron, waited for 5 s, and dipped again. The patient's hand was covered with a bag and wrapped in a towel, and waited for 20 min[9].

Radial extracorporeal shock wave therapy

Both the study groups received a total of four sessions of rESWT once a week. A Modus rESWT Touch Shock Waves device (Inceler Medikal, Ankara, Turkey) was used for rESWT with a frequency of 5 Hz and 2000 shock pulses for both groups[5]. The only difference was in pressures as the HDG received the rESWT with a pressure of 4.0 bars, while the LDG received 1.5 bars pressure [5].

Outcome measurements

Outcome measures included pain intensity, hand grip strength, pinch strength, neurophysiological status, and functional status of the upper extremity. Measurements were taken before treatment (baseline), after treatment (week 4), and 12 weeks post-treatment (week 16). The nerve conduction studies (NCS) were conducted twice, at baseline and week 16.

Primary outcomes

Visual analog scale

The patients were requested to indicate the intensity of the pain they experienced over the past 24 h by marking a 10-cm line scale, where 0="no pain" and 10="maximum pain." Pain was assessed using three distinct parameters: night pain, resting pain, and activity pain[10].

Electroneuromyography

A Nihon Kohden Neuropack S1 MEB-9400 electroneuromyography (ENMG) device (Nihon Kohden Corp., Tokyo, Japan) was utilized. Values of median sensory distal latency (mSDL) <3.6 ms, median motor distal latency (mMDL) <4.2 ms, and median sensory nerve conduction velocity (mSNCV) >50 m/s were deemed normal[11]. The classification for CTS provided by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) was utilized[12].

Secondary outcomes

Hand grip strength

Grip strength for both hands was assessed using the Jamar® Hand Dynamometer (Patterson Medical, Warrenville, IL, USA), and the results were expressed in kilograms[13].

Pinch strength

The pinch strength of both hands was measured using the Jamar® Pinch Meter (Patterson Medical, Warrenville, IL, USA), and the results were expressed in kilograms[14].

Boston Carpal Tunnel Syndrome Questionnaire

The valid and reliable Turkish adaptation of the Boston Carpal Tunnel Syndrome Questionnaire (BCTSQ) was utilized, as it assesses both symptom severity and functional status in patients with CTS[15].

Sample size

The G-Power program (version 3.1.9.4, University of Düsseldorf, Düsseldorf, Germany) was utilized for this calculation. To achieve 80% power with an α error level of 0.05, repeated-measures analysis of variance (ANOVA) was conducted for both within-group and between-group interactions, employing a large effect size of 0.30 to account for the two groups.

Statistical analysis

The IBM SPSS software (version 25.0, IBM Corp., NY, USA) was employed for statistical analysis. A two-way ANOVA was conducted to assess changes over time in the measured outcomes of the study groups and their group–time interactions. Eta squared (η^2) was calculated to classify effect sizes as 0.02 (small), 0.13 (moderate), and 0.26 (large). A statistical significance level of $p<0.05$ was established.

RESULTS

Primary outcomes

There was a significant decrease in visual analog scale (VAS) rest, VAS activity, and VAS night measurements after treatment compared to pre-treatment measurements for both groups. While the highest decrease occurred in the VAS night of the HDG (7.06±2.89 vs. 2.13±2.78), the least decrease was in the VAS rest value of the LDG (5.11±2.17 vs. 2.61±2.12). The intragroup analyses of pain parameters indicated no significant group-by-time interaction (Table 1).

There was an improvement with moderate effect sizes in post-treatment (week 16) mMDL, mSNCV, mSDL, and median sensory nerve action potential (mSNAP) measurements compared to pre-treatment measurements for the HDG (Table 2).

Secondary outcomes

The sociodemographic information of the participants is shown in Table 2. There was a significant increase in grip and pinch strength measurements after treatment compared to pre-treatment

Table 1. Intergroup and intragroup analyses.

Variables	Groups	Baseline mean±SD	Week 4 mean±SD	Week 16 mean±SD	Intragroup p*	Intergroup p**	η^2
VAS rest (cm)	LDG	5.11±2.17	3.28±1.87	2.61±2.12	**0.000***	0.291	0.038
	HDG	5.5±3.18	4.25±3.38	2.38±2.87			
VAS activity (cm)	LDG	7.67±2.66	4.44±3.28	4.44±3.18	**0.000***	0.076	0.077
	HDG	7.63±2.8	5.25±3.34	3.19±3.08			
VAS night (cm)	LDG	6.17±2.28	3.06±1.83	2.61±2.4	**0.000***	0.248	0.043
	HDG	7.06±2.89	3.94±3.4	2.13±2.78			
mMDL (ms)	LDG	4.1±0.73	-	4.05±0.78	**0.014***	**0.005****	0.221
	HDG	4.35±1.22	-	3.6±0.78			
mSNCV (m/s)	LDG	41.75±6.74	-	40.22±9.07	0.084	**0.005****	0.223
	HDG	39.86±8.42	-	45.75±10.05			
mSDL (ms)	LDG	2.99±0.6	-	3.3±1.51	0.784	**0.032****	0.136
	HDG	3.11±0.74	-	2.71±0.64			
mSNAP	LDG	40.22±18.1	-	37.49±26.87	0.737	0.333	0.029
	HDG	20.31±11.38	-	25.9±10.81			
Grip strength (kg)	LDG	15.74±4.0	18.64±5.29	22.46±6.56	**0.000***	**0.003****	0.168
	HDG	20.16±6.03	22.61±6.25	22.99±5.73			
Pinch strength (kg)	LDG	5.25±1.79	6.28±1.9	6.21±1.93	**0.000***	0.231	0.045
	HDG	6.4±1.57	6.87±1.66	7.09±1.51			
BCTSQ symptom severity	LDG	3.13±0.74	2.05±0.86	2.22±0.83	**0.000***	0.162	0.055
	HDG	3.27±1.01	2.27±0.71	1.96±0.84			
BCTSQ functional status	LDG	3.25±0.89	2.78±0.95	2.87±0.91	**0.000***	**0.04****	0.103
	HDG	3.33±1.06	2.92±0.98	2.44±1.02			

SD: Standard deviation; LDG: low-dose group; HDG: high-dose group; mMDL: median motor distal latency; mSNCV: median sensory nerve conduction velocity; mSDL: median sensory distal latency; mSNAP: median sensory nerve action potential; BCTSQ: Boston Carpal Tunnel Syndrome Questionnaire; VAS: visual analog scale; kg: kilogram; cm: centimeter; ms: millisecond; m/s: meter/second; $p<0.05$; *p: intragroup analysis; **p: intergroup analysis; η^2: effect size, statistically significant values are denoted in bold.

Table 2. Sociodemographic and baseline clinical characteristics of the groups.

Variables	LDG (n=18) mean±SD	HDG (n=16) mean±SD	p*
Age (years)	51.89±12.21	56.88±7.25	0.164
Body mass index (kg/m^2)	31.77±4.94	31.88±4.88	0.94
Sex (female:male)	15:3	15:1	0.347
CTS grade (mild:moderate)	3:15	4:12	0.549
Occupation (n)			
Homemaker	11	15	0.164
Teacher	4	1	
Worker	3	0	
Affected side (right:left)	10:8	10:6	0.681
Dominant side (right:left)	18:0	16:0	-

SD: standard deviation; LDG: low-dose group; HDG: high-dose group; kg: kilogram; m: meter; CTS: carpal tunnel syndrome, *$p<0.05$.

measurements for both groups (Table 2). However, only grip strength indicated a statistically significant group-by-time interaction with a moderate effect size in favor of the LDG (HDG: 20.16±6.03 vs. 22.99±5.73; LDG: 15.74±4.0 vs. 22.46±6.56; p=0.003; η^2=0.17).

According to the intergroup analysis, there was a significant decrease in BCTSQ symptom severity and functional status subscale measurements after treatment compared to pre-treatment measurements for both groups. However, only the BCTSQ functional status subscale (HDG: 3.33±1.06 vs. 2.44±1.02; LDG: 3.25±0.89 vs. 2.87±0.91; p=0.04; η^2=0.10) indicated a significant group-by-time interaction with a small effect size in favor of the HDG (Table 2).

DISCUSSION

In accordance with the findings, it was noted that both groups demonstrated improvements in pain, grip strength, pinch strength, and functional status following the intervention. However, those in the HDG were significantly better on the NCS parameters and BCTSQ functional status compared to those in the LDG 12 weeks after the intervention.

In a dose-dependent rESWT study, it was reported that three sessions of 4.0 bars rESWT improved mSNCV scores in patients with mild-to-moderate CTS[16]. In a randomized prospective study, the effectiveness of 1.5 bars rESWT and corticosteroid iontophoresis was compared in patients with CTS[17]. According to the literature, both low-dose and high-dose rESWT improved NCS parameters. Despite these findings, there were improvements in mMDL, mSNCV, mSDL and mSNAP measurements after the intervention in HDG.. Also, intragroup analysis of the mMDL, mSNCV, and mSDL measurements demonstrated a statistically significant intragroup interaction in favor of the HDG. In a systematic review on the use of NCS in the diagnosis of CTS, it was reported that the cutoff value for sensory latency was 3.37 ms (2.8–4 ms) and for motor latency was 4.28 ms (3.8–4.6 ms)[18]. When the values in our study were compared with the reported cutoff values, the sensory latency values in our study were significant in favor of the HDG (4.0 bars) and parallel to the literature.

There is presently no established standard treatment protocol regarding application frequency, energy intensity, or total shots for the use of rESWT in CTS[19]. However, numerous studies have employed two or more sessions of ESWT for chronic musculoskeletal disorders[5,17,19]. Consequently, clinical experience suggests that repeated sessions of ESWT may be more effective than a single application. In the present study, the more frequently used applications of rESWT in the literature were preferred, and rESWT was applied with 2,000 shots, 1.5 bars and 4.0 bars intensity of energy, and a frequency of 5 Hz. Especially, in the literature, there are conflicting applications for rESWT pressure intensity for treating CTS. A randomized controlled trial compared rESWT and corticosteroid iontophoresis, with an application of 1.5 bars rESWT[17]. In another study, rESWT, local corticosteroid injection, and splint groups were compared, with an application of 4.0 bars rESWT[5]. Thus, different pressure applications were used in studies examining the impact of rESWT treatment on CTS, and all studies reported that rESWT reduced the symptoms of CTS[5-7,17]. In our study, the effects of low- and high-pressure values on the symptoms of CTS were compared in order to investigate which pressure severity of rESWT is superior in the management of CTS. As a result, the application of rESWT at a high pressure (4.0 bars) in the treatment of CTS could be more effective in reducing clinical symptoms.

In this study, one of the limitations was that functional measurements were subjective based on patient statements. Also, the sample size was small, which may have limited the generalizability of the findings. Clinical functional tests could be useful as an objective method in future studies. Similarly, the use of ultrasound imaging which objectively measures the median nerve diameter would strengthen the level of evidence in future studies.

CONCLUSION

Both groups experienced improvements in pain, grip strength, pinch strength, and functional status following the intervention. However, high-dose rESWT was significantly better than low-dose rESWT with small-to-moderate effect sizes in the recovery of the function and NCS parameters of patients with CTS.

ETHICAL APPROVAL

Ethical clearance was granted by the local ethics committee (protocol number: 2022-21/185).

AUTHORS' CONTRIBUTIONS

İC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **BK:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **FT:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **MC:** Conceptualization, Formal Analysis, Investigation, Methodology, Writing – orijinal draft, Writing – review & editing. **HA:** Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **AT:** Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Yetiş M, Kocaman H, Canlı M, Yıldırım H, Yetiş A, Ceylan İ. Carpal tunnel syndrome prediction with machine learning algorithms using anthropometric and strength-based measurement. PLoS One. 2024;19(4):e0300044. https://doi.org/10.1371/journal.pone.0300044
2. Ceylan İ, Büyükturan Ö, Aykanat Ö, Büyükturan B, Şaş S, Ceylan MF. The effectiveness of mobilization with movement on patients with mild and moderate carpal tunnel syndrome: a single-blinded, randomized controlled study. J Hand Ther. 2023;36(4):773-85. https://doi.org/10.1016/j.jht.2023.02.004
3. Hausner T, Nógrádi A. The use of shock waves in peripheral nerve regeneration: new perspectives? Int Rev Neurobiol. 2013;109:85-98. https://doi.org/10.1016/B978-0-12-420045-6.00003-1
4. Mariotto S, Cavalieri E, Amelio E, Ciampa AR, Prati AC, Marlinghaus E, et al. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric Oxide. 2005;12(2):89-96. https://doi.org/10.1016/j.niox.2004.12.005
5. Öztürk Durmaz H, Tuncay F, Durmaz H, Erdem HR. Comparison of radial extracorporeal shock wave therapy and local corticosteroid injection effectiveness in patients with carpal tunnel syndrome: a randomized controlled study. Am J Phys Med Rehabil. 2022;101(7):685-92. https://doi.org/10.1097/PHM.0000000000001891
6. Habibzadeh A, Mousavi-Khatir R, Saadat P, Javadian Y. The effect of radial shockwave on the median nerve pathway in patients with mild-to-moderate carpal tunnel syndrome: a randomized clinical trial. J Orthop Surg Res. 2022;17(1):46. https://doi.org/10.1186/s13018-022-02941-9
7. Menekseoglu AK, Korkmaz MD, Segmen H. Clinical and electrophysiological efficacy of extracorporeal shock-wave therapy in carpal tunnel syndrome: a placebo-controlled, double-blind clinical trial. Rev Assoc Med Bras (1992). 2023;69(1):124-30. https://doi.org/10.1590/1806-9282.20220943
8. Abdolrazaghi HA, Khansari M, Mirshahi M, Ahmadi Pishkuhi M. Effectiveness of tendon and nerve gliding exercises in the treatment of patients with mild idiopathic carpal tunnel syndrome: a randomized controlled Trial. Hand (N Y). 2023;18(2):222-9. https://doi.org/10.1177/15589447211006857
9. Mansiz Kaplan B, Akyuz G, Kokar S, Yagci I. Comparison of the effectiveness of orthotic intervention, kinesiotaping, and paraffin treatments in patients with carpal tunnel syndrome: a single-blind and randomized controlled study. J Hand Ther. 2019;32(3):297-304. https://doi.org/10.1016/j.jht.2017.12.006
10. Fender B, Thomas K, Hannon K, Shepherd H. The effect of biofeedback therapy and overnight splinting on vas in patients with existing cts pain. 2020.
11. Dumitru D, Amato AA, Zwarts MJ. Electrodiagnostic medicine. Hanley & Belfus; 2002.
12. Stevens JC. AAEM minimonograph #26: the electrodiagnosis of carpal tunnel syndrome. Am Assoc Electrodiagnostic Med Muscle Nerve. 1997;20(12):1477-86. https://doi.org/10.1002/(sici)1097-4598(199712)20:12<1477::aid-mus1>3.0.co;2-5
13. Trajković N, Radanović D, Madić D, Andrašić S, Cadenas-Sanchez C, Mačak D, et al. Normative data for handgrip strength in Serbian children measured with a bulb dynamometer. J Hand Ther. 2021;34(3):479-87. https://doi.org/10.1016/j.jht.2020.03.001
14. Fess E. Clinical assessment recommendations. American Society of Hand Therapists; 1981. p. 6-8.
15. Sezgin M, Incel NA, Serhan S, Camdeviren H, As I, Erdoğan C. Assessment of symptom severity and functional status in patients with carpal tunnel syndrome: reliability and functionality of the Turkish version of the Boston Questionnaire. Disabil Rehabil. 2006;28(20):1281-5. https://doi.org/10.1080/09638280600621469
16. Ke MJ, Chen LC, Chou YC, Li TY, Chu HY, Tsai CK, et al. The dose-dependent efficiency of radial shock wave therapy for patients with carpal tunnel syndrome: a prospective, randomized, single-blind, placebo-controlled trial. Sci Rep. 2016;6:38344. https://doi.org/10.1038/srep38344
17. Osmanoğlu K, Yildizgören MT, Güler H, Turhanoğlu AD. Comparison of the therapeutic efficacy of extracorporeal shock wave therapy versus corticosteroid iontophoresis in carpal tunnel syndrome: a prospective randomized study. J Phys Med Rehabil Sci. 2022;25(1):63-72. https://doi.org/10.31609/jpmrs.2021-84159
18. Demino C, Fowler JR. The sensitivity and specificity of nerve conduction studies for diagnosis of carpal tunnel syndrome: a systematic review. Hand (N Y). 2021;16(2):174-8. https://doi.org/10.1177/1558944719855442
19. Koçak Ulucaköy R, Yurdakul FG, Bodur H. Extracorporeal shock wave therapy as a conservative treatment option for carpal tunnel syndrome: a double-blind, prospective, randomized, placebo-controlled study. Turk J Phys Med Rehabil. 2020;66(4):388-97. https://doi.org/10.5606/tftrd.2020.3956