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Cytomegalovirus and pregnancy: current evidence for clinical practice

Karina Felippe Monezi Pontes[1,2], Edward Araujo Júnior[1,3*]

Cytomegalovirus (CMV) is an enveloped DNA virus that, due to several intrinsic characteristics, establishes itself in granulocytes and monocytes after primary infection and becomes a lifelong latent infection[1,2]. CMV is the most common congenital viral infection in the world, with a prevalence rate of approximately 0.5–2.0% among all live births[1-3]. CMV is the first cause of permanent sequelae in childhood, accounting for one-fourth of cases of congenital sensorineural hearing loss, 10% of cases of cerebral palsy, and severe neurological abnormalities, vision loss, and growth disorders[1-3].

Global serum prevalence in women of childbearing age is approximately 86%[4]. This is important because only 50% of congenital CMV cases are maternal primary infections[5]. A Brazilian study confirmed the fact that most newborns affected by CMV come from previously infected/immune mothers (1–3% vertical transmission), but, in maternal primary infection, the vertical transmission rate is five times higher (30–40% vertical transmission)[6].

CMV is transmitted by direct contact of mucous membranes with contaminated body fluids such as urine, saliva, blood, genital secretions, tears, contaminated breast milk, solid organ transplants, and stem cells[7-9]. Symptoms in immunocompetent individuals are few and nonspecific or absent, but it can cause severe disease in immunosuppressed individuals, including fetuses[1,8]. There is no vaccine for CMV, despite numerous ongoing studies[10]. Until 2020, it was believed that the only way to prevent vertical transmission of CMV was through behavioral measures such as hand hygiene, avoiding contact with children's diapers, and avoiding kissing young children[10].

Until 2022, no guideline published in English suggested testing for CMV in prenatal care[7]. Reasons varied, including lack of vaccine, difficulty interpreting tests, inability to treat, and lack of randomized controlled trials[7]. Eventually, serologies were requested by physicians at random or when CMV was suspected because of maternal symptoms, contact with children with symptoms, or fetal findings suggestive of CMV[7].

The research on CMV in pregnancy is carried out mainly through specific antibody tests (IgG, IgM, and IgG avidity) or by detecting CMV DNA in body fluids (blood, urine, and saliva)[3]. Table 1 summarizes maternal serologies and how to interpret the results. Congenital CMV infection can damage the fetus directly or indirectly through placental dysfunction, resulting in miscarriage, preterm birth, or fetal growth restriction (FGR)[10,11]. The gestational age can influence vertical transmission, being higher with the progression of pregnancy[10,12]. When the virus crosses the placental barrier, the first fetal organ to be infected replicates in the tubular epithelium of the fetal kidney, with tropism for reticuloendothelial cells and the central nervous system (CNS)[10,12]. Shahar-Nissan et al.[13] describe that there is a cascade of events that culminate in fetal infection. This cascade of events can take 7–8 weeks, and it is described as maternal viremia, placental infection, and fetal dissemination via the hematogenous route. Therefore, amniotic fluid testing should be performed 8 weeks after the presumed period of infection and preferably after 22 weeks of gestation to reduce the risk of false negative results[10,14]. In newborns, it is performed by viral detection in body fluids (urine, saliva, and blood) by PCR, culture, or antigen testing until 3 weeks of life[2,10]. After this period, it is difficult to distinguish congenital from acquired postnatal infection[2,10].

Chatzakis et al.[12] in a meta-analysis, divided the fetal findings according to the period of maternal infection: periconceptional (4 weeks before to 3–6 weeks after the last menstrual period), first (6–13 weeks), second (14–26 weeks), and third trimester (>26 weeks). Fetal abnormalities were limited to periconceptional and first-trimester infections with rates of 28.8, 19.3, 0.9, and 0.4% for periconceptional, first-, second-, and third-trimester infections, respectively.

When the virus crosses the placental barrier and reaches the fetus, fetal damage is progressive and the first ultrasound findings are usually due to systemic infection and nonspecific (FGR, abnormal amniotic fluid volume, ascites, pleural effusion, skin edema, hydrops, placentomegaly, hyperechogenic bowel, splenomegaly, liver calcifications)[15]. CNS findings usually occur after weeks, and severe brain involvement is usually a predictor of poor prognosis, with microcephaly being the only finding that actually predicts an unfavorable outcome in up to 95% of cases[15,16]. The most common

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ultrasound findings are ventriculomegaly, periventricular changes, temporal cysts, and brain parenchymal lesions[16].

Since 2005, when Nigro et al.[17] published a nonrandomized study proposing the use of hyperimmune globulin for the treatment and prevention of congenital CMV, several promising studies have been published. The efficacy of hyperimmune globulin has not been proven in subsequent studies[18,19]; however, high-dose valacyclovir has been shown in several studies and systematic reviews to be effective and safe in preventing vertical transmission of CMV in primary maternal infections acquired during the periconceptional period and the first trimester of pregnancy[3,5,13,15,20-24]. Acyclovir is the precursor drug to valacyclovir and is converted to acyclovir in the first hepatic passage. Valacyclovir has been a drug of choice for herpes virus infections as it is more effective than acyclovir[24], which is classified as class B in pregnancy[22]. Treatment with valacyclovir is contraindicated in people who are unable to swallow capsules, in cases of severe vomiting, pre-existing liver disease, renal dysfunction, bone marrow suppression, patients receiving immunotherapy, or in cases of hypersensitivity to acyclovir[13]. The most common adverse reactions of valacyclovir are thrombocytopenia (usually mild), nausea, headache, abdominal pain, and nonspecific rash, none of which were significant and did not require discontinuation of the drug in a study by Shahar-Nissan et al.[13].

In 2016, Leruez-Ville et al.[15] in their nonrandomized study, showed a reduction in asymptomatic newborns from 43% (no treatment) to 82% with the use of high-dose valacyclovir (8 g/day) in fetuses with extra-brain and brain findings suggestive of vertical transmission of CMV. In 2020, Shahar-Nissan et al.[13] published a double-blind, randomized trial of valacyclovir (8 g/day) for the prevention of CMV congenital infection acquired periconceptionally or in the first trimester. The amniotic fluid PCR positivity rate was 30% in the control group compared with 11% in the treated group. Since this publication, at least six large studies, including meta-analyses and phase 3 trials, have been published confirming the use of valacyclovir 8 g/day for the prevention of CMV vertical transmission of maternal primary infection in the early stages of pregnancy (periconceptional and first trimester)[3,5,15,20-24].

Given the serious consequences of congenital CMV, the number of children worldwide who develop permanent and often severe sequelae each year, and the high prevalence of CMV in the population together with the strong evidence that valacyclovir is effective and safe in preventing vertical transmission, we suggest that protocols be revised to include routine CMV serology in the prenatal period (first visit and repeated at 12–14 weeks) when resources are available and especially in the event of seroconversion. Treatment with valacyclovir 8 g/day (4 g 12/12 h) should be started for at least 7 weeks after the estimated date of seroconversion and until

Table 1. Maternal serology and interpretation of the results.

Serology	Interpretation of the results
IgG - IgM -	Susceptible
IgG + IgM -	Immune/previous contact
IgG + IgM + high IgG avidity	Infection older than 12 weeks
IgG + IgM + low IgG avidity	Infection less than 12 weeks old
IgG - IgM + IgG + IgM + after 15 days IgG - IgM + after 15 days	Possible recent infection, repeat serology in 15 days Recent infection/ seroconversion False positive for cytomegalovirus

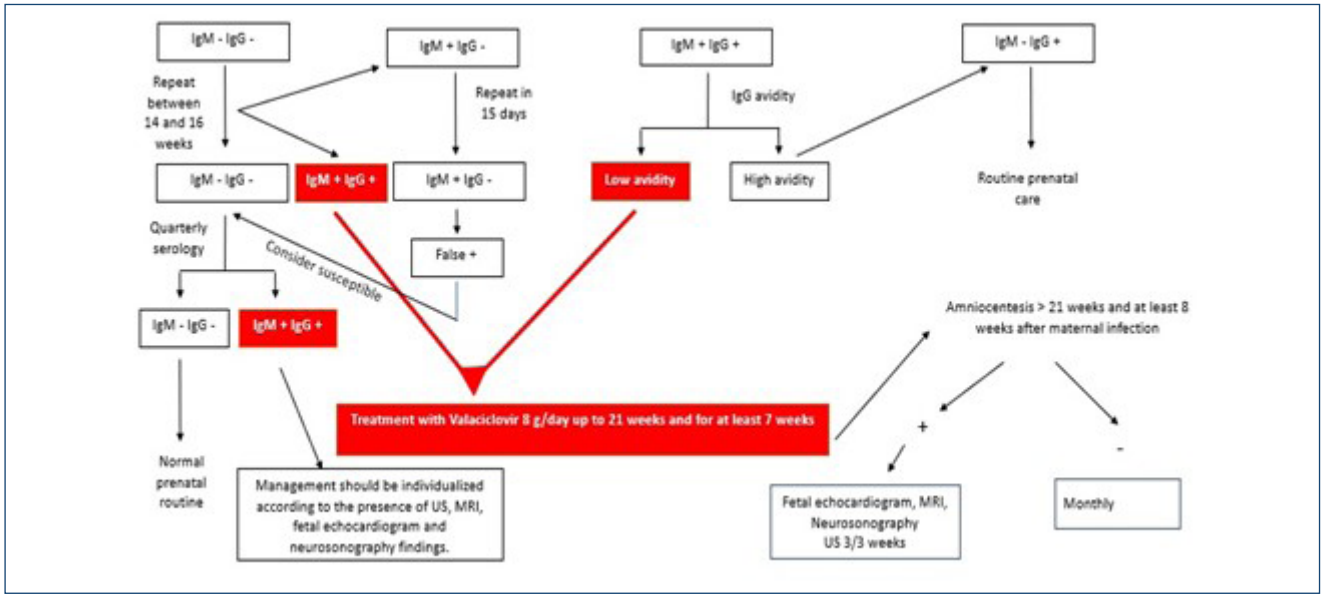

Figure 1. Flowchart of the suggested follow-up and treatment according to the maternal serologies during prenatal care.

at least 21 weeks when amniocentesis for amniotic fluid PCR for CMV is indicated[3,5,13,15,20-24]. Figure 1 shows suggested follow-up and treatment according to the serologies found during prenatal care.

AUTHORS' CONTRIBUTIONS

KFMP: Writing – original draft. EAJ: Supervision, Writing – original draft.

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Photoselective vaporization with green laser versus monopolar transurethral resection for benign prostatic hyperplasia

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct and assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.
Societies: Brazilian Medical Association

DESCRIPTION OF THE EVIDENCE COLLECTION METHOD

The objective was to evaluate the efficacy and safety of photoselective vaporization of the prostate with green light laser (PVP-GL) compared to monopolar transurethral resection (TURP-M) in reducing lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) in a systematic review and meta-analysis of randomized clinical trials (RCTs). The data sources were Medline, CENTRAL/Cochrane, LILACS, and ClinicalTrials.gov (CT.gov) up to February 2024. The eligibility criteria were RCTs comparing the safety and efficacy of PVP-GL versus TURP-M for LUTS and resulting from BPH. The data extracted were perioperative outcomes (surgical time, hospitalization time, and catheterization time); complication rates, including treatment-related adverse events; and functional outcomes, such as International Prostate Symptom Score (IPSS), maximum urinary flow rate (Qmax), and post-void residual volume (PVR). The synthesis was based on the risk differences or pooled mean differences and their corresponding 95% confidence intervals were calculated.

QUALITY OR CERTAINTY OF EVIDENCE

The certainty of evidence was assessed based on GRADE, graduated in very low, low, moderate, or high.

GOALS

The objective was to evaluate the efficacy and safety of photoselective vaporization of the prostate with green light laser (PVP-GL) compared to monopolar transurethral resection (TURP-M) in reducing lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) in a systematic review and meta-analysis of randomized clinical trials (RCTs).

INTRODUCTION

Surgical treatment is one of the cornerstones in managing lower urinary tract symptoms secondary to benign prostatic obstruction. It aims to remove the prostate adenoma through resection, enucleation, or evaporation[1,2]. Transurethral resection of the prostate (TURP), in both monopolar (TURP-M) and bipolar (TURP-B) forms, remains a widely investigated alternative[3]. Due to its widespread availability and effectiveness, TURP-M (the method of choice since the 1970s) is considered the reference technique for the surgical treatment of lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) in men with prostates between 30 and 80 mL. The technique removes tissue from the transition zone of the gland in varying degrees, resulting in a reduction in prostate volume and prostate-specific antigen by 25–58%[1,4]. TURP has demonstrated a high success rate and low reintervention rate in long-term follow-up[5]. However, increasing evidence indicates that this invasive procedure is also associated with serious complications such as bleeding, urethral strictures, urinary incontinence, and transurethral resection syndrome (TURS)[6-8].

In recent years, various techniques have been developed as safe and effective alternatives to TURP-M. One of these is photoselective vaporization of the prostate with PVP-GL. This technique is generally performed with a green laser with a wavelength

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of 532 nm, generated by potassium-titanyl-phosphate (KTP) or lithium tri borate (LBO) crystals[9]. Unlike other types of lasers, the green laser is easily absorbed by the hemoglobin in soft tissue, while it is hardly incorporated by other fluids (e.g., the irrigant used in the procedure), resulting in better coagulation and a lower risk of injuries to deeper tissues during vaporization[10,11].

These characteristics also allow the rapid vaporization of prostatic tissue. Photoselective vaporization of the prostate with this laser uses an 80-W KTP generator, a 120-W LBO generator, or a 180-W LBO generator.

This evaluation was conducted to determine whether PVP-GL has advantages over TURP-M in terms of efficacy and safety (perioperative or postoperative outcomes), by rigorously performing a meta-analysis of RCTs. This will provide stronger evidence that will help clinical decision-makers make a more appropriate choice between PVP-GL and TURP-M.

OBJECTIVE

The objective was to evaluate the efficacy and safety of photoselective vaporization of the prostate with green light laser (PVP-GL) compared to monopolar transurethral resection (TURP-M) in reducing lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH). This comparison will be established through a systematic review and meta-analysis of randomized clinical trials (RCTs).

METHODOLOGY

This assessment is supported by scientific information obtained through a systematic review of the literature, and its conclusions are based on a meta-analysis of the results obtained from the included studies. The exposition of the method used in the systematic review follows the items of the standardized checklist from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[12]. It has been registered in PROSPERO [PROSPERO (york.ac.uk)], with the registration number CRD42024551534.

Eligibility criteria

The eligibility criteria define the specific elements to address the clinical question outlined in the objectives of this evaluation, the requirements of greater consistency and scientific strength for study inclusion, and the main reasons for the exclusion of the retrieved evidence.

Inclusion criteria for studies

- Patients: with lower urinary tract symptoms secondary to benign prostatic hyperplasia, with surgical indication.
- Intervention: selective photovaporization of the prostate with a green light laser.
- Comparison: monopolar transurethral resection of the prostate.
- Outcomes: relevant clinical outcomes of efficacy and safety.
- Study design: double-blind, parallel-controlled RCTs.
- Language: no restrictions.
- Consulted period: no restrictions.
- Full text available.

Excluded studies: Crossover RCTs; systematic reviews with or without meta-analysis; narrative reviews; observational studies and/or case series; studies with surrogate endpoints; and the absence of extractable data regarding outcomes (absolute numbers and/or means) or the absence of another study measuring the same outcome, thereby preventing aggregation of their results in the meta-analysis.

Evidence search

Searches were conducted in the following databases of published scientific information: Medline/PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and ClinicalTrials.gov (CT.gov) for unpublished registry studies. Additional manual searches were performed in the reference lists of included studies and other relevant sources. The search in these databases was conducted till February 2024.

The search strategies used in each database were as follows:

- **Medline/PubMed**—(Prostate OR Prostatic Hyperplasia OR Benign Prostatic Hyperplasia OR Benign Prostate Hyperplasia OR BPH OR Benign Prostatic Hypertrophy OR Prostatic adenoma) AND (Laser Therapy OR Laser Coagulation* OR Laser Thermocoagulation* OR Vaporization OR Volatilization) AND Random*;
- **CENTRAL/Cochrane**—(Prostatic Hyperplasia OR Benign Prostatic Hyperplasia OR BPH) AND (Laser AND Transurethral Resection Prostate);
- **LILACS**—(Prostatic Hyperplasia OR Benign Prostatic Hyperplasia OR BPH) AND (Laser) AND [db: ("LILACS")];
- **ClinicalTrials.gov**—(Prostatic Hyperplasia OR Benign Prostatic Hyperplasia) AND (Laser AND Transurethral Resection Prostate).

Study selection and data extraction process

The evidence retrieved from the consulted databases is initially selected based on the title and abstract to meet the eligibility criteria. The studies identified in this initial selection then have

their full texts accessed to confirm their eligibility. The retrieval process and the evaluation of the obtained titles and abstracts were conducted independently and in a blinded manner by two researchers skilled in systematic reviews (AS and IF), following the inclusion and exclusion criteria. Subsequently, the selected articles were critically evaluated for inclusion in the review. When there was a disagreement about the study selection between the researchers, a third reviewer (WMB) was consulted.

From the eligible studies, the following data will be extracted: the name of the first author and year of publication, the studied population, intervention and comparison methods, and follow-up time. Regarding the extracted data for relevant outcomes, these may include an absolute number of events or means and/or medians with their respective standard deviations or 95% confidence intervals, depending on the type of outcome.

Risk of bias and quality of evidence

Two independent reviewers assessed the risk of bias in the included studies using the items from the Cochrane Risk of Bias Tool for Randomized Trials (RoB 2)[13], supplemented by other essential elements, and expressed as high, moderate, and low. Each domain was classified as having no bias, insufficient information, or presence of bias. Publication bias was evaluated through inspection of the funnel plot and by conducting Egger's test[14].

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE)[15] criteria were used as the method to assess the certainty of the effect estimate in the pooled evidence, categorizing the quality of evidence into four levels: high, moderate, low, and very low. Two reviewers evaluated the risk of bias, inconsistency, indirect evidence, imprecision, and publication bias for all reported outcomes. The quality of evidence was assessed using the Guideline Development Tool (GRADEpro GDT)[16] application and presented in GRADE evidence profiles and summary of findings tables, using standardized terminology.

Method of analysis and synthesis of results

Data will be analyzed according to the intention-to-treat principle, and the most recent follow-up data available will be included in each trial. The results for categorical outcomes will be expressed using the risk difference (RD) between intervention and control groups, using the Mantel-Haenszel method. If the RD between groups is statistically significant, it will be accompanied by a 95% confidence interval (CI) and the number needed to treat (NNT) or the number needed to harm (NNH). For continuous outcomes, the results will be the mean difference (MD) or standardized mean difference (SMD) if different scales were reported, with a 95%CI.

If there are multiple studies included with common outcomes, they will be pooled using meta-analysis, employing the Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration)[17]. The overall risk difference or mean difference, with 95%CIs, will be the final measure used to support the synthesis of evidence that addresses the clinical question (Objective). For studies that reported data as medians and interquartile ranges, the statistical formula proposed by Hozo et al.[18] was used to estimate means and standard deviations, in accordance with the methodological guidelines of the Cochrane Handbook for Systematic Reviews[19]. For studies that did not report standard deviation (SD), it will be calculated based on sample size and standard error (SE) or 95%CI.

The estimation of the combined effect size will be conducted using a fixed-effect or random-effects model after assessing the heterogeneity results. Based on statistical heterogeneity findings, the inconsistency was assessed using the I^2 metric, which measures the percentage of variation attributable to the difference among studies rather than random variation[20]. Heterogeneity values greater than 50% were considered high. A sensitivity analysis was performed to assess the reliability of the findings of this study. A funnel plot was used to analyze asymmetry, which was evaluated after excluding outliers.

Evidence synthesis and conclusion

The evidence synthesis will present the results directly from the analyses, considering the benefits, harm, and lack of difference between the use of PVP-GL compared to TURP-M. The conclusions will primarily consider evidence of at least moderate quality, assessing the presence of beneficial or harmful effects. Additionally, it will consider the favorable balance between benefit and harm in patients with lower urinary tract symptoms caused by benign prostatic hyperplasia and surgical indications.

RESULTS

In seeking evidence, 1,102 articles were retrieved from the Medline, CENTRAL, LILACS, and CT.gov databases. Manual and/or gray literature searches did not identify any additional works. After removing duplicates and selecting based on title and/or abstract, 39 articles met the previously established eligibility criteria (Methodology). The full texts of these 39 articles were accessed for analysis.

After reading the full texts, 13 parallel RCTs with placebo were included to support the conclusions of this assessment[21-33]. Two studies[22,25] were derived from the same clinical trials but with different follow-up periods. A total of 1,538 patients were involved, with 760 treated with PVP-GL and 778 with TURP-M.

The reasons for excluding the other 26 studies are detailed in Figure 1 and in the References section, under the heading "References of Excluded Studies and Their Reasons." Figure 1 presents a flow diagram illustrating the sequence from the retrieval to the selection of evidence for this assessment. The main baseline characteristics and details of each included trial are reported in Table 1 (Appendices).

Risk of bias in the studies

Of the 13 RCTs included[21-33], only one study reported blinding of the assessors but did not perform a sample size calculation[27] (with 10 patients); four studies did not conduct an intention-to-treat (ITT)[21,22,24,28], and a total of five studies did not perform a sample size calculation[22,24,26,27,33]. The risk of bias assessment for each individual study, using the RoB 2 tool[13] and additional key elements, is reported in Table 2 (Appendices). The nature of the intervention prevented the blinding of the surgeons. The study was considered double-blinded if patients and outcome assessors were blinded. Any disagreements were resolved by consensus.

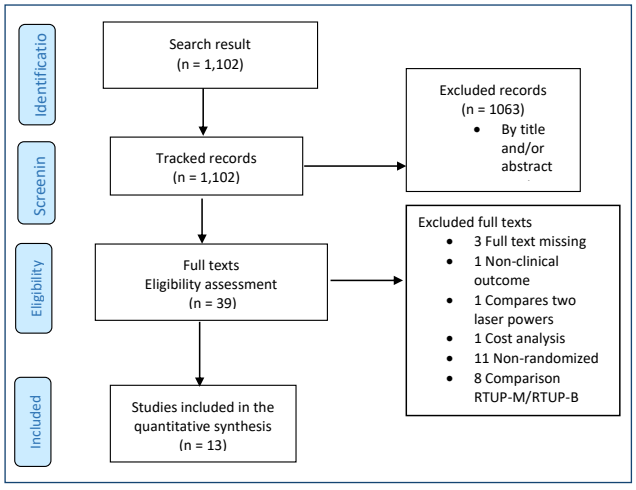

Figure 1. Flow diagram representing the study selection process. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097

EFFICACY

Perioperative outcomes

Surgical time (min): Surgical time was recorded in 10 RCTs encompassing a total of 1,165 patients[22,23,26-29,30-33]. There was an average increase of 7.74 min in operation time (MD=7.74 [95%CI, 4.53–10.96]; p<0.00001; I^2=70%) (Figure 2) with the use of PVP-GL, compared to TURP-M. The certainty of the evidence is moderate (Table 3 in Appendices).

The Egger's test (funnel plot) did not identify any outlier studies that would justify the observed heterogeneity (publication bias) (Figure 3 in Appendices). The 70% heterogeneity (I^2) was not altered with sensitivity analysis due to the absence of outlier studies and/or publication bias.

Hospitalization time (days): Hospitalization time was reported in seven RCTs encompassing a total of 878 patients[24,26,29,30-33]. PVP-GL, compared to TURP-M, reduces hospitalization time by an average of 2 days (MD=-2.18 [95%CI, -2.59 to -1.77]; p<0.0001; I^2=88%) (Figure 4). The certainty of the evidence is low (Table 3 in Appendices).

The Egger's test did not identify any outlier studies that would justify the observed heterogeneity (Figure 3 in Appendices). The high heterogeneity (I^2=88%) was not altered with sensitivity analysis due to the absence of outlier studies and/or publication bias.

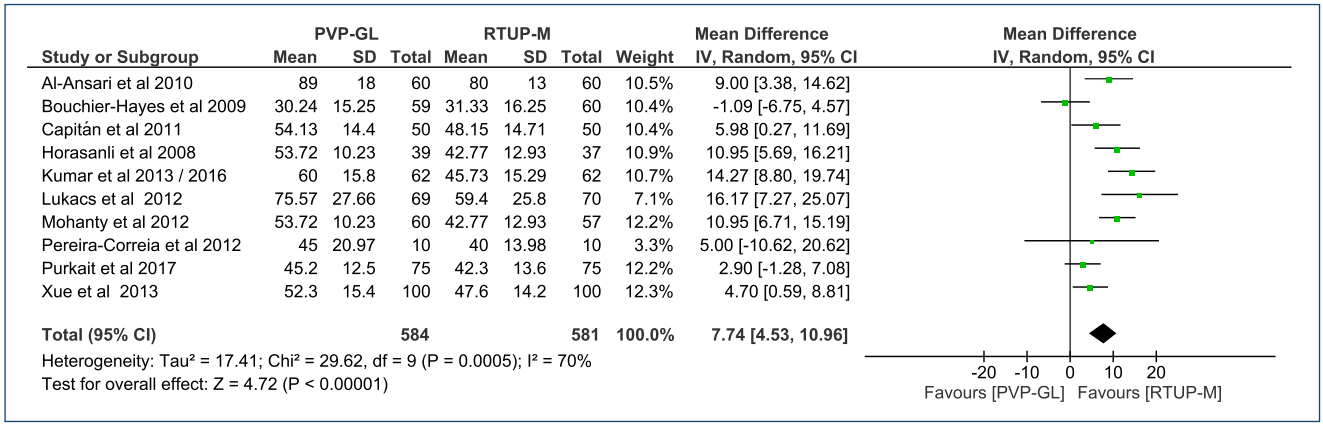

Figure 2. Forest plot of the comparison: 1 Green light laser photoselective vaporization versus monopolar transurethral of the prostate; outcome: 1.1 Surgical time (min).

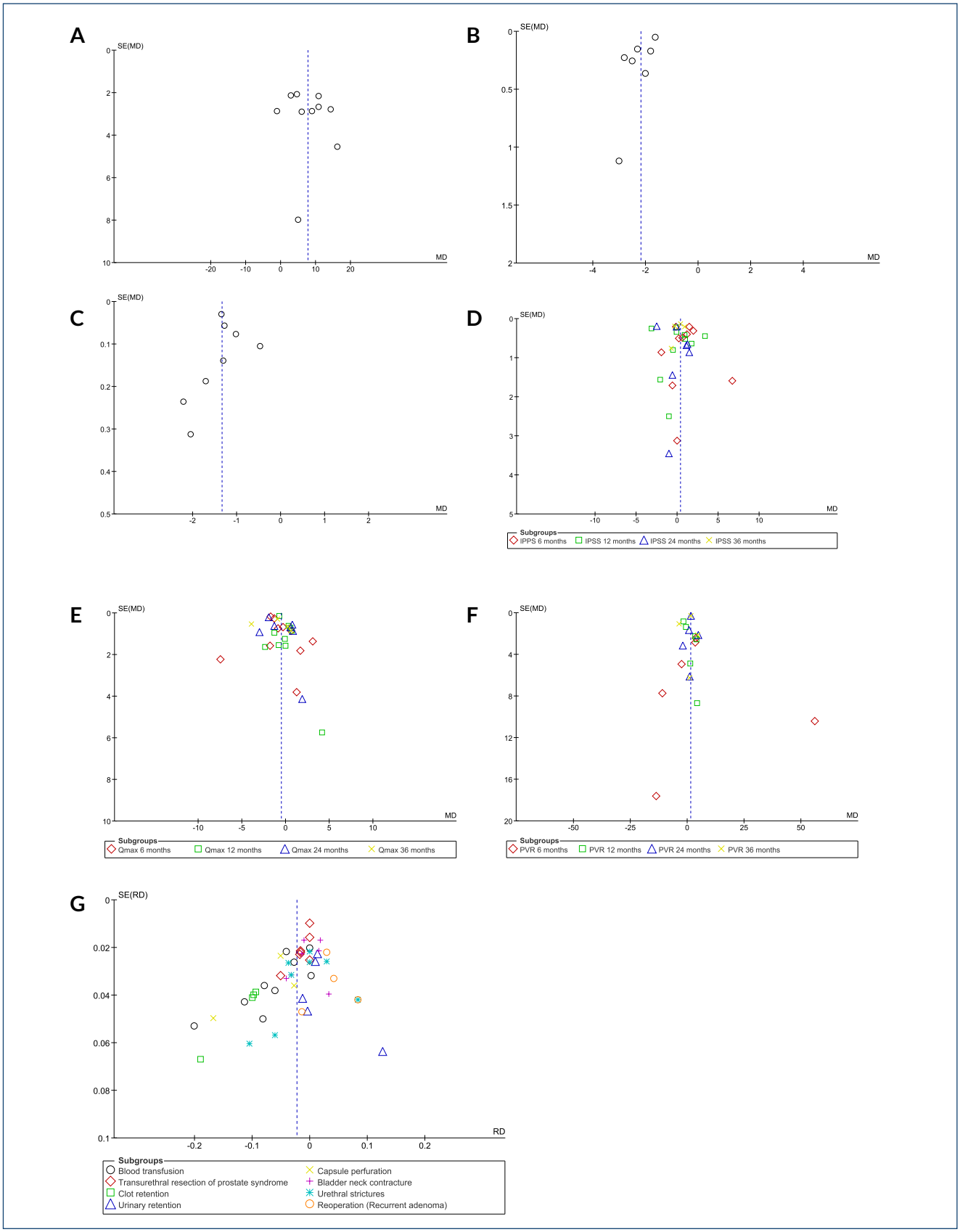

Figure 3. Funnel plots: **(A)** Surgical time. **(B)** Hospitalization time. **(C)** Catheterization time. **(D)** International prostate symptom score. **(E)** Maximum urinary flow rate (Qmax). **(F)** Post-void residual volume (PVR). **(G)** Complications. SE, standard error; MD, mean difference.

Catheterization time (days): Catheterization time was reported in eight RCTs, encompassing a total of 974 patients[22,23,26,28,30-33]. Compared to TURP-M, PVP-GL reduces catheterization time by an average of 1 day (MD=-1.33 [95%CI, -1.57 to -1.10]; p<0.0001; I^2=93%) (Figure 5). The certainty of the evidence is low (Table 3 in Appendices).

The Egger's test did not identify any outlier studies that would justify the observed heterogeneity (Figure 3 in Appendices). The extreme heterogeneity across this sample (I^2=93%) was not altered with sensitivity analysis due to the absence of outlier studies and/or publication bias.

Functional outcomes

Initial data, including IPSS, Qmax, and PVR for all participants in the PVP-GL and TURP-M groups, were similar (Table 1 in Appendices).

Prostate symptoms: In a subgroup analysis by follow-up time (6, 12, 24, and 36 months), prostate symptoms were evaluated using the IPSS, with a total score ranging from 0 to 35, classifying patients from asymptomatic to very symptomatic.

At 6 months, compared to TURP-M, PVP-GL showed a less favorable effect, resulting in an average increase of 0.85 points in the IPSS score (MD=0.85 [95%CI, 0.04–1.65]; p=0.04; I^2=87%) (Figure 6). The certainty of evidence for this difference was classified as low (Table 4 in Appendices).

At 12, 24, and 36 months, there was no difference in the IPSS between the two procedures (p>0.05 for all comparisons) (Figure 6). The certainty of evidence for this lack of difference is very low (Table 4 in Appendices).

The Egger's test did not identify any outlier studies that would justify the observed heterogeneity (Figure 3 in Appendices). High heterogeneity was observed across all follow-up periods (87–94%), but this was not altered by sensitivity analysis due to the absence of outlier studies and/or publication bias.

Maximum urinary flow rate (Qmax, mL/s): In 1998, the International Continence Society (ICS) defined Qmax values above 15 mL/s as normal, values between 10 and 15 mL/s as inconsistent, and values below 10 mL/s as pathological[34].

A subgroup analysis by follow-up time (6, 12, 24, and 36 months) evaluated Qmax. At no time points during follow-up,

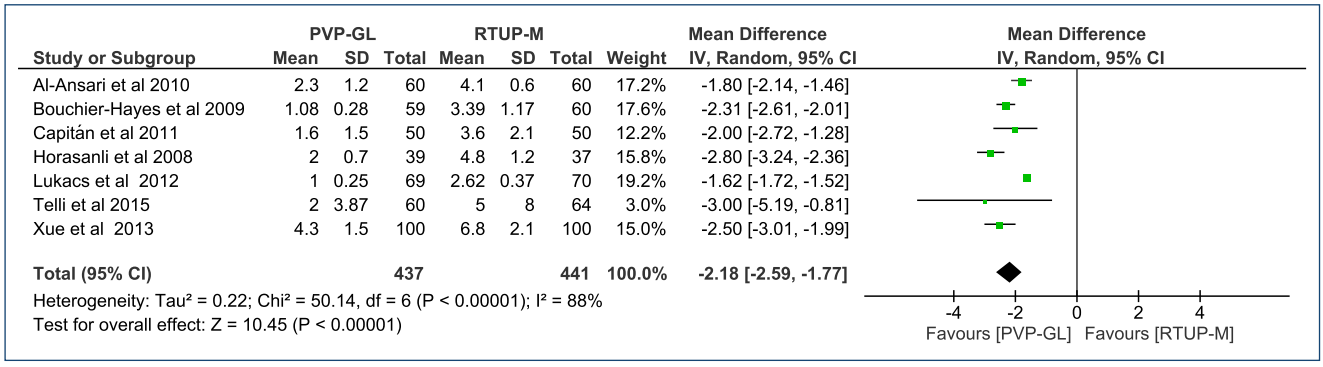

Figure 4. Forest plot of the comparison: 1 Green light laser photoselective vaporization versus monopolar transurethral of the prostate; outcome: 1.2 Hospitalization time (days).

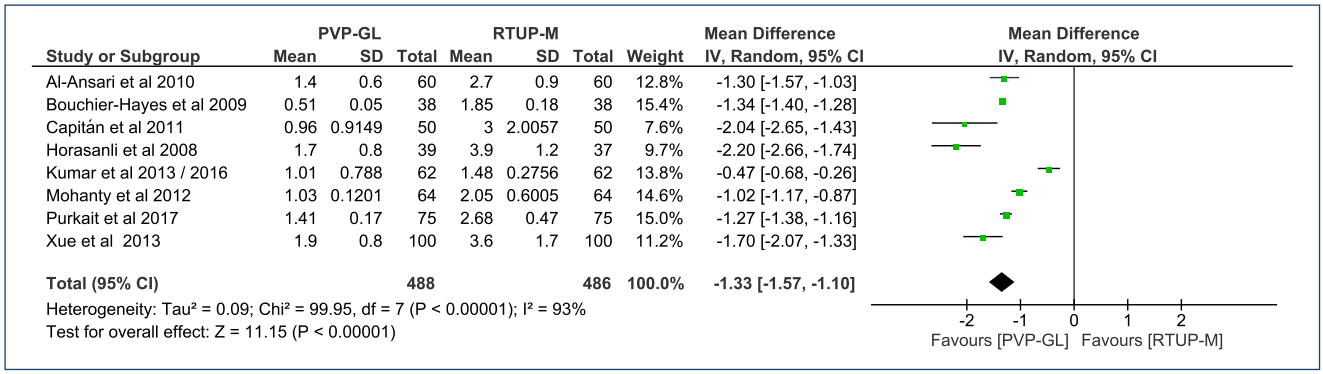

Figure 5. Forest plot of the comparison: 1 Green light laser photoselective vaporization versus monopolar transurethral of the prostate; outcome: 1.3 Catheterization time (days).

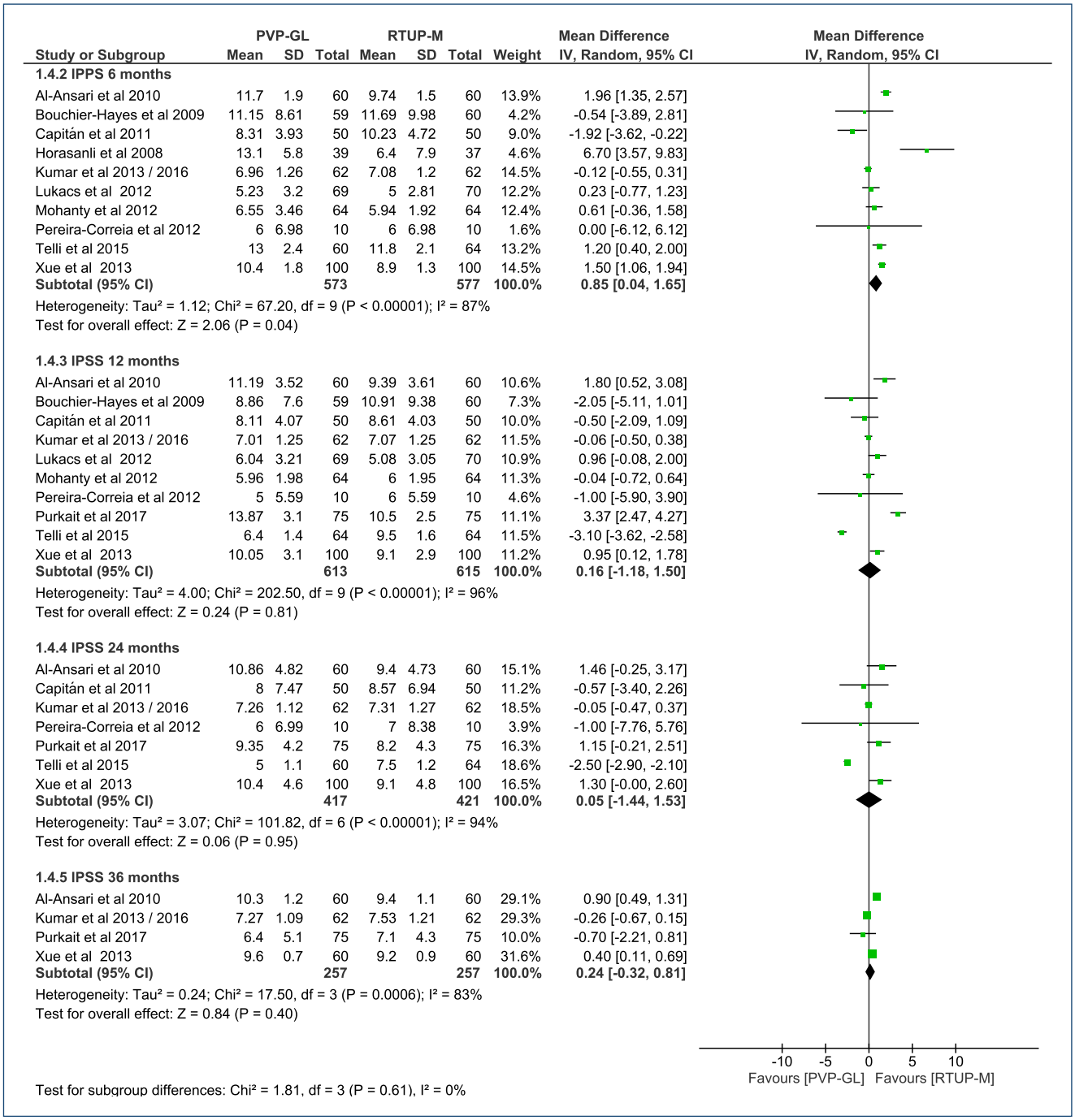

Figure 6. Forest plot of the comparison: 1 Green light laser photoselective vaporization versus monopolar transurethral of the prostate; outcome: 1.4 International Prostate Symptom Score.

there was a difference in Qmax between the two procedures (p>0.05 for all comparisons) (Figure 7). The certainty of evidence for this lack of difference ranged from low to very low (Table 4 in Appendices).

The Egger's test did not identify any outlier studies that would justify the observed heterogeneity (Figure 3 in Appendices). There was high heterogeneity in the 6-, 24-, and 36-month follow-ups (72–91%), but this heterogeneity was not altered by sensitivity analysis due to the absence of outlier studies and/or publication bias.

Post-void residual volume (PVR, mL): A subgroup analysis by follow-up time (6, 12, 24, and 36 months) including six, six, five, and four RCTs, respectively, assessed PVR.

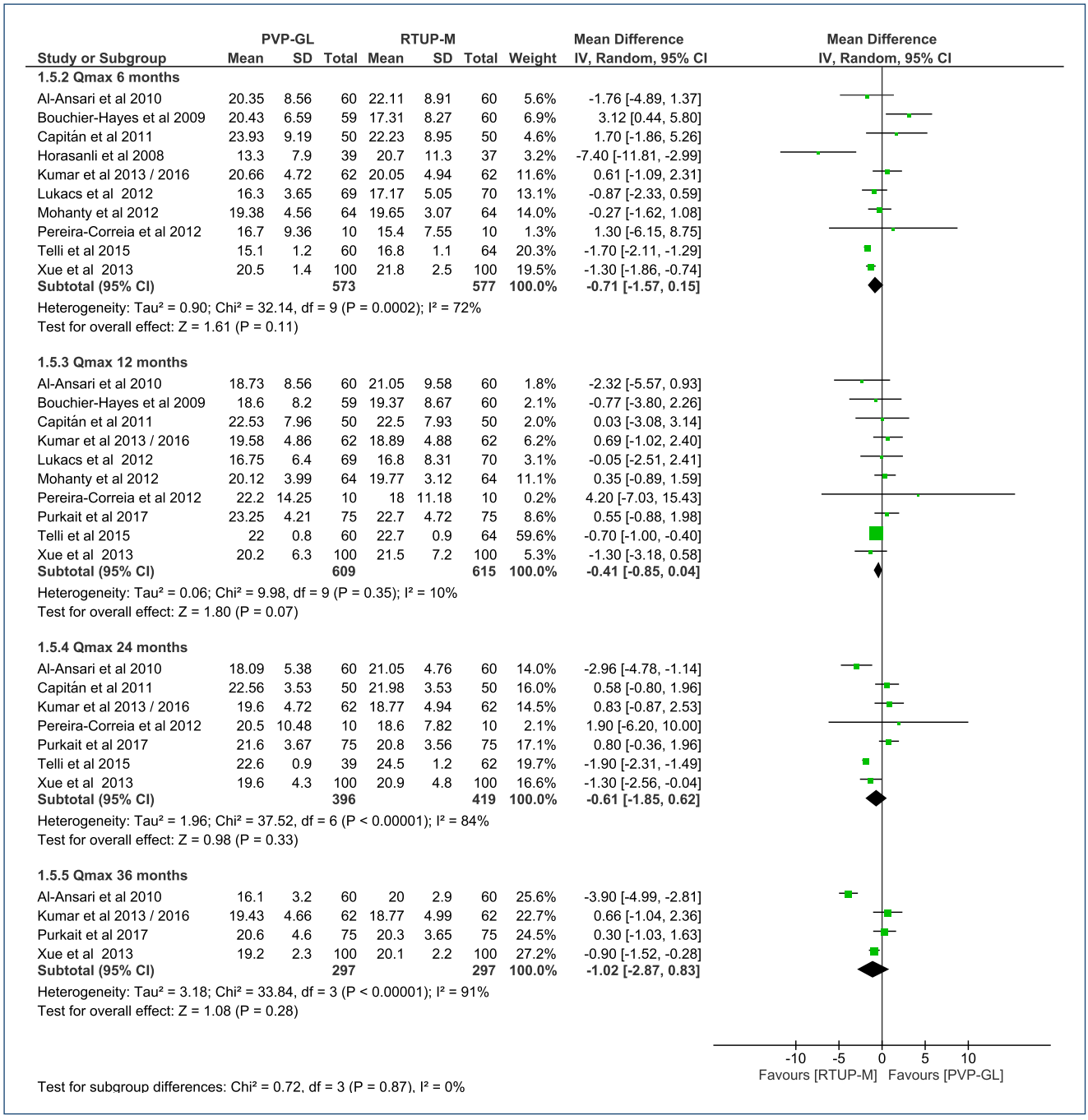

Figure 7. Forest plot of the comparison: 1 Green light laser photoselective vaporization versus monopolar transurethral of the prostate; outcome: 1.5 Qmax (mL/s).

At 6 months, there was no difference between the two groups (MD=5.47 mL [95%CI, -4.82 to 15.75 mL]; p=0.30; I^2=84%). At 12 months, there was no difference either (MD=0.52 mL [95%CI, –1.75 to 2.78 mL]; p=0.66; I^2=44%). At 36 months, there was no difference in PVR (MD=0.55 mL [95%CI, -3.20 to 4.31 mL]; p=0.77; I^2=87%) (Figure 8). The evidence certainty ranged from low to very low (Table 4 in Appendices).

At 24 months, PVP-GL has a less favorable outcome, increasing the PVR by 1.52 mL (MD=1.52 [95%CI, 0.89–2.5 mL]; p=0.00001; I^2=0%) (Figure 8). The evidence certainty was moderate (Table 4 in Appendices).

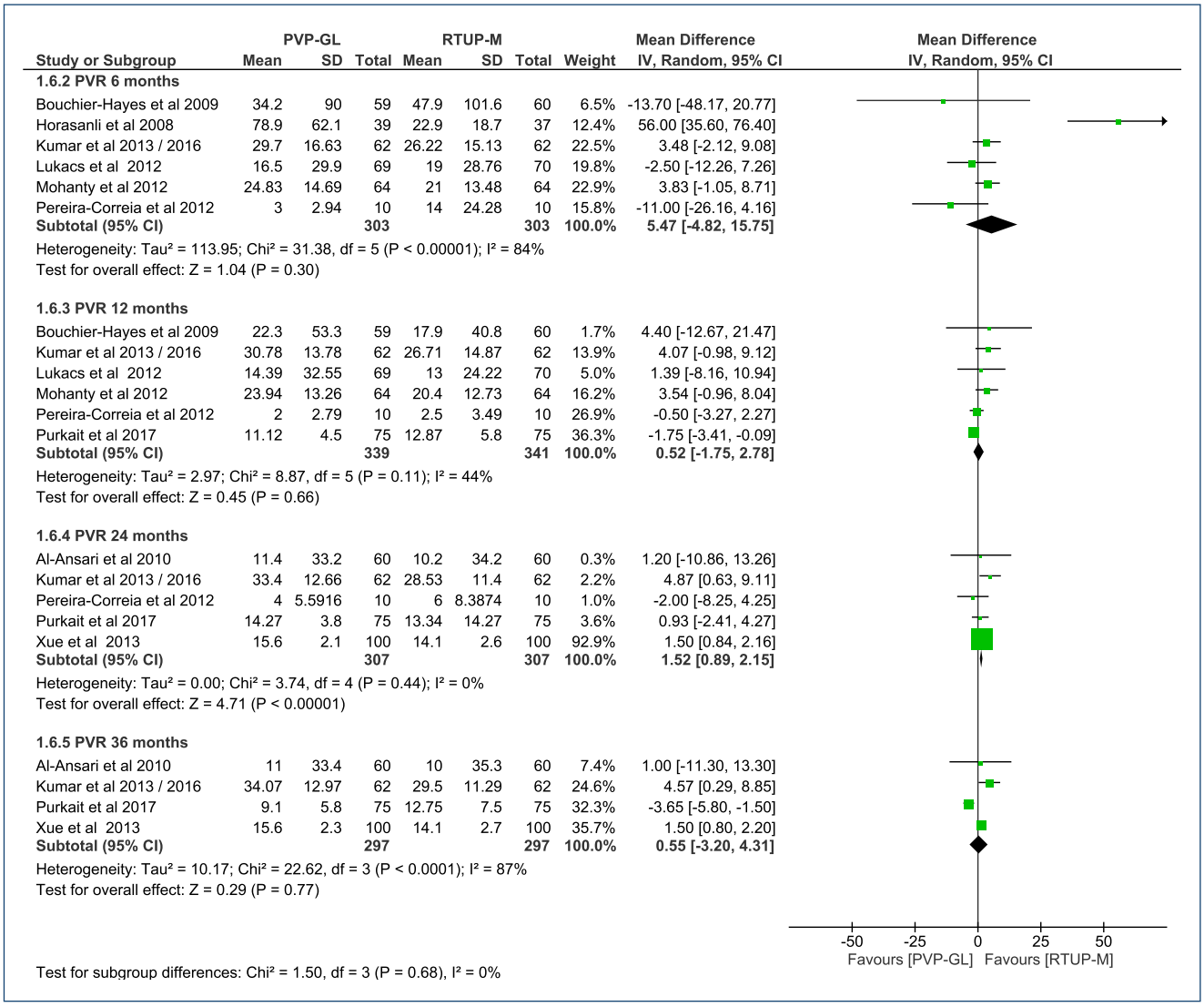

Figure 8. Forest plot of the comparison: 1 Green light laser photoselective vaporization versus monopolar transurethral resection of the prostate; outcome: 1.6 PVR (mL).

The Egger's test identified studies with divergent results that justified the observed heterogeneity at 6 and 36 months (Figure 3 in Appendices). To evaluate the influence of these studies, a sensitivity analysis was performed.

At 6 months, the study by Horasanli et al. was removed due to a much larger effect compared to other studies. This adjustment decreased heterogeneity (I^2=24%) but did not change the significance of the difference in PVR between the procedures.

At 36 months, the study by Purkait et al. was removed due to a result contradicting the other studies. This adjustment eliminated the heterogeneity (I^2=0%) and increased the MD to 1.58 mL (95%CI, 0.89–2.26 mL; p<0.00001). This result, like the 24-month observation, was unfavorable to PVP-GL.

SAFETY

Perioperative and late complications

In comparison with TURP-M, PVP-GL reduces the risk of blood transfusion by 6.25% (95%CI, 4–8.4%), with 16 patients who need treatment (95%CI, 12–25) to avoid one transfusion (NNT); reduces the risk of clot retention by 11% (95%CI, 7–16%), NNT=9 (95%CI, 7–14); and reduces the risk of capsule perforation by 8% (95%CI, 4–12%), NNT=12 (95%CI, 8–23) (Figure 9). The certainty of the evidence for blood transfusion and clot retention is moderate, while for capsule perforation, it is low (Table 5 in Appendices).

There is no difference between the two procedures for transurethral resection syndrome (DR=0.01 [95%CI,

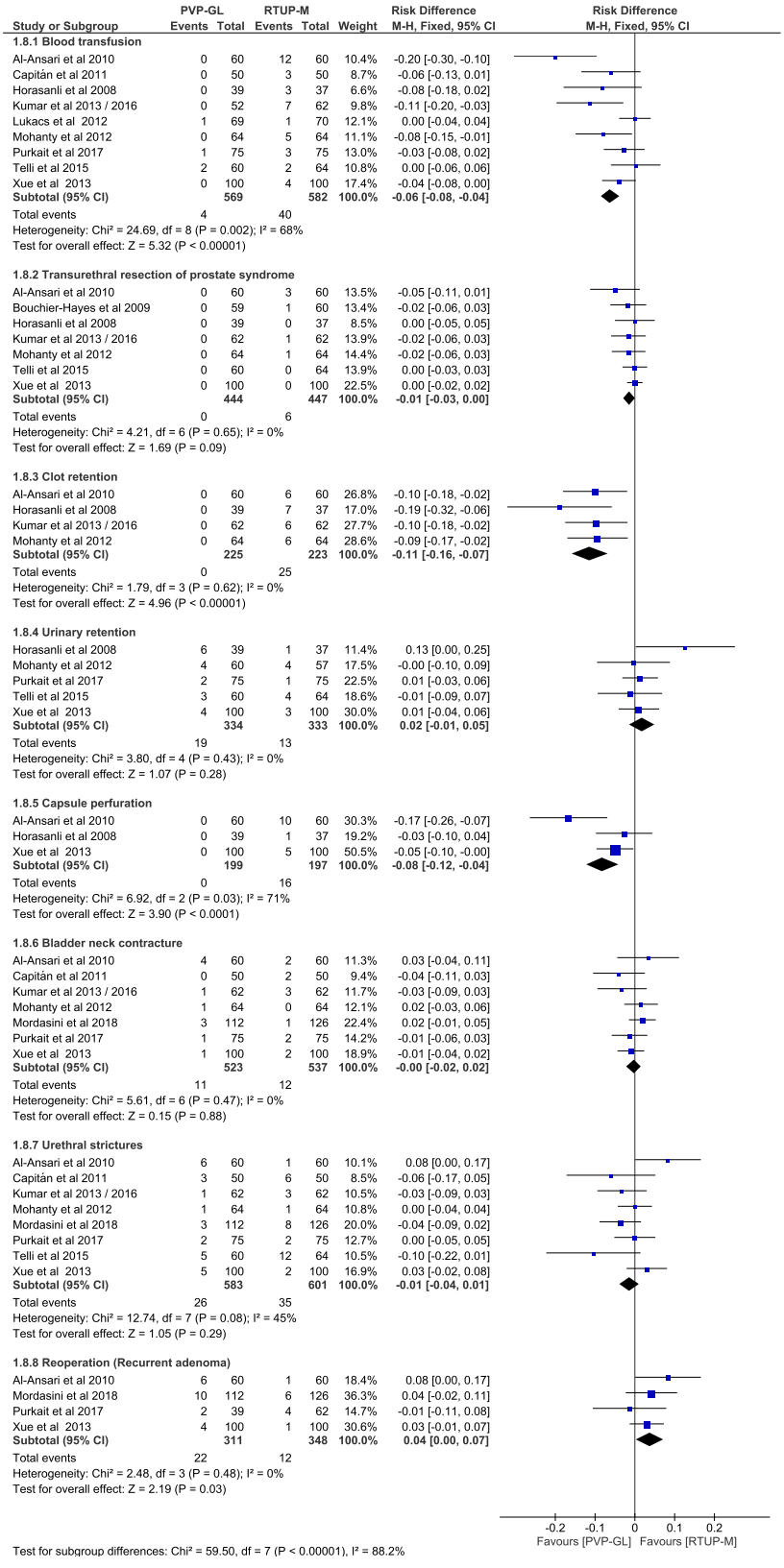

Figure 9. Forest plot of the comparison: 1 Green light laser photoselective vaporization versus monopolar transurethral resection of the prostate; outcome: 1.7 Complications.

0.00–0.03]; p=0.09), urinary retention (DR=-0.02 [95%CI, -0.05 to 0.014]; p=0.28), bladder neck contracture (DR=0.001 [95%CI, -0.02 to 0.02]; p=0.88), and urethral stricture (DR=0.01 [95%CI, -0.01 to 0.04]; p=0.29) (Figure 9). The certainty of evidence for urinary retention and bladder neck contracture is moderate, while for transurethral resection syndrome and urethral stricture, it is low (Table 5 in Appendices).

The risk of reoperation for recurrent adenoma was higher with PVP-GL by 4% compared to TURP-M (DR=4% [95%CI, 0.3–7%]; NNH=27 [95%CI, 14–372]; p=0.03; I^2=0%) (Figure 9). The certainty of evidence is low (Table 5 in Appendices).

Egger's test (funnel plot) identified one study[31] with discrepant results that accounted for the observed heterogeneity (publication bias) regarding the outcomes of blood transfusion and capsule perforation. Figure 3 (G) in Appendices presents these results. To assess the influence of this study, a sensitivity analysis was conducted.

For the outcome of blood transfusion, the study by Al-Ansai et al. was removed due to its significantly larger effect compared to the others. This adjustment reduced heterogeneity (I^2 from 68 to 41%) and the risk difference by 1%. The significance of the difference between the procedures remained (DR=5% [95%CI, 0.025–0.07]; p<0.0001; NNT=22 [95%CI, 15–40]), with a still favorable benefit to PVP-GL.

For the outcome of capsule perforation, the study by Al-Ansari et al. was also removed for the same reason as in the blood transfusion outcome. Heterogeneity was reduced from 71 to 0% and the risk difference by 4%. The significance of the difference between the procedures remained (DR=4.4% [95%CI, 0.08–0.10]; p=0.03; NNT=23 [95%CI, 13–104]), as well as the favorable benefit to PVP-GL.

EVIDENCE SYNTHESIS

The PVP-GL compared to TURP-M

1. Perioperative outcomes

- Increases the surgical time by an average of 8 min [95%CI, 4.53–10.96]. The certainty of evidence is moderate.
- Reduces the length of hospitalization by an average of 2 days [95%CI, 2.59–1.77]. The certainty of evidence is low.
- Reduces the catheterization time by an average of 1 day [95%CI, 1.57–1.10]. The certainty of evidence is low.

2. Functional outcomes

IPSS

- At 6 months, it shows a less favorable effect, as it increases the IPSS score by an average of 0.85 points (95%CI, 0.04–1.65). The certainty of evidence for this difference was classified as low.
- At 12, 24, and 36 months, there is no difference in IPSS (p>0.05 for these comparisons). The certainty of evidence is very low for this lack of difference.

Qmax (mL/s)

- There is no difference in Qmax at the 6-, 12-, 24-, and 36-month follow-ups (p>0.05 for these comparisons). The certainty of evidence for this lack of difference varies from low to very low.

PVR (mL)

- It does not show a difference at 6, 12, and 36 months (p>0.05 for these comparisons). The certainty of evidence for this lack of difference varies from low to very low.
- At 24 months, it shows a less favorable result, as it increases the PVR by 1.52 mL (95%CI, 0.89–2.5). This response does not persist at 36 months, as seen above. The certainty of evidence for this difference is moderate.

3. Complications (perioperative and late)

- Reduces risk of blood transfusion by 6.25% (95%CI, 4–8.4%), NNT=16 (95%CI, 12–25). The certainty of evidence is moderate.
- Reduces the risk of clot retention by 11% (95%CI, 7–16%), NNT=9 (95%CI, 7–14). The certainty of evidence is moderate.
- Reduces the risk of capsule perforation by 8% (95%CI, 4–12%), NNT=12 (95%CI, 8–23). The certainty of evidence is low.
- Does not show a difference in outcomes related to transurethral resection syndrome of the prostate, urinary retention, bladder neck contracture, and urethral stricture (p>0.05 for these comparisons). The certainty of evidence is moderate for urinary retention and bladder neck contracture, while for transurethral resection syndrome of the prostate and urethral stricture, it is considered low.
- Increases the risk of reoperation for recurrent adenoma by 4% (DR=4% [95%CI, 0.3–7%], NNH=27 [95%CI, 14–372]), and the certainty of evidence is low.

DISCUSSION

Green light laser photoselective vaporization (PVP-GL) has emerged as a promising technique in the management of benign prostatic hyperplasia, showing favorable results when compared to monopolar transurethral resection of the prostate (TURP-M)[35-37]. Our meta-analysis addressed a variety of perioperative outcomes, functional outcomes, and complications. We provided a comprehensive view of the effectiveness and safety of this technique, including only RCTs using green light lasers (KTP, 532 nm wavelength) for PVP. A separate analysis of the use of 80-W and 120-W lasers was challenging due to the scarcity of available data. Therefore, despite well-known limitations and subsequent improvements in the laser, these were considered similar interventions for the purposes of this meta-analysis.

Regarding perioperative outcomes, we observed that PVP-GL increases the average procedure time by 8 min. Although this increase is statistically significant (MD=7.74 min [95%CI, 4.53–10.96 min]; p<0.00001), it is important to note that the difference is moderate and may not be clinically relevant. Additionally, the average reduction of 2 days in hospitalization time and 1 day in catheterization time, although statistically significant, are based on low-certainty evidence, which requires caution in interpreting these results.

PVP-GL showed mixed results compared to TURP-M for functional outcomes. We observed that PVP-GL showed an average increase in IPSS score at 6 months (MD=0.85 [95%CI, 0.04–1.65]; p=0.04), but this difference did not persist in subsequent follow-ups at 12, 24, and 36 months. The lack of significant difference in IPSS in the long term suggests that PVP-GL maintains comparable results to TURP-M over time.

Similarly, there were no significant differences in Qmax and PVR at different follow-ups, highlighting the equivalence of these techniques in terms of functional performance. Sensitivity analysis for IPSS and Qmax outcomes did not identify outlier studies and/or publication bias, maintaining high heterogeneity at follow-up periods. However, for RVR outcome, discrepant studies were identified at 6 and 36 months. Removing these studies resulted in changes in heterogeneity, but not with the same significance as the result at 6 months; at 36 months, the elimination of heterogeneity was accompanied by a less favorable result for PVP-GL (increased MD to 1.58 mL [95%CI, 0.89–2.26 mL; p<0.00001]), although it is a small difference and may not be clinically relevant.

Regarding complications, PVP-GL showed significant advantages. Reductions in the risk of blood transfusion (DR=6.25% [95%CI, 4–8.4%], NNT=16), clot retention (DR=11% [95%CI, 7–16%], NNT=9), and capsule perforation (DR=8% [95%CI, 4–12%], NNT=12) were observed, with moderate certainty evidence. However, no significant differences were found in other complications such as transurethral resection syndrome, urinary retention, bladder neck contracture, and urethral stricture, although the certainty of evidence ranges from moderate to low. PVP-GL increases the risk of reoperation for recurrent adenoma by 4% (DR=4% [95%CI, 0.3–7%], NNH=27 [95%CI, 14–372]).

In summary, our analysis suggests that PVP-GL offers advantages in terms of recovery time and perioperative complications, with comparable functional outcomes to TURP-M in the long term. However, it is important to recognize the limitations of the available evidence, especially regarding perioperative and functional outcomes. For these events, the certainty of evidence is low or very low due to a high risk of bias in the included studies, high heterogeneity, and very wide confidence intervals for many of the outcomes. Despite these limitations, this study provides the most up-to-date information on the comparison of PVP-GL and TURP-M in the surgical treatment of BPH. Future studies with robust designs are needed to confirm and expand these findings, providing a more solid basis, especially in relation to the certainty of evidence, and offering more precise guidelines for clinical practice.

CONCLUSION

In our meta-analysis of functional outcomes up to 3 years of follow-up after PVP-GL and TURP-M, we found that both procedures showed similar results. Although PVP-GL offers advantages in terms of recovery time and perioperative complications, it is important to highlight the potential risk of reoperation for recurrent adenoma in the long term. However, it is crucial to note that the certainty of evidence available, especially regarding perioperative and functional outcomes, is low or very low.

AUTHORS CONTRIBUTIONS

AS: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **IF:** Conceptualization, Data curation, Formal Analysis. Writing – review & editing. **WMB:** Conceptualization, Writing – review & editing.

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APPENDICES

Table 1. Key patient baseline characteristics and details of each trial.

First author/year	Patients (N)	Laser power (W)	Age, years	Prostate size (mL)	IPSS	Qmax (mL/s)	PVR (mL)	Follow-up duration (months)
	PVP-GL RTUP-M		PVP-GL (DP) RTUP-M (DP)	PVP-GL (DP) RTUP-M (DP)	PVP-GL (DP) RTUP-M (DP)	PVP-GL (DP) RTUP-M (DP)	PVP-GL (DP) RTUP-M (DP)	
Al-Ansari31 2010	60 60	120-w	66.3 ± 9.4 67.1 ± 8.0	61.8 ± 22.0 60.3 ± 20.0	27.2 ± 2.3 27.9 ± 2.7	6.9 ± 2.2 6.4 ± 2.0	53.2 ± 25 57.0 ± 21	1, 3, 6, 12, 24, and 36
Bouchier-Hayes32 2010	59 60	80-w	65.1 ± 5.0 66.3 ± 4.2	38.7 ± 11.2 33.4 ± 8.7	25.28 ± 5.93 25.41 ± 5.72	8.81 ± 2.55 8.86 ± 2.99	129.2 ± 155.7 111.3 ± 113.7	3, 6, and 12
Capitán30 2011	50 50	120-w	69.8 ± 8.4 67.7 ± 6.7	51.3 ± 14.7 53.1 ± 13.8	23.7 ± 5.2 23.5 ± 4.4	8.0 ± 3.1 3.9 ± 2.7	Não avaliado	1, 3, 6, 12, and 24
Horasanli33 2008	39 37	80-w	69.2 ± 7.1 68.3 ± 6.7	86.1 ± 8.8 88.0 ± 9.2	18.9 ± 5.1 20.2 ± 6.8	8.6 ± 5.2 9.2 ± 5.6	183.0±50.1 176.9±45.3	3 and 6
Kumar22,25 2013/2016	62 62	120-w	≥ 50 ≥ 50	52.8 ± 16.1 52.2 ± 15.9	20.0 ± 2.7 20.7 ± 2.6	6.68 ± 2.00 7.00 ± 1.97	143.3 ± 52.6 148.4 ± 60.3	1, 3, 6, 12, and 36
Lukacs29 2012	69 70	120-w	66.9 ± 7.8 67.6 ± 7.6	50.5 ± 16.5 50.1 ± 14.7	21.7 ± 2.7 19.4 ± 2.4	7.8 ± 2.8 7.8 ± 2.6	89.5 ± 92 75.0 ± 73	1, 3, 6, and 12
Mohanty28 2012	64 64	80-w	66.9 ± 8.62 65.7 ± 9.09	44.7 ± 14.09 49.0 ± 15.93	19.9 ± 3.27 20.8 ± 3.87	7.4 ± 2.07 6.7 ± 1.63	145.8 ± 70.33 143.2 ± 65.96	1, 3, 6, and 12
Mordasini21 2018	112 126	80-w	68.4 ± 8.7 67.6 ± 8.4	36.1 ± 11.5 37.9 ± 14.3	20.3 ± 7.0 20.4 ± 7.5	8.9 ± 4.1 8.5 ± 4.6	91.1 ± 88.3 114.5 ± 36.4	60
Pereira27 2012	10 10	120-w	64.0 ± 6.0 67.0 ± 5.5	46.4 ± 7.1 45.6 ± 7.2	21.1 ± 3.1 20.6 ± 2.8	8.4 ± 3.4 7.9 ± 2.8	109.8 ± 103.9 116.6 ± 78.5	1, 3, 6, 9, 12, and 24
Purkait23 2017	75 75	120-w	63.6 ± 8.12 65.3 ± 7.86	70.3 ± 15.5 69.6 ± 16.3	26.1 ± 4.8 25.9 ± 5.2	8.5 ± 2.7 8.3 ± 2.4	238.0 ± 31.0 213.0 ± 23.0	12, 24, 36, and 48
Teli24 2015	60 64	120-w	67.0 ± 9.1 69.0 ± 7.8	60.7 ± 8.1 55.7 ± 8.1	20.0 ± 2.7 19 ± 2.6	10.6 ± 3.0 12.5 ± 4.5	60.5 ± 104.1 65.2 ± 100.5	6, 12, and 24
Xue26 2013	100 100	120-w	72.1 ± 11.3 71.0 ± 10.8	65.8 ± 23.6 67.3 ± 24.7	23.0 ± 5.1 23.2 ± 5.0	8.0 ± 3.6 8.2 ± 3.8	Não avaliado	1, 3, 6, 12, 24, and 36

Continuous variables were expressed as (mean±SD). PVP-GL, photoselective vaporization of the prostate with green-light laser; RTUP-M, monopolar transurethral resection of the prostate; IPSS, International Prostate Symptom Score; Qmax, maximum flow rate; PVR, post-void residual volume.

Table 2. Risk of bias in studies.

First author/ Year (Ref. #)	Randomization	Blind allocation	Double-blind	Outcome researcher blind	Losses	Prognostic characteristics	Appropriate outcomes	Intention to treat analysis	Sample size calculation	Early interruption	Global risk of viruses
Al-Ansari A[31], 2010											HIGH
Bouchier-Hayes DM[32], 2010											HIGH
Capitán C[30], 2011											HIGH
Horasanli K[33], 2008											HIGH
Kumar A[22,25], 2013/2016											HIGH
Lukacs B[29], 2012											HIGH
Mohanty NK[28], 2012											HIGH
Mordasini L[21], 2018											HIGH
Pereira-Correia JA[27], 2012											HIGH
Purkait B[23], 2017											HIGH
Telli O[24], 2015											HIGH
Xue B[26], 2013											HIGH
LEGENDA	LOW RISK			NOT INFORMED				HIGH RISK			

Table 3. GRADE: Perioperative outcomes.

Summary of findings: Perioperative outcomes			
Patient or population: Benign prostatic hyperplasia **Setting:** Therapeutic efficacy, safety **Intervention:** Photoselective vaporization of the prostate with green light laser (PVP-GL) **Comparison:** Transurethral resection of the prostate in the monopolar form (TURP-M)			
Outcomes	**Anticipated absolute effects* (95% CI) Mean difference**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**
Operation time (min)	MD **7.74 higher** (4.53 higher to 10.96 higher)	1165 (10 RCTs)	⨁⨁⨁◯ Moderate[a]
Hospitalization time (days)	MD **2.18 lower** (2.59 lower to 1.77 lower)	878 (7 RCTs)	⨁⨁◯◯ Low[b,c]
Catheterization time (days)	MD **1.33 lower** (1.57 lower to 1.1 lower)	974 (8 RCTs)	⨁⨁◯◯ Low [b,d]
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI, confidence interval; MD, mean difference.			

[a]There was no blinding of the patient in any study and only one blinded the evaluator. Two studies had >20% loss. [b]There was no blinding of the patient and the evaluator in any study and one had a loss greater than 20%. [c]I^2 = 88% and sensitivity analysis does not justify heterogeneity. [d]I^2 = 93% and sensitivity analysis does not justify heterogeneity.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 4. GRADE: Functional outcomes.

Summary of findings: functional outcomes			
Patient or population: Benign prostatic hyperplasia **Setting:** Therapeutic efficacy, safety **Intervention:** Photoselective vaporization of the prostate with green light laser (PVP-GL) **Comparison:** Transurethral resection of the prostate in the monopolar form (TURP-M)			
Outcomes	**Anticipated absolute effects* (95% CI) Mean difference**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**
IPSS - IPPS 6 months	MD **0.85 higher** (0.04 higher to 1.65 higher)	1150 (10 RCTs)	⨁⨁◯◯ Low[b,c]
IPSS - IPSS 12 months	MD **0.16 higher** (1.18 lower to 1.5 higher)	1228 (10 RCTs)	⨁◯◯◯ Very Low[a,d,e]
IPSS - IPSS 24 months	MD **0.05 higher** (1.44 lower to 1.53 higher)	838 (7 RCTs)	⨁◯◯◯ Very Low[e,f,g]
IPSS - IPSS 36 months	MD **0.24 higher** (0.32 lower to 0.81 higher)	514 (4 RCTs)	⨁◯◯◯ Very Low[b,e,h]
Qmax (mL/s) - Qmax 6 months	MD **0.71 lower** (1.57 lower to 0.15 higher)	1150 (10 RCTs)	⨁⨁◯◯ Low[b,e]
Qmax (mL/s) - Qmax 12 months	MD **0.41 lower** (0.85 lower to 0.04 higher)	1224 (10 RCTs)	⨁⨁◯◯ Low[b,e]
Qmax (mL/s) - Qmax 24 months	MD **0.61 lower** (1.85 lower to 0.62 higher)	815 (7 RCTs)	⨁◯◯◯ Very Low[b,e,i]
Qmax (mL/s) - Qmax 36 months	MD **1.02 lower** (2.87 lower to 0.83 higher)	594 (4 RCTs)	⨁◯◯◯ Very Low[b,e,j]
PVR (mL) - PVR 6 months	MD **5.47 higher** (4.82 lower to 15.75 higher)	606 (6 RCTs)	⨁◯◯◯ Very Low[e,f,k]
PVR (mL) - PVR 12 months	MD **0.52 higher** (1.75 lower to 2.78 higher)	680 (6 RCTs)	⨁⨁◯◯ Low[e,f]
PVR (mL) - PVR 24 months	MD **1.52 higher** (0.89 higher to 2.15 higher)	614 (5 RCTs)	⨁⨁⨁◯ Moderate[f]
PVR (mL) - PVR 36 months	MD **0.55 higher** (3.2 lower to 4.31 higher)	594 (4 RCTs)	⨁◯◯◯ Very Low[b,c,l]
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI, confidence interval; MD, mean difference.			

[a]There was no blinding of the patient in any study and only one blinded the evaluator. Two studies had >20% loss. [b]There was no blinding of the patient and the evaluator in any study and one had a loss >20%. [c]I^2 = 87%, and sensitivity analysis does not justify heterogeneity. [d]I^2 = 96%, and sensitivity analysis does not justify heterogeneity. e. Wide confidence interval. [f]There was no blinding of the patients and only one study blinded the evaluator. One study with a loss of more than 20%. [g]I^2 = 94%, but the sensitivity analysis justifies the heterogeneity. [h]I^2 = 83%, and sensitivity analysis does not justify heterogeneity. [i]I^2 = 84%, and sensitivity analysis does not justify heterogeneity. [j]I^2 = 91%, but the sensitivity analysis justifies the heterogeneity. [k]I^2 = 84%, but the sensitivity analysis justifies the heterogeneity. [l]Very wide confidence interval.

Table 5. GRADE: complications outcomes.

Summary of findings: complications outcomes					
Patient or population: Benign prostatic hyperplasia **Setting:** Therapeutic efficacy, safety **Intervention:** Photoselective vaporization of the prostate with green light laser (PVP-GL) **Comparison:** Transurethral resection of the prostate in the monopolar form (TURP-M)					
Outcomes	**Anticipated absolute effects* (95% CI)**		**Risk difference (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**
	With PVP-GL	**With TURP-M**			
Blood transfusion	4/569 (0.7%)	**40/582 (6.9%)**	-0.06 [-0.08, -0.04]	1151 (9 RCTs)	⨁⨁⨁◯ Moderate[b]
Transurethral resection of prostate syndrome	0/444 (0%)	**6/447 (1.3%)**	-0.01 [-0.03, 0.00]	891 (7 RCTs)	⨁⨁◯◯ Low[b,c]
Clot retention	0/225 (0%)	**25/223 (2%)**	-110/1000 [-160, -70]	448 (4 RCTs)	⨁⨁⨁◯ Moderate[d]
Urinary retention	19/334 (5.7%)	**13/333 (3.9%)**	-0.11 [-0.16, -0.07]	667 (5 RCTs)	⨁⨁⨁◯ Moderate[b]
Capsule perforation	0/199 (0%)	**16/197 (8.1%)**	-0.08 [-0.12, -0.04]	396 (3 RCTs)	⨁⨁◯◯ Low[d,e]
Bladder neck contracture	11/523 (2.1%)	**12/537 (2.2%)**	-0.00 [-0.02, 0.02]	1060 (7 RCTs)	⨁⨁⨁◯ Moderate[a]
Urethral strictures	26/583 (4.5%)	**35/601 (5.8%)**	-0.01 [-0.04, 0.01]	1184 (8 RCTs)	⨁⨁◯◯ Low[c,f]
Reoperation (recurrent adenoma)	22/311 (4.5%)	**12/348 (3.4%)**	0.04 [0.00, 0.07]	659 (4 RCTs)	⨁⨁◯◯ Low[c,g]
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI, confidence interval.					

[a]There was no blinding of the patient in any study and only one study blinded the evaluator. Two studies had >20% loss. [b]There was no blinding of the patient and the evaluator in any study and one had >20% loss. [c]Wide confidence interval. [d]There was no blinding of the patient and the evaluator in any study. [e]I^2=71%, but the sensitivity analysis justifies the heterogeneity. [f]There was no blinding of the patients and only one study blinded the evaluator. Two studies had >20% loss. [g]There was no blinding of the patients and the evaluator. Two studies had >20% loss.

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Response to "Evaluation of the injuries in earthquake victims with computed tomography"

Gokhan Tonkaz[1], Demet Sengul[2*], Tumay Bekci[1], Ilker Sengul[3,4], Ismet Mirac Cakir[1], Esma Cinar[2], Duygu Erkal Tonkaz[5], Tugrul Kesicioglu[4], Iskender Aksoy[6], Serdar Aslan[1]

Dear Editor,

We read with a great deal of interest the article "Evaluation of the injuries in earthquake victims with computed tomography," published in *Revista da Associação Médica Brasileira*, Volume 70[1]. We appreciate the authors' interest in our work and would like to respond and address some of the issues raised by the authors and dispel some possible misconceptions about our work. The authors considered the major limitation of our study to be its dependence on computed tomography (CT) scans alone, which may not always provide complete information in all cases[1]. Indisputably, it would be helpful to expand the scope of the study by including a larger sample size and more diagnostic tools as the authors have mentioned. However, we have already stated that our article solely investigated CT imaging characteristics of earthquake victims after those catastrophic disasters, such as the 2023 Turkey–Syria earthquakes, by using the Teleradiology Reporting System (TRS) of the Ministry of Health, Republic of Turkey[2]. For this purpose, we retrospectively analyzed hospital data from a total of 11 cities affected by the earthquake in Turkey and presented the CT imaging characteristics of adult and pediatric earthquake survivors even in two separate studies, parts I and II, recently published in *Revista da Associação Médica Brasileira*, Volume 69[2,3]. Our study is on the "imaging" but not the laboratory characteristics of the victims of the aforementioned catastrophic great disasters, and we would like to emphasize the awareness of the situation that the authors have criticized in their letter. Therefore, in the "limitations" section of our study, we already included (i) not possessing trauma score data or patient outcomes such as mortality as a retrospective study, (ii) involving just the cases with CT images, and (iii) excluding the victims not undergoing CT scans, but diagnosing by imaging strategies such as direct radiography, sonography, or magnetic resonance imaging. We kindly like to express and render again that our original preliminary work is a needful, unique, and in-place evaluation of these great disasters right just 1 month after they happened, conversely being a kind of follow-up study[3]. In conclusion, our study is a revealing work in that the frequency of earthquake-related injuries varies according to different regions based solely on CT imaging by utilizing TRS, Turkey. We hope that the outcomes of our preliminary work might be beneficial in the development of relevant guidelines and disaster preparedness globally, particularly for future undesirable and unwelcome earthquakes.

AUTHORS' CONTRIBUTIONS

GT: Conceptualization, Methodology, Project administration, Resources, Software, Validation, Visualization. **DS:** Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **TB:** Project administration, Resources, Validation, Visualization. IS: Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – review & editing. **IMC:** Investigation, Resources, Validation, Visualization. **EC:** Investigation, Validation, Visualization. **DET:** Investigation, Validation, Visualization. **TK:** Investigation, Validation, Visualization. **IA:** Validation, Visualization. **SA:** Validation, Visualization.

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Comment on "Overweight status, abdominal circumference, physical activity, and functional constipation in children"

Baogui Wang[1], Haibo Xu[1]*

Dear Editor,

We would like to share a few thoughts on the study titled "Overweight status, abdominal circumference, physical activity, and functional constipation in children."[1] The objective of this study was to assess the prevalence of functional constipation and its association with food intake, overweight status, and physical activity in children. In this study, 452 children aged 6–12 years from two public schools were evaluated using a cross-sectional study. First, functional constipation was diagnosed based on Rome IV criteria clinical presentation for more than 2 months. Next, food intake, body mass index, height-for-age z-score, abdominal circumference, abdominal circumference for height, and physical activity indicators were tested separately. The results showed that a larger abdominal circumference was associated with functional constipation in girls (p=0.036) and boys induced by increase in consumption of fat (p=0.041). However, there are two issues that require further elaboration.

First, we believe that the overall study design is flawed. However, the choice of a cross-sectional study for this study is not appropriate with the study content, after all, the occurrence of functional constipation is a long period of time, and it is not reasonable to just intercept the data for a certain period of time. For example, in the food intake analysis, the study used a 24-h dietary recall survey. We believe that obtaining data in this way is incomplete, and simply investigating dietary status over a 24-h period can easily lead to inaccurate results. Therefore, we suggest the authors repeat the use of 24-h dietary recall survey to collect food intake data for analysis in the established research cycle to ensure the randomness and accuracy of the data.

Second, the study's finding that "functional constipation is associated with a larger abdominal circumference in girls" is challenged. The study ignored the fact that the amount of abdominal fat is a key factor in abdominal circumference[2] and thus did not specifically address the question of the amount of abdominal fat in the respondents. If the girls in the study had increased abdominal circumference due to the accumulation of subcutaneous fat, the results of this study would have resulted in false positives. Therefore, we recommend adding the measurement of abdominal fat content to rule out such false positive results.

AUTHORS' CONTRIBUTIONS

BW: Funding acquisition, Writing – original draft.
HX: Methodology, Writing – review & editing.

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LETTER TO THE EDITOR

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Comment on "Does the presence of radiculopathy affect sleep quality and lower extremity functionality in neuropathic low back pain?"

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Dear Editor,

First and foremost, we would like to express our gratitude to our esteemed authors for their interest in and contribution to our article[1]. This study was conducted with 79 patients diagnosed with lumbar disc herniation (LDH) presenting neuropathic-type low back pain[2]. Patients included in the study were those who sought treatment at the clinic due to chronic low back pain. Rather than the variety of current treatments received, whether patients were taking medications that could cause neuropathy or disrupt sleep quality was more important for this study. Patients diagnosed with sleep disorders or neuropathy were not included in the study, as stated in the exclusion criteria.

The exclusion criteria of this study included past disc surgery, vasculitis, spinal cord injury, and conditions such as HSV and HIV. Patients with inflammatory, infectious, congenital, or traumatic pathologies involving the lumbar region were not included in the study. Spinal stenosis can occur due to pressure from a herniated disc inherently[3]; hence, congenital or structurally caused spinal stenosis could have been added to the exclusion criteria. Although the inclusion criterion of having received a diagnosis of LDH partially explains this situation, the condition of spinal stenosis could have been elaborated further.

The role of depression and anxiety disorders in both chronic pain and sleep disorders is well-established. This issue is discussed in the discussion section of our article. Due to the numerous studies in the literature on this topic, the potential contributions of our findings were limited in terms of positivity or negativity. The main aim of this study was to investigate the impact of electroneuromyographically (ENMG) proven radiculopathy on sleep and lower extremity functions and compare it with patients without radiculopathy.

During routine examinations of our patients, their habits are questioned. None of the patients included in this study had alcohol or stimulant substance dependencies, although some participants were smokers. This information could be mentioned as general knowledge and evaluated in the table assessing sleep quality.

Conditions such as weakness accompanying neuropathic pain (NP), allodynia, and decreased deep tendon reflexes mentioned in the introduction of our article are not prerequisites for the diagnosis of NP. When the referenced article is reviewed, it is observed that NP can occur without these findings[4]. Given our clinical experience encountering NP exactly as described by the authors[1] and our belief that the concept of NP needs to be evaluated more broadly, this study was conducted. NP can persist in individuals with no neurological deficits, no disc herniation, and non-specific lower back pain, either related to disc herniation or due to untreated prolonged nociceptive pain and pathologies in pain processing pathways[5]. This issue is discussed in the discussion section of our article. Furthermore, upon reviewing the inclusion criteria, it was observed that 148 participants who underwent ENMG and were diagnosed with disc herniation were examined. There were also patients with ENMG findings who did not meet the DN4 criteria for NP, and these patients were not included in the study.

Contrary to what the authors mentioned, we did not have an evaluation or conclusion similar to patients with and without radicular pain in this study. When the inclusion criteria were examined, all patients had radicular pain. Our differentiation was based on whether patients had radiculopathy, according to ENMG findings.

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The concept of chronic pain and neuropathic pain is a condition with many causes, and research into its etiopathogenesis continues. In this sense, every study will contribute to shedding light on the subject.

AUTHORS' CONTRIBUTIONS

BKA: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **MT:** Data curation, Writing – review & editing.

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ChatGPT in reducing vaccine hesitancy and enhancing vaccine acceptance: correspondence

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Dear Editor,

"Application of ChatGPT in reducing vaccine hesitancy and enhancing vaccine acceptance: Hope or myth?[1]" is an interesting article. In conclusion, vaccine hesitancy has been effectively addressed by using ChatGPT, a text-generative artificial intelligence tool, which clears up myths and provides correct facts. This has been especially important during the COVID-19 pandemic when efforts to promote public health have been severely hampered by reluctance and false information. ChatGPT has the capacity to inform and empower people to make knowledgeable vaccination decisions, which could ultimately result in a rise in vaccine adoption and better public health outcomes.

But even with all of its apparent advantages, ChatGPT is not without flaws. Depending on the version utilized, it can give false information, which could cause confusion and even injury if people depend only on its answers when making medical decisions. Furthermore, ChatGPT might not have the most recent information after a certain point, which would restrict its usefulness in addressing pressing problems and changing healthcare difficulties. Moreover, the instrument might not encompass the subtleties of personalized patient care and might not provide the comprehensiveness and precision necessary for intricate medical situations.

Going forward, it is imperative to recognize and rectify these shortcomings in ChatGPT in order to optimize its efficacy in mitigating vaccine reluctance. Future developments can include adding real-time updates and making sure that the data the tool provides are accurate and dependable. The ability of the tool to handle a variety of patient groups and customize responses to suit each person's requirements and preferences should also be improved. Partnerships between medical practitioners, IT specialists, and public health authorities can maximize ChatGPT's usage by encouraging vaccine acceptance and successfully dispelling false information.

In conclusion, even though ChatGPT has demonstrated promise in reducing vaccination hesitancy and encouraging vaccine acceptance, it is critical to acknowledge its limits and keep enhancing and perfecting the tool in order to meet the changing demands of the medical field. By utilizing ChatGPT and other AI-powered healthcare tools, we can improve communication, give people accurate information, and encourage them to make well-informed immunization decisions. ChatGPT has the potential to significantly influence how healthcare is delivered in the future and how public health activities are carried out with additional development and cooperation.

AUTHORS' CONTRIBUTIONS

HD: Formal Analysis, Writing – original draft. **VW:** Supervision.

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ORIGINAL ARTICLE

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Are maternal serum subfatin levels altered in women with one abnormal glucose tolerance test value?

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SUMMARY

BACKGROUND: Subfatin, a newly discovered adipokine, plays a pivotal role in the regulation of glucose metabolism. The relationship between gestational diabetes mellitus and maternal dyslipidemia is well-documented.

AIMS: This study aims to assess serum subfatin levels and the triglyceride/high-density lipoprotein cholesterol ratio in women with one abnormal glucose tolerance test value and those with gestational diabetes mellitus.

METHODS: In this case–control study, 105 pregnant women were categorized into three groups: women with normal 3-h oral glucose tolerance test results (n=35), women with one abnormal 3-h oral glucose tolerance test result (n=35), and women diagnosed with gestational diabetes mellitus (n=35). Serum subfatin levels were measured using human enzyme-linked immunosorbent assay kits.

RESULTS: Serum subfatin levels were significantly lower in the gestational diabetes mellitus group (0.94±0.15 ng/mL) compared to the normal oral glucose tolerance test group (1.48±0.55 ng/mL) and the group with one abnormal oral glucose tolerance test result (1.50±0.59 ng/mL). The triglyceride/high-density lipoprotein cholesterol ratio was also lower in the healthy control group than in the gestational diabetes mellitus and one abnormal oral glucose tolerance test result groups.

CONCLUSION: Serum subfatin levels in women with one abnormal abnormal glucose tolerance test value are compared to those in the control group, while the triglyceride/high-density lipoprotein cholesterol ratio is significantly altered in women with one abnormal abnormal glucose tolerance test value when compared to the control group.

KEYWORDS: Cholesterol. Gestational diabetes mellitus. Glucose tolerance test. Subfatin. Triglyceride.

INTRODUCTION

Gestational diabetes mellitus (GDM) is described as insulin resistance that emerges or is first identified during pregnancy[1]. As the prevalence of GDM continues to rise, understanding the mechanisms underlying glucose regulation and insulin resistance during pregnancy becomes increasingly crucial. Various studies have proposed a relationship between adipokines and GDM[2-4]. Unlike most adipokines identified in obesity models, subfatin was first described in the PGC-1α4 transgenic mice model[5]. Subfatin, an adipokine predominantly produced by adipose tissue, is crucial in regulating insulin sensitivity through the peroxisome proliferator-activated receptor-gamma (PPAR-γ) pathway[2-6]. Besides, subfatin is particularly intriguing due to its dual role in enhancing energy expenditure through the browning of white adipose tissue and its potential impact on insulin sensitivity[7]. However, findings on the relationship between subfatin levels and GDM show discrepancies. For instance, Yavuzkir et al. discovered that subfatin levels were significantly elevated in mothers with GDM compared to those with normal pregnancies[2]. Conversely, subfatin levels have been associated with a negative correlation with serum glucose levels and an exacerbation of glucose tolerance test (GTT) outcomes[8,9]. A single abnormal value on an oral glucose tolerance test (OGTT) is considered a pathological indicator. Patients with a single abnormal test result exhibited no difference from those diagnosed with GDM in terms of fasting insulin levels and insulin resistance[10]. This study also aims to explore if patients with a single abnormal test result exhibit altered subfatin levels.

The triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio has been positively linked to insulin resistance[11]. Significant disparities in the TG/HDL-C ratio have been observed between women with and without GDM[12]. For instance, lower HDL-C[13] and the TG/HDL-C ratio[14] are indicators of insulin resistance. Since insulin resistance is a key underlying factor of GDM, various lipid ratios have been utilized to assess GDM risk[15]. The early diagnosis of GDM is crucial, yet there is a lack of

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comprehensive information on universal or case-specific screening tests for GDM. Coupled with alterations in lipid metabolism in GDM patients and the potential pathophysiology of the disease, there is a pressing need for additional research like this study. This study aims to examine serum subfatin levels and the TG/HDL-C ratio in women with abnormal GTTs (AGTT) and GDM, and its correlation with AGTT and its broader implications for insulin resistance in GDM. By exploring the function of subfatin, this research seeks to uncover novel insights into the metabolic adjustments during pregnancy that could influence the development and management of GDM.

METHODS

This case–control study was conducted at the Obstetrics, Gynecology, and Perinatology Clinics of Etlik Zubeyde Hanim Women's Health Education and Training Hospital between March 2021 and October 2021. Approval was obtained from the local ethics committee on December 30, 2020 (Approval No: 2020/175).

Inclusion–exclusion criteria

In diagnosing GDM, we opted for the National Institute for Health and Care Excellence (NICE) guidelines rather than the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommendations[16]. This decision was informed by this study, which indicates that the NICE guidelines provide a more favorable cost–benefit ratio in terms of diagnostic efficacy and healthcare resource allocation[16]. Details of this study and the rationale for our choice are briefly outlined in this section to assist other researchers in understanding the contextual factors influencing the selection of diagnostic criteria.

The study included singleton pregnancies of women aged 18–39 years within 24–28 gestational weeks. Exclusion criteria encompassed any of the following: a history of macrosomia (birth weight >4,000 g) or stillbirth, previous GDM, congenital malformations or chromosomal abnormalities in the fetus, fetal death, multiple pregnancies, maternal polycystic ovary syndrome, pregestational diabetes mellitus (DM) or a first-degree relative with DM, pregnancy-induced hypertension, chronic maternal diseases (such as chronic hypertension, dyslipidemia, renal failure, or diseases of the thyroid, liver, lung, or heart, and malignancy), use of drugs affecting lipid or glucose metabolism, and alcohol consumption.

Study design

GDM screening was performed using a 50 g glucose challenge test (GCT) between 24 and 28 gestational weeks. Pregnant women with GCT results above 140 mg/dL underwent a 3-h OGTT and were categorized into three groups, each comprising 35 participants: women with normal OGTT results (Group 1), women with one abnormal OGTT value (Group 2), and women diagnosed with GDM (Group 3).

Collection and storage of biological samples

Blood samples were collected from participants between 24 and 28 gestational weeks to measure serum subfatin, insulin, selected serum lipid profiles (TG, LDL, VLDL, HDL-C), and glucose levels. About 8 mL of blood, drawn using sterile syringes, was centrifuged at 3,000 × g for 5 min. The plasma was then aliquoted into Eppendorf tubes and stored at -80°C until analysis.

Laboratory analysis of biological samples

Serum subfatin levels were measured using human enzyme-linked immunosorbent assay (ELISA) kits (Catalog No. E3941Hu, HEALES MB-530, Shanghai, China). The standard curve for subfatin ranged from 0.05 to 15 ng/mL, with a sensitivity of 0.023 ng/mL. Lipid profiles and blood glucose levels were analyzed using the Advia 2400 Clinical Chemistry System (Siemens, Tarrytown, NY, USA).

We compared the fasting plasma glucose levels, fasting serum insulin levels, selected serum lipid metabolism parameters (TC, LDL-C, HDL-C, VLDL-C, and TG), and specifically serum subfatin levels obtained between the 24th and 28th weeks of pregnancy.

Statistical analyses

Data were analyzed using the SPSS software, version 21.0 (IBM Corporation, Armonk, NY, USA)[17]. Power analysis was conducted with G*Power 3.1, suggesting a sample size of approximately 70 cases and 35 controls to detect the association with 95% power at a 0.05 alpha level[18]. Group comparisons and categorical variables were analyzed using the chi-square and ANOVA tests. The Kruskal-Wallis test was applied for comparisons among the three groups, followed by the Mann-Whitney U-test for post-hoc analysis upon detecting significant differences. The association strength between parameters was assessed using Spearman's rank correlation coefficient, with a p-value of 0.05 deemed significant.

RESULTS

The demographic characteristics of the study groups are presented in Table 1. There were no statistically significant differences across the groups in terms of maternal age, body mass index (BMI),

smoking habits, number of pregnancies (gravida), number of births (parity), and gestational age at the time of the OGTT.

Significant differences were observed in fasting plasma glucose and serum TG levels among the groups, with p-values <0.05. The TG/HDL-C ratio varied widely, ranging from 0.82 to 9.11, with an average ratio of 3.23±1.52. This ratio also showed significant variation among the groups, as indicated by a p-value <0.05. Serum subfatin levels were found to be between 0.71 and 3.82 ng/mL, averaging 1.31±0.54 ng/mL. The difference in serum subfatin levels was statistically significant across the groups, with a p-value <0.05 (Table 2).

However, there was no significant correlation between serum subfatin levels and the TG/HDL-C ratio (rho=-0.096; p=0.332), suggesting that while both parameters significantly varied among the groups, they did not show a direct relationship with each other.

Table 1. Demographic characteristics of the study groups.

		Normal 3-h OGTT (n=35)	One abnormal 3-h OGTT (n=35)	GDM (n=35)	Chi-square	p-value
		n (%)	n (%)	n (%)		
Age (years)	<31	18 (51.4)	16 (45.7)	15 (42.9)	1.163	0.884
	31–35	9 (25.7)	9 (25.7)	8 (22.9)		
	>35	8 (22.9)	10 (28.6)	12 (34.3)		
BMI (kg/m^2)	18.5–24.9	9 (25.7)	4 (11.4)	5 (14.3)	8.068	0.089
	25–29.9	15 (42.9)	12 (34.3)	20 (57.1)		
	30–34.9	11 (31.4)	19 (54.3)	10 (28.6)		
Smoking status	Smoker	3 (8.6)	5 (14.3)	5 (14.3)	0.702	0.704
	Nonsmoker	32 (91.4)	30 (85.7)	30 (85.7)		
		Mean±SD	Mean±SD	Mean±SD	F	p-value
Gravida		2.94±1.39	2.69±1.37	3.06±1.57	2.744	0.840
Parity		1.48±0.95	1.11±0.83	1.40±1.06	6.293	0.391
Gestational age at OGTT (weeks)		26.22±1.42	26.40±1.48	26.40±1.38	17.036	0.058

Table 2. Comparison of biochemical parameters among the study groups.

	Normal 3-h OGTT (n=35)	One abnormal 3-h OGTT (n=35)	GDM (n=35)	f	p-value
	Mean±SD	Mean±SD	Mean±SD		
FBG (mg/dL)	78.11±6.62	82.22±21.13	91.31±14.56	6.693	0.002
Fasting insulin (mIU/mL)	9.95±7.57	15.00±17.10	15.73±14.46	1.861	0.161
TC (mg/dL)	252.40±46.74	244.92±48.53	245.76±56.35	0.229	0.796
LDL-C (mg/dL)	145.39±34.80	137.87±44.45	136.89±45.28	0.434	0.649
HDL-C (mg/dL)	70.01±14.79	67.96±13.20	65.49±14.57	0.886	0.415
VLDL-C (mg/dL)	37.86±11.53	39.77±14.91	45.92±16.36	2.991	0.055
TG (mg/dL)	187.11±58.81	198.69±74.58	231.14±82.09	3.471	0.035
TG/HDL-C ratio	2.80±1.06	3.13±1.61[a]	3.75±1.69[a]	3.720	0.028
				*	p-value
Serum subfatin levels (ng/mL)	1.48±0.55	1.50±0.59[b]	0.94±0.15[c]	47.561	<0.001

Data are presented as the mean ± standard deviation (SD).
FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; TG, triglyceride; F, value get after ANOVA test. [a]p < 0.05 compared with the control group.
[b]p = NS compared with the control group. [c]p <0.001 compared with the control group and one AGTT value group. *Kruskal-Wallis test.

DISCUSSION

To the best of our knowledge, this study is the inaugural exploration of subfatin levels and the TG/HDL-C ratio in individuals with one AGTT value. Extensive research has been conducted to uncover the mechanisms behind GDM, focusing on the role of adipokines and myokines[2,19,20]. In recent years, the study of hormones derived from adipokines and myokines has become crucial for understanding GDM's underlying mechanisms[21,22]. Subfatin, a highly expressed adipokine in subcutaneous fat, has been scrutinized for its potential involvement in GDM[2,6-9], yielding mixed results that underscore the need for further investigation.

Wang K et al. embarked on a study to examine the relationship between meteorin-like protein (Metrnl) serum levels, blood glucose status, and insulin resistance[23]. Their findings suggest that elevated serum levels of Metrnl (including subfatin, cometin, etc.) are significantly associated with an increased risk of type 2 DM, independent of insulin resistance[23]. Similarly, Chung et al. found that Metrnl levels were significantly higher in diabetic patients compared to a healthy control group, with levels correlating with fasting plasma glucose and lipid profiles after adjusting for age and sex[24]. Contrary to Wang K et al. and Chung et al., Dadmanesh et al. reported decreased serum Metrnl levels in individuals with type 2 DM[8]. Our study revealed that serum subfatin levels were lower in the GDM group but higher in the AGTT group, with control group levels falling between these groups. Dadmanesh et al. suggested that discrepancies in subfatin levels might stem from medical treatments or ethnic differences[6]. Contrasting with Chung et al., Lee et al. found that medical treatment did not affect serum Metrnl levels after 12 weeks[25]. In our research, participants with GDM and/or AGTT were not subjected to any medical treatment apart from dietary advice at the time of diagnosis; hence, their serum subfatin levels were measured.

We also observed an increase in serum subfatin levels in the AGTT group and a decrease in the GDM group, aligning with Dadmanesh et al's findings[8]. There are limited studies on individuals with type 2 diabetes, and only one study discusses serum subfatin level changes in GDM[2,8,21-25]. This makes our study the first to report on maternal serum subfatin levels in women with GDM and one AGTT value.

Yavuzkir et al. conducted a study to assess serum subfatin levels in GDM patients[2]. Their results indicated that GDM led to increased subfatin levels, suggesting the protein's potential as a biomarker for GDM diagnosis and management[2]. Our findings show that serum subfatin levels increase with one AGTT value and decrease in GDM cases, statistically.

Furthermore, our study found a significant difference in TG/HDL-C ratios among groups, with non-GDM or one AGTT value individuals exhibiting lower TG/HDL-C ratios than those with GDM or one AGTT value. This is consistent with other studies that affirm the link between hyperlipidemia and GDM[12,26,27]. However, some research contradicts this, pointing to the influence of diet, exercise, lifestyle, and ethnicity on lipid profiles[12,15,26,27].

In this study, we restricted our women participants' age to 39 years and younger. This decision was based on data suggesting that metabolic and hormonal profiles can differ significantly in women aged over 40 years, potentially confounding the effects of subfatin levels on glucose tolerance and GDM outcomes. Research indicates that age-related hormonal changes, especially around the perimenopausal period, can significantly alter glucose metabolism and insulin sensitivity, which might mask the specific effects of subfatin we aimed to investigate. Furthermore, age-related increases in the prevalence of comorbid conditions such as cardiovascular disease and type 2 diabetes could introduce additional variability, complicating the interpretation of our findings. Thus, focusing on a younger cohort allows for a more controlled analysis of subfatin's role in the early stages of metabolic dysregulation typically observed in pregnancy and pre-diabetic states[28].

This study marks a significant contribution to GDM research by pioneering the investigation of serum subfatin levels and the TG/HDL-C ratio in individuals with one abnormal AGTT value, offering valuable insights into metabolic changes associated with GDM. The observed increase in subfatin levels in subjects with abnormal AGTT values suggests a potential compensatory mechanism that enhances insulin sensitivity and glucose regulation. This aligns with subfatin's known function in promoting the browning of adipose tissue, a process that not only increases energy expenditure but also improves insulin action. The relationship between subfatin and insulin resistance is critical, especially given that its upregulation in response to metabolic stress (such as exercise and cold exposure) has been shown to improve glucose uptake and metabolic health[29]. However, the dynamics of subfatin expression and its impact on insulin sensitivity during pregnancy remain complex. Its comprehensive approach, which builds on existing contradictory findings regarding subfatin levels, and its acknowledgment of potential confounders, such as medical treatment and ethnic differences, highlight its strengths. However, the study faces limitations due to its small sample size, which affects the statistical power and generalizability of its findings. Additionally, its cross-sectional design limits the ability to

establish causality or observe longitudinal changes, and it does not fully address other potential confounding factors, such as lifestyle and socioeconomic status, which could influence the outcomes. Furthermore, the study's focus on a specific population may limit its applicability to wider demographic groups, and a lack of in-depth analysis into the underlying biological mechanisms connecting subfatin and lipid metabolism to GDM calls for further research. Addressing these weaknesses through larger, more diverse, and longitudinal studies could enhance the robustness and applicability of the findings, providing clearer insights into the pathophysiological pathways involved in GDM.

CONCLUSION

The mean serum subfatin levels in women with GDM were lower than those in women with one AGTT value and healthy control groups; women with one AGTT value had the highest serum subfatin level in the present study. Also, TG/HDL-C ratio was lower in the healthy control group. Larger studies are required to clarify the relationship between subfatin and GDM and one AGTT value.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies were conducted (Etlik Zubeyde Hanim Women's Health Education and Training Hospital; December 30, 2020; no: 2020/175) and with the 2013 Helsinki Declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

AUTHORS' CONTRIBUTIONS

YAR: Conceptualization, Data curation, Formal Analysis. **FBF:** Conceptualization, Data curation, Formal Analysis. **AA:** Conceptualization, Data curation, Formal Analysis, Writing – original draft. **CK:** Conceptualization, Formal Analysis. **HET:** Conceptualization, Formal Analysis. **YU:** Conceptualization, Data curation, Formal Analysis, Writing – original draft.

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ORIGINAL ARTICLE

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Female genital mutilation and urinary incontinence: an analytical comparison with Sudan's prevalent demography

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SUMMARY

OBJECTIVE: Female genital mutilation/cutting impacts over 200 million women globally and is linked to obstetric complications as well as long-term urogynecological and psychosexual issues that are frequently overlooked and inadequately addressed. This study aimed to assess the impact of female genital mutilation/cutting on urinary incontinence.

METHODS: This cross-sectional study was conducted in the gynecology department of the Research Hospital located in the Nyala rural region of Sudan. The participants were interviewed to gather socio-demographic and background information. In addition, they received a thorough gynecological examination to evaluate the presence and type of female genital mutilation/cutting. The Incontinence Impact Questionnaire and the Urogenital Distress Inventory were applied to the group with female genital mutilation/cutting and the control group without female genital mutilation/cutting to evaluate urinary incontinence and related discomfort. Subsequently, the scores of both participant groups were compared.

RESULTS: The study compared age, weight, height, BMI, gravida, parity, and sexual intercourse averages between groups. The mean Urogenital Distress Inventory-6 and Incontinence Impact Questionnaire-7 scores of individuals who underwent mutilation were higher than those of individuals who did not undergo mutilation ($p<0.001$). Notably, participants subjected to infibulation exhibited significantly higher average scores on both measures in contrast with the other groups ($p<0.001$).

CONCLUSION: A higher proportion of mutilated participants, specifically those with infibulation, are afflicted with symptoms of incontinence.

KEYWORDS: Genital mutilation, female. Infibulation. Sudan. Urinary incontinence.

INTRODUCTION

The cultural practice of female genital mutilation (FGM), also known as female genital mutilation/cutting (FGM/C), has been deeply rooted in the cultural customs of certain regions in Sudan for many centuries[1]. FGM/C is a cultural practice that is also widespread in Africa and Asia. It is usually performed by traditional practitioners and has a significant impact on more than 200 million women globally[2,3]. FGM/C involves the partial or total removal of the external female genitalia often performed without medical supervision or proper hygiene.

The World Health Organization (WHO) classifies the act of cutting the female genital region as "mutilation"[4]. WHO categorized FGM into four distinct kinds. Type I is also referred to as clitoridectomy. Type II entails the partial or total excision of the labia minora and majora, as well as the removal of the clitoris. Type III, which is often referred to as infibulation, entails the surgical removal of a part or the totality of the external genitalia, followed by the surgical approximation of the remaining labia majora. Type IV comprises a range of injuries to the female vaginal organs[5].

While some argue that FGM is a customary practice or an important rite of passage. Its potential harmful health effects have gained global recognition[6]. Among these, health risks is an increased incidence of urinary incontinence (UI) among women who have undergone the procedure.

UI refers to the involuntary release of urine, which can significantly affect an individual's quality of life, self-esteem, and overall well-being. The severity and frequency of this condition can vary from occasional minor leakage to more frequent and debilitating symptoms[7].

While the physical and psychological health effects of FGM have been well examined, the urinary issues resulting from the procedure have not received adequate attention in the existing literature. Abdulcadir et al.'s study conducted in Sudan demonstrated a significant association between FGM and UI among women[8].

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Similarly, Dirie and Lindmarks's study done in Somalia revealed a high prevalence rate of 80% for UI among women who had undergone FGM[8].

This study aims to conduct a comprehensive examination of the prevalence of UI among Indigenous Sudanese women who have experienced FGM. This study also aims to examine differences in the characteristics and severity of UI according to different classifications of FGM.

METHODS

This study used a cross-sectional design to evaluate the effect of mutilation on UI in an endemic Sudanese female population. A total of 307 people participated in the study. The research was conducted in collaboration with healthcare professionals, researchers, and local communities within Sudan. Approval was granted by the institutional ethics committee (NSTH.03/903.07.03/689, date: 01.03.2021). The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of Turkey.

A representative sample of women who had undergone FGM was selected using a multi-stage sampling technique. Efforts were made to ensure diversity in age groups, marriage status, educational status, circumcise type, and menopausal status to capture a comprehensive picture of the endemic population. Informed consent was obtained from all participants before their inclusion in the study. The exclusion criteria were the presence of a urinary tract infection identified through clinical examination or urine analysis, confirmed renal disease, cervicitis and/or vaginitis, diabetes diagnosis, vaginal and/or urethral surgery, and rejection to participate in the study.

Data collection was carried out through face-to-face interviews using structured questionnaires. The questionnaires were designed based on established instruments used in previous studies exploring the impact of female genital circumcision on UI. We use the Urogenital Distress Inventory (UDI)-6 and the Incontinence Impact Questionnaire (IIQ)-7. Both questionnaires underwent validation in the Arabic language[9,10].

The UDI-6 is a validated health-related quality-of-life (HRQOL) tool that assesses the level of distress caused by three categories of urine symptoms: irritative, obstructive/discomfort, and stress[11]. The total score is from 0 to 100[12]. The IIQ-7 is a psychometric questionnaire specifically designed to assess UI. This questionnaire evaluates the psychological and social effects of UI in women. The overall score spans from 0 to 100[13].

The UDI-6 Total Score of 33.33 and IIQ-7 Total Score of 9.52 were identified as the most effective thresholds for differentiating between women with symptoms and those without symptoms[14].

The questionnaires were administered to the patients by the local gynecologist. Participants were asked about the frequency, amount, and impact of urine leakage, as well as any associated physical or emotional discomfort.

In the analysis of the data, the SPSS version 25.0 program was used. The suitability of the variables for normal distribution was examined with histogram graphs and the Kolmogorov-Smirnov test. While presenting descriptive analyses, mean, standard deviation, median, and minimum–maximum values were used. The 2×2 eyes were compared with the Pearson chi-square test. Variables not showing normal distribution (nonparametric) were evaluated between groups using the Mann-Whitney U test, and among more than two groups using the Kruskal-Wallis test. Situations, where the p-value is below 0.05, were considered statistically significant results.

RESULTS

The study included a total of 307 participants. The mutilation group consisted of 161 (52.44%), whereas the control group had 146 (47.56%) participants. The average UDI-6 and IIQ-7 scores of circumcised individuals were higher than those of uncircumcised individuals.

The marital status, education, and menopausal status of the circumcised and uncircumcised individuals were compared in this study. The findings indicate that there were no significant differences between the groups. The study compared several factors including age, weight, height, BMI, gravida, parity, and sexual intercourse averages between the two groups. The results indicated that unmutilated participants had a higher average sexual intercourse frequency compared with circumcised individuals ($p<0.001$).

The UDI-6 and IIQ-7 averages were compared between the groups. The average UDI-6 and IIQ-7 scores of circumcised individuals were higher than those of uncircumcised individuals (Table 1).

A comparison was made between different mutilation types based on their associated UDI 6 and IIQ 7 scores (Table 2). Notably, participants subjected to infibulation exhibited significantly higher average scores on both measures in contrast with the other groups ($p<0.001$). Evidently, this pattern persisted across both measures (UDI 6 and IIQ 7) illustrating a distinct disparity between those who received infibulation versus those who did not ($p<0.001$).

The hierarchical regression results for UDI-6 and IIQ-7 scores are detailed in Table 3.

Table 1. The average UDI-6 and IIQ-7 scores of individuals.

	Group				p
	Mutilated		Unmutilated		
	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)	
UDI-6	22.27±28.13	5.55 (0–88.8)	15.05±22.67	0 (0–83.25)	**0.036**
IIQ-7	18.21±25.28	4.75 (0–91.84)	10.38±18.49	0 (0–80.87)	**0.015**

Mann-Whitney U test.
Statistically significant values are indicated in bold.

Table 2. Comparison of UDI-6 and IIQ-7 scores by circumcision type.

	Circumcised type								p
	Uncircumcised		Clitoridectomy		Excision		Infibulation		
	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)	
UDI-6	15.05±22.67	0 (0–83.25)	3.77±11.3	0 (0–49.95)	13.23±20.28	0 (0–77.7)	40.08±30.96	44.4 (0–88.8)	**<0.001**
IIQ-7	10.38±18.49	0 (0–80.87)	2.65±8.73	0 (0–42.42)	9.5±17.44	0 (0–76.11)	34.49±28.46	38.05 (0–91.84)	**<0.001**

Kruskal-Wallis test.
Statistically significant values are indicated in bold.

DISSCUSSION

FGM has long been an area of research interest due to its profound social, cultural, and health implications. Our study is set against this backdrop, aiming to explore the relationship between FGM's different forms and UI symptoms in Sudan.

Out of 307 participants in our study, 52.44% reported undergoing FGM. This percentage echoes broader statistics within Sudan, where FGM remains a widespread and culturally deep-rooted practice[15].

An elevated risk of health problems is just one of the many negative physical, mental, and emotional outcomes that may result. UI is one of the possible side effects of FGM. Problems with urinating and an increased chance of urine incontinence are among the potential consequences that can arise from the procedure's removal or injury to genital tissues. The level of incontinence that results from mutilation can differ in intensity based on the procedures that were carried out.

FGM procedures involve the removal or alteration of tissues around the urethra[16]. This can result in stenosis or occlusion of the urethral orifice, causing urinary flow obstruction. Various degrees of scar tissue occur in the external genitalia, depending on the severity of the excision. Scar tissue can be less elastic and flexible than normal tissue, potentially causing structural changes that affect the normal functioning of the urinary system. This scarring can contribute to UI[17].

The removal of sensitive genital tissues during FGM procedures can lead to nerve damage[18]. Neuronal stimulation occurs in the medial paracentral lobule as a result of vulvar sensations. The anus and vagina are "mapped" together on the medial surface of the cortex, namely, between the central and precentral (marginalis) sulci. If there is a reorganization of neuronal input at the body surface, it may also lead to a reorganization of input to the somatosensory cortex[19].

The connection between mutilation and UI can be comprehended by examining the existing body of literature on childhood sexual abuse and UI[20]. Several women who have been mutilated recall experiencing intense terror, excruciating pain, and a profound sense of helplessness. Mutilation, such as sexual abuse, is recognized to be a causative factor for post-traumatic stress disorder, somatization, depression, and anxiety[21,22]. In their study, Geynisman-Tan et al. attributed the increase in UI prevalence in patients with FGM to this relationship[7].

Furthermore, Emanulle et al.'s systematic review strongly advocated for rigorous evidence in the form of randomized controlled trials to conclusively determine the urological complications associated with FGM, particularly Type III. Our study reaffirms this stance, indicating that infibulation (Type III FGM) is a significant contributor to UI, a sentiment our findings support. In particular, infibulation showed a strong association with UI symptoms[23]. Recognizing the study's limitations, particularly its sample size, is crucial.

We determined in this study that the more circumcision damages neighboring tissues and anatomical structures, the higher the rate of incontinence becomes.

Table 3. Hierarchical regression results for UDI-6 and IIQ-7.

UDI-6							
	B	Std. error	Beta	t	95%CI for B		p
Model 1					LL	UL	
Age	0.696	0.097	0.391	7.199	-19.319	38.276	0.518
BMI	-0.456	0.426	-0.055	-1.071	0.506	0.887	<0.001
Gravida	1.827	1.150	0.138	1.588	-1.294	0.382	0.285
Parity	1.781	1.890	0.082	0.943	-0.436	4.090	0.113
Sexual intercourse	-0.757	0.608	-0.064	-1.245	-1.938	5.501	0.347
Model 2					-1.955	0.440	0.214
Age	0.694	0.096	0.390	7.242	0.505	0.883	<0.001
BMI	-0.439	0.422	-0.053	-1.039	-1.269	0.392	0.300
Gravida	1.723	1.140	0.130	1.511	-0.521	3.966	0.132
Parity	1.842	1.873	0.084	0.984	-1.843	5.527	0.326
Sexual intercourse	-0.297	0.628	-0.025	-0.473	-1.534	0.939	0.637
Group*	6.968	2.694	0.135	2.586	1.666	12.270	0.010
IIQ-7							
	B	Std. error	Beta	t	95%CI for B		p
Model 1					LL	UL	
Age	0.642	0.085	0.413	7.589	0.476	0.809	<0.001
BMI	-0.339	0.373	-0.047	-0.909	-1.072	0.395	0.364
Gravida	1.130	1.006	0.097	1.123	-0.850	3.109	0.262
Parity	1.627	1.653	0.085	0.984	-1.626	4.880	0.326
Sexual intercourse	-1.064	0.532	-0.103	-01.999	-2.111	-0.017	0.047
Model 2							
Age	0.640	0.083	0.411	7.670	0.476	0.804	<0.001
BMI	-0.320	0.367	-0.044	-0.871	-1.043	0.403	0.384
Gravida	1.020	0.992	0.088	1.028	-0.932	2.972	0.305
Parity	1.691	1.630	0.089	1.038	-1.516	4.898	0.300
Sexual intercourse	-0.579	0.547	-0.056	-1.058	-1.655	0.498	0.291
Group*	7.349	2.345	0.163	3.135	2.735	11.963	0.002

Note: 0=unmutilated, 1=mutilated.
*The "Group" parameter was included in the model with two groups coded as 0 for unmutilated and 1 for mutilated.

The primary limitations of this study were the omission of urodynamic investigations and the reliance on urine analysis data instead of urine cultures for diagnosing urinary tract infections. These are notable flaws. Notwithstanding these constraints, the study offers an initial understanding of the impact of FGM on the occurrence of UI.

CONCLUSION

Individuals who have been circumcised, particularly those with infibulation, are more likely to experience incontinence symptoms. Healthcare providers attending to patients with FGM/C should inquire about UI.

AUTHORS' CONTRIBUTIONS

MCD: Data curation, Project administration, Writing – original draft. **HA:** Formal Analysis, Project administration, Writing – original draft. **SMAS:** Writing – original draft, Writing – review & editing. ÖA: Data curation, Formal Analysis. **MH:** Data curation, Formal Analysis. **ME:** Data curation, Formal Analysis, Project administration.

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ORIGINAL ARTICLE

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The relationship between women's personality traits and fear of childbirth, birth satisfaction, and postpartum depression

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SUMMARY

OBJECTIVE: This study was conducted to determine the relationship between women's personality traits and their fear of childbirth, birth satisfaction, and postpartum depression.

METHODS: This cross-sectional study was conducted between April and August 2022 among healthy third-trimester pregnant women aged 18–49 years who applied to the obstetrics and gynecology outpatient clinic of a state hospital. Data were collected by the researchers by face-to-face interview method in three stages. Participants were administered the Personal Information Form, the Five-Factor Personality Scale, and the Birth Anticipation/Experience Scale at the first interview; the Birth Satisfaction Scale on the 10th day after normal birth; and the Edinburg Postpartum Depression Scale 4 weeks after birth.

RESULTS: There was a significant positive correlation between neurotic personality traits and fear of childbirth and postpartum depression, while there was a negative correlation with other personality traits ($p<0.001$). There was no significant relationship between birth satisfaction and personality traits ($p>0.05$). The effect of personality traits on fear of childbirth and postpartum depression was analyzed by multiple linear regression analysis. The regression model tested for the effect of personality traits on fear of childbirth and postpartum depression was found significant ($p<0.001$). According to the model, 26% of the variability in fear of childbirth and 9.1% of the variability in postpartum depression were explained by personality traits.

CONCLUSION: This study showed that neuroticism, which is one of the personality traits of women, had a positive effect on fear of childbirth and postpartum depression. No significant relationship was found between birth satisfaction and personality traits.

KEYWORDS: Woman. Personality traits. Fear. Parturition. Patient satisfaction. Postpartum depression.

INTRODUCTION

Childbirth, which is a physiological process, is the most special and meaningful moment for women, but it is a process that every woman experiences differently. Although the literature shows that fear of childbirth is associated with negative birth satisfaction and postpartum depression, it may also cause many problems such as pregnancy and birth complications, difficulties in mother–infant attachment, and cesarean section[1,2]. It is mentioned that fear of childbirth, the etiology of which is based on many factors such as age, education, income level, lack of information, fear of intervention, negative birth stories, and previous traumatic experiences[3], is closely related to the personality traits of women[4].

Personality traits of women are considered to be an important factor, especially in perceiving stressful events and developing coping strategies[4]. The Five-Factor Model, which is frequently used to assess personality traits, defines five dimensions of personality: extraversion (*sociable*, *sociable*, *positive emotions*), openness to experience (*curious*, *creative*, *questioning*), agreeableness (*trustworthy*, *obedient*, *compassionate*), conscientiousness (*hardworking*, *planned*, *determined*), and neuroticism (*anxiety*, *depression*, *pessimistic*, *angry*). Personality traits, particularly neurotic and extraverted personality, have been reported to be associated with health outcomes[5]. Likewise, it is observed that women's personality traits have an impact on their feelings, thoughts, expectations, and experiences during pregnancy, birth, and postpartum periods[6]. It has been reported that women with certain distinct personalities experience severe fear of childbirth and experience the birth and postpartum periods as traumatic[7]. In particular, neurotic personality structure may contribute to women's dissatisfaction with their birth experiences. Studies have shown that women with neurotic traits are less likely to have a positive birth experience[7] and are at risk for postpartum depression[8].

Fear of childbirth, birth satisfaction, and postpartum depression are interrelated and important issues in terms of maternal, infant, family, and community health as well as the quality of health care. Being aware of the effect of personality traits on these issues may enable early interventions to be made. Therefore, it is thought that determining the personality traits of women in the antenatal

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period may contribute to the provision of care and counseling in pregnancy, birth, and postpartum processes. There are a limited number of studies in the literature on the relationship between personality traits and fear of childbirth, labor satisfaction, and postpartum depression. This study was conducted to determine the relationship between women's personality traits and their fear of childbirth, birth satisfaction, and postpartum depression.

METHODS

Study design

This is a descriptive and correlational study.

Participants

The study was conducted between April and August 2022 in the obstetrics and gynecology outpatient clinic of a state hospital in southern Turkey. The population of the research consisted of 24,828 pregnant women who came to the delivery clinic of a hospital. In sample selection, the sample calculation formula (95% confidence interval, 5% margin of error, 50% incidence) was used. According to the calculation result, the sample size was determined as 358. Initially, 556 participants were interviewed, but 34 of them underwent cesarean section and 24 of them did not volunteer to participate in the next phase of the study. The study was completed with a total of 498 women. Inclusion criteria in the study were (1) being between the ages of 18–49 years (reproductive age), (2) being in the third trimester of pregnancy (28–40 weeks), (3) planning a vaginal birth,(4) avoiding communication problems, and (5) volunteering to participate in the research. Exclusion criteria were (1) experiencing complications during pregnancy, (2) failure of vaginal delivery, and (3) postpartum complications.

Data collection tools

Personal Information Form, Five-Factor Personality Scale, Wijma Birth Anticipation/Experience Scale, Birth Satisfaction Scale, and Edinburg Postpartum Depression Scale were used as data collection tools. The personal information form includes questions about the socio-demographic characteristics of the women.

The Five-Factor Personality Scale (BFKO) developed by Rammstedt and John is used to determine the personality traits of individuals[9]. The scale consists of 10 items on a 5-point Likert scale. BFKO consists of five factors: extraversion, agreeableness, conscientiousness, openness to experience, and emotional instability. Wijma Birth Anticipation/Experience Scale (W-DEQ), adapted into Turkish by Korukcu et al., is used to measure the fear of childbirth experienced by women[10]. The scale consists of 33 items and is a 6-point Likert-type scale. A high total score indicates a high level of fear.

Scale for Assessing Maternal Satisfaction in Normal Delivery (NDAMDÖ) was developed by Gungor and Beji to evaluate the experiences of mothers during labor and early postpartum period in the hospital[11]. As the total score obtained from the scale increases, the mother's satisfaction with the care she received in the hospital during vaginal delivery also increases. The Edinburgh Postnatal Depression Scale (EDSDO) was developed by Cox et al. to determine the depression and risks of women in the postpartum period[12]. The scale is a 10-item, 4-point Likert-type self-report scale.

Procedure

Data were collected by a single researcher by conducting face-to-face interviews at the hospital. The study was conducted in three stages. In the first step, the Personal Information Form, Five-Factor Personality Scale, and Birth Anticipation/Experience Scale were applied to pregnant women who applied to the obstetrics and gynecology outpatient clinic and agreed to participate. They were informed about the other steps of the study and their contact information was obtained. In the second stage, women who participated in the first study, had a normal delivery, and were in the first 10 days postpartum were called, and the Birth Satisfaction Scale was applied. In the last stage, women who completed at least 4 weeks postpartum were contacted by phone and evaluated with the Edinburg Postpartum Depression Scale. The administration of the questionnaires took an average of 25 min.

Statistical analysis

Data were analyzed in the IBM SPSS Statistics 26.0 program. The Pearson correlation method was used in the relationship between scale scores and personality traits. In addition, the effect of personality traits on postpartum depression level and fear of childbirth was examined by the multiple linear regression analysis method. For comparison by groups, independent-sample t-test and ANOVA were used. A significance level of $p<0.05$ was used for statistical analysis.

Ethical procedure

Ethics committee approval was received for the research by the decision of the Cukurova University Non-Interventional Clinical Research Ethics Committee (Date: April 02, 2022; Decision no: 121/84). Participants were informed about the purpose of the study and their consent was obtained. Data were collected from women who voluntarily agreed to participate in the study. The study was conducted in alignment with the Principles of the Declaration of Helsinki.

RESULTS

Of the 498 participants in the study, 91.2% were under 35 years of age, 36.7% had secondary education, 50% were employed, and 49.6% lived in the province. Notably, 64.1% of the women were multiparous and 71.7% had planned pregnancies. There was no difference between the fear of childbirth, postpartum satisfaction, and postpartum depression scores of the women according to their age, educational level, place of residence, and number of births (p>0.05). The mean score comparisons of the scales according to the sociodemographic characteristics of the participants are presented in detail in Table 1.

Descriptive statistics for the total scores of fear of childbirth, birth satisfaction, and postpartum depression and the sub-dimension scores of personality traits are shown in Table 2.

Table 1. Distribution of women according to demographic variables and comparison table between fear of childbirth, postpartum satisfaction, and postpartum depression levels according to these variables.

Variable	f (%)	Fear of childbirth	Birth satisfaction	Postpartum depression
		Mean (SD)	Mean (SD)	Mean (SD)
Age** (years)				
Under 35	454 (91.2)	29.77 (0.19)	182.78 (25.31)	11.94 (4.01)
35 and above	44 (8.8)	29.8 (10.21)	185.82 (27.12)	12.5 (4.38)
p		0.986	0.451	0.384
Education level***				
Literate	63 (12.7)	28.92 (8.13)	185.21 (23.34)	12.43 (4.03)
Primary education	155 (31.1)	29.79 (10.86)	185.43 (26.12)	11.62 (3.82)
Secondary education	183 (36.7)	30.49 (10.32)	181.03 (25.88)	12.17 (4.06)
High education	97 (19.5)	28.93 (10.06)	181.67 (24.84)	11.98 (4.34)
p		0.572	0.357	0.493
Employment status**				
Yes	249 (50)	31.05 (10.75)	180.12 (25.37)	12.08 (3.93)
No	249 (50)	28.49 (9.44)	185.98 (25.25)	11.9 (4.15)
p		0.005*	0.01*	0.618
Place of residence***				
Province	247 (49.6)	30 (9.62)	182.68 (25.66)	11.89 (3.94)
County	175 (35.1)	29.76 (11.1)	184.69 (25.07)	12.35 (4.07)
Village	76 (15.3)	29.05 (9.89)	180.49 (25.75)	11.51 (4.25)
p		0.666	0.321	0.699
Total number of births**				
Primiparous	179 (35.9)	30.03 (9.88)	184.6 (25.85)	11.68 (3.98)
Multiparous	319 (64.1)	29.62 (10.36)	182.18 (25.23)	12.17 (4.06)
p		0.671	0.31	0.188
Pregnancy being planned**				
Yes	357 (71.7)	30.34 (10.69)	182.99 (25.81)	12.04 (4.09)
No	141 (28.3)	28.31 (8.66)	183.21 (24.62)	11.87 (3.91)
p		0.045*	0.932	0.655
Getting adequate midwife support during birth**				
Yes	384 (77.1)	29.87 (10.12)	183.47 (25.95)	12.22 (4.03)
No	114 (22.9)	29.44 (10.44)	181.65 (23.78)	11.25 (3.99)
p		0.694	0.504	0.024*

*p<0.05; **independent groups t-test; ***ANOVA test.

Scores for all personality traits ranged between 2 and 10, with the highest mean being openness to experience (X=5.92) and the lowest mean being neuroticism (X=4.76) (Table 2).

In the study, the relationship between women's personality traits and fear of birth, birth satisfaction, and postpartum depression levels was examined. There is a moderate relationship between fear of childbirth and extroversion (r=-0.414), agreeableness (-0.413), conscientiousness (r=-0.416) scores, and a low and negative relationship between openness to experience scores (r=-0.354) (p<0.001). There was a positive and moderately significant relationship between fear of childbirth and neuroticism (r=0.469; p<0.001). There is a low and negative relationship between postpartum depression and personality traits of extroversion (r=-0.202), agreeableness (r=-0.198), conscientiousness (r=-0.199), and openness to experience (r=-0.213) (p<0.001). There was a positive and low-level significant relationship between postpartum depression and neuroticism (p<0.001). There is no significant relationship between birth satisfaction and personality traits (p>0.05).

The effect of personality traits on fear of childbirth and postpartum depression was examined with the multiple linear regression analysis method (Table 3). The regression model tested for the effect of personality traits on fear of childbirth was found to be significant (F=34.52, p<0.001). According to the model, 26% of the variability in fear of childbirth is explained by personality traits. Neuroticism and conscientiousness were found to be significant predictors of fear of childbirth in women.

The regression model tested for the effect of personality traits on postpartum depression was found to be significant (F=34.52, p<0.05). According to the model, 9.1% of the variability in postpartum depression is explained by personality traits. Among the personality traits, only neuroticism was a significant predictor of postpartum depression in women and its effect was found to be positive (r=0.285; p<0.001).

DISCUSSION

This study was conducted to determine the relationship between women's personality traits and their fear of childbirth, birth satisfaction, and postpartum depression. In this study, it was found that extraversion, agreeableness, conscientiousness, and openness to experience had a negative effect on fear of childbirth and postpartum depression, while neuroticism had a positive effect. No significant relationship was found between personality traits and birth satisfaction. In the limited number of studies in the literature, it has been reported that women's personality traits are a variable that may affect fear of childbirth[13-15]. Dursun et al. found that there was a relationship

Table 2. Descriptive statistics related to personality traits and total scores of fear of childbirth, birth satisfaction, and postpartum depression.

Score	Min	Max	Mean (SD)	Skewness	Kurtosis
Fear of childbirth	8	70	29.77 (10.19)	1.096	1.915
Birth satisfaction	110	215	183.05 (25.46)	-0.294	-0.812
Postpartum depression	0	20	11.99 (4.04)	0.239	-0.348
Extroversion	2	10	5.82 (2.61)	-0.09	-1.386
Agreeableness	2	10	5.81 (2.6)	-0.08	-1.378
Conscientiousness	2	10	5.81 (2.6)	-0.077	-1.372
Openness to experience	2	10	5.92 (2.62)	-0.147	-1.374
Neuroticism	2	10	4.76 (2.78)	0.678	-0.93

Table 3. Regression model testing the effect of personality traits on fear of childbirth and postpartum depression.

Independent variable	Fear of childbirth		Postpartum depression	
	B	p	β	p
Extroversion	-0.207	0.748	-0.616	0.389
Agreeableness	0.208	0.761	0.953	0.207
Conscientiousness	-0.701	<0.001	-0.057	0.931
Openness to experience	0.137	0.725	-0.301	0.057
Neuroticism	0.337	<0.001	0.279	<0.001
Model statistics	F=34.52; p<0.001		F=9.901; p<0.001	
	R^2=0.26		R^2=0.091	

between personality traits and fear of childbirth; it was found that fear of childbirth was higher in pregnant women with neurotic and psychotic personalities, while fear of childbirth was lower in pregnant women with extroverted personality[15]. Conrad and Trachtenberg reported significant correlations between personality traits and fear of childbirth and birth experience; neuroticism was associated with birth experiences[6]. It is observed that our research findings are in parallel with the literature. In addition, the regression model tested according to the effect of women's personality traits on fear of childbirth was significant, and neuroticism and conscientiousness were found to be significant predictors of fear of childbirth. While neuroticism has a positive effect on fear of childbirth, conscientiousness has a negative effect. Similarly, Uludağ et al. used personality traits to predict fear of childbirth and found that pregnant women with extroverted personality traits were significantly less likely to experience fear of childbirth and those with personality traits close to neuroticism had a high level of fear of childbirth[14]. The characteristics of individuals with neurotic personality such as being anxious and agitated suggest that women with this personality increase the risk of experiencing fear of childbirth. It can be said that extroverted individuals can cope with the fear of childbirth by adapting to the pregnancy process more easily with their positive outlook on life and their ability to cope with the difficulties they face.

In this study, personality traits were found to be an effective variable on postpartum depression. When the literature was examined, it was found that personality traits of women did not have a direct effect on postpartum depression[16], while some studies found that personality traits were associated with psychological and mental disorders[8,17]. Studies have shown that there is a significant positive correlation between postpartum depression and neuroticism, while there is a significant negative correlation with other personality traits[17,18]. Sunay et al. found a significant negative correlation between postpartum depression and extraversion, conscientiousness, emotional stability, and agreeableness. The multiple linear regression model showed that personality traits such as conscientiousness, emotional stability, and mildness are important determinants of postpartum depression[17]. These results support our current research findings. According to our regression model, 9.1% of the variability in postpartum depression is explained by personality traits. Neuroticism is a significant predictor of postpartum depression in women and its effect was found to be positive. Marín-Morales et al. found that postpartum depression had a predictive effect on extraversion and agreeableness[19]. Although our results cannot be generalized to all women, it is important to evaluate personality traits along with other risk factors in order to identify women at risk of postpartum depression at an early stage.

In this study, no significant relationship was found between birth satisfaction and personality traits. However, the results of a few studies in the literature report that agreeableness and conscientiousness are associated with higher birth satisfaction, while neuroticism is associated with lower satisfaction[20,21]. It would be useful to consider the personality characteristics of women in the evaluation of birth satisfaction, which is an important parameter for maternal, infant, and family health, and to provide care and support accordingly.

LIMITATIONS

The fact that the study was conducted with women who applied to the obstetrics and gynecology outpatient clinics of a hospital in Turkey limits the generalization of the results to other health centers and other regions of the country.

CONCLUSION

In this study, it was determined that neuroticism had a positive effect. No significant relationship was found between birth satisfaction and personality traits. Fear of childbirth, birth satisfaction, and postpartum depression are interrelated and important issues for improving maternal, infant, and family health. Women's personality traits should be evaluated at an early stage, the negative role of neuroticism should be recognized, and necessary care and counseling should be provided.

ETHICS APPROVAL

Ethics approval was obtained from the Ethics Committee of Çukurova University Medical Faculty (dated April 8, 2022, numbered 121/84).

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AUTHORS' CONTRIBUTIONS

FAR: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ED:** Data curation, Formal analysis, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Respiratory muscle strength in stroke: a case–control study

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SUMMARY

AIM: The aim of the study was to determine the respiratory muscle strength of stroke patients and compare them with healthy individuals.

METHOD: The study was conducted with 171 patients who had a stroke between 2017 and 2021 and 32 healthy controls. Respiratory muscle strength and inspiratory and expiratory mouth pressure (MIP and MEP) were measured using the portable MicroRPM device (Micro Medical, Basingstoke, UK).

RESULTS: The stroke group exhibited significantly lower values in both MIP for men ($p<0.001$) and women ($p=0.013$) and maximal expiratory pressure for men ($p<0.001$) and women ($p=0.042$), compared with the healthy control group. Notably, there was a significant difference in the MIPmen ($p=0.026$) and MEPmen ($p=0.026$) values when comparing the reference values, which were calculated based on age and sex, with those of the healthy group. The baseline values calculated according to age for stroke patients were as follows: MIPmen 31.68%, MIPwomen 63.58%, MEPmen 22.54%, and MEPwomen 42.30%.

CONCLUSION: This study highlights the significant respiratory muscle weakness experienced by stroke patients, with gender-specific differences. It highlights the importance of incorporating respiratory assessments and interventions into stroke rehabilitation protocols to improve the overall health and well-being of stroke patients.

KEYWORDS: Stroke. Muscle strength. Rehabilitation.

INTRODUCTION

Stroke is a significant contributor to long-term disability globally. Although the effects of stroke on motor and cognitive function have been extensively studied, its impact on respiratory muscle strength remains an area requiring further research[1]. Understanding the changes in respiratory muscle strength following a stroke is essential, as it directly influences a patient's capacity to breathe effectively and can have a substantial impact on their overall quality of life[2].

The literature has revealed that stroke affects not only the upper and lower extremity muscles but also the muscles associated with the respiratory system[3,4]. Stroke survivors frequently exhibit characteristic alterations in their respiratory patterns, including reduced ventilation, diminished respiratory muscle strength, and decreased activity in the diaphragm on the affected side[5,6]. Furthermore, these alterations are linked to reduced respiratory function, deconditioning, decreased levels of physical activity, and an elevated risk of experiencing respiratory complications. Therefore, it is justifiable to prioritize interventions aimed at enhancing respiratory function in stroke patients to mitigate morbidity and mortality risks[7]. The assessment of respiratory muscle strength in individuals with stroke is of paramount importance because it can significantly decline compared with healthy individuals. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are common metrics employed to evaluate respiratory muscle strength. In reference studies on respiratory muscle strength, MIP and MEP values of 74.2 and 66.7%, respectively, were reported in stroke patients compared with healthy controls[3], and another study reported lower values of 55.5% for MIP and 60.6% for MEP in stroke patients[8].

The significance of respiratory muscle function within the context of stroke rehabilitation cannot be overstated. Impaired respiratory muscle strength can result in respiratory complications, reduced exercise tolerance, and a decline in functional independence. In summary, this study seeks to assess the respiratory muscle strength potential in stroke patients and provide a reference point for comparison with a healthy control group. As healthcare professionals continually refine stroke rehabilitation strategies, the findings of this study hold the potential to inform the development of targeted interventions aimed at enhancing respiratory muscle strength and, consequently, the overall quality of life for stroke survivors. By addressing the knowledge gap in this critical domain, we aimed to contribute to the advancement of stroke rehabilitation practices and foster a deeper comprehension of the multifaceted consequences of

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stroke on individuals' lives. Therefore, the aim of this study was to determine the respiratory muscle strength of stroke patients and compare them with healthy individuals.

METHODS

This study was conducted at a private neurological rehabilitation center in Istanbul Physical Therapy and Rehabilitation Hospital, as well as a public association catering to individuals with acquired stroke. Patient recruitment took place from April 11, 2017, to October 10, 2021.

Participants

The stroke group consisted of 171 chronic stroke patients and the control group consisted of 32 age- and gender-matched healthy individuals. The inclusion criteria for stroke participants were as follows: (a) diagnosis of hemiplegia/hemiparesis; (b) being older than 18 years; (c) able to walk independently or with support (assistive devices, etc.); (d) able to understand instructions; and (e) willing to participate in the study. The inclusion criteria for control group participants were as follows: (a) being older than 18 years; (b) never smoked tobacco products (never smokers); (c) able to follow simple instructions; and (d) no pathology in visual ability and hearing. For all participants, the exclusion criteria were as follows: (a) not volunteering to participate in the study; (b) diagnosis of pulmonary disorder, severe cardiovascular disorders, and other neurological disorders; and (c) individuals receiving specialized cardiopulmonary training.

Outcome measure

The respiratory muscles' strength was evaluated by maximal inspiratory and expiratory pressures (MIP and MEP, respectively). The participants' MIP and MEP were measured and recorded according to ATS/ERS criteria using a portable MicroRPM device (Micro Medical, Basingstoke, UK)[9]. The highest of at least three measurements that did not differ by more than 5 cm H_2O was recorded for MIP and MEP. A percentage of the predicted values of MIP and MEP was specified as described by Black and Hyatt[10].

Statistical analysis

A descriptive analysis of the registered variables was conducted in this study. Demographic quantitative variables were reported as mean values along with their standard deviations (mean±SD), while qualitative variables were presented as absolute counts. For MIP and MEP, these values were expressed as percentages of the predictive values. The independent-sample t-tests were used. For comparisons, $p<0.05$ was considered statistically significant.

RESULTS

The study encompassed a total of 171 participants in the stroke group and 32 healthy controls. Within the stroke group, 39.60% were male and 61.40% were female, while the healthy group consisted of 56.25% males and 43.75% females. Table 1 shows that there were no statistically significant differences between the groups in terms of gender, age, weight, height, and body mass index ($p>0.05$). In stroke patients, the proportion of affected sides was equally distributed between right and left. The average time since stroke onset was 388 days.

Table 2 presents the results of MEP and MIP measurements for both the stroke group and the control group. The stroke group demonstrated significantly lower values in both MIP for men (MIPmen) ($p<0.001$) and women (MIPwomen) ($p=0.013$), and MEP for men (MEPmen) ($p<0.001$) and women (MEPwomen) ($p=0.042$), compared with the control group. Notably, there was a significant difference in the MIPmen and MEPmen values when comparing the reference values, which

Table 1. Characteristics of the participants.

Variable	Stroke group (n=171)	Healthy group (n=32)	Differences between groups	
	Mean±SD n (%)	Mean±SD n (%)	Diff. means	p
Sex (male/female)	66 (39.60)/105 (61.40)	18 (56.25)/14 (43.75)		0.063
Age (years)	54.53±10.27	51.28±7.40	3.28	0.091
Height (cm)	167.05±8.14	165.50±8.44	1.55	0.326
Weight (kg)	76.69±12.52	72.66±16.25	4.03	0.113
BMI (kg/m^2)	27.44±4.45	26.36±4.58	1.08	0.210
Time since stroke onset (days)	388.39±731.96			

BMI: body mass index; Diff. means; difference between the means of both groups.

Table 2. Comparison of respiratory muscle strength of groups.

Variable	Stroke group (n=171)	Healthy group (n=32)	Differences between groups		95%CI
	Mean±SD	Mean±SD	Diff. means	p	
MIP_{men} (cmH2O)	36.17±20.87	56.89±16.55	-20.72	<0.001*	-31.33 to -10.12
MIP_{men} (cmH2O) R.V.**	114.17±6.89	117.92±2.29	-3.75	0.026*	-34.85 to -10.23
MEP_{men} (cmH2O)	47.02±25.17	69.56±13.77	-22.54	<0.001*	-7.03 to -0.45
MEP_{men} (cmH2O) R.V.**	208.62±14.19	216.33±4.72	-7.71	0.026*	-14.49 to 0.93
MIP_{women} (cmH2O)	47.52±23.59	64.43±22.39	-16.91	0.013*	-30.13 to -3.69
MIP_{women} (cmH2O) R.V.**	74.74±5.70	77.12±5.08	-2.38	0.140	-28.94 to -0.54
MEP_{women} (cmH2O)	59.05±25.14	73.79±25.62	-14.74	0.042*	-5.55 to 0.79
MEP_{women} (cmH2O) R.V.**	139.59±5.92	142.06±5.28	-2.47	0.140	-5.77 to 0.82

CI: confidence interval; Diff. means; difference between the means of both groups; R.V.: reference value. *Statistical significance. **Reference values were calculated using Black and Hyatt predictive equations.

were calculated based on age and sex, with those of the control group. However, no significant difference was observed in the reference values for other parameters. The baseline values calculated according to age for stroke patients were as follows: MIPmen 31.68%, MIPwomen 63.58%, MEPmen 22.54%, and MEPwomen 42.30%.

DISCUSSION

Respiratory muscle strength in stroke patients is usually ignored in neurological rehabilitation training programs. We aimed to draw attention to this issue clinically and to obtain comprehensive data on the MIP and MEP assessment scores of patients in Türkiye. When compared with the healthy individuals and the reference values determined according to age, respiratory muscle strength was found to be significantly lower in stroke patients. According to the reference values, the results obtained in stroke patients were MIPmen 31.68%, MIPwomen 63.58%, MEPmen 22.54%, and MEPwomen 42.30%. The data clearly indicate that stroke patients exhibit lower values in MIP for both MIPmen and MIPwomen, as well as MEP for both MEPmen and MEPwomen compared with healthy individuals. This suggests that stroke has a significant impact on respiratory muscle strength and is consistent with the literature showing respiratory complications that can occur after stroke. It is also important to note that decreased respiratory muscle strength may lead to impaired lung function. A prior study reported mean values of MIP ranging from 17 to 57 in people after stroke, compared with approximately 100, and mean values of MEP ranging from 25 to 68, compared with approximately 120 cmH_2O in healthy adults[11]. Comparison with the data of this study shows that we obtained results in a similar range.

According to the studies evaluating MIP and MEP values separately for men and women in the literature, Luvizutto et al. found 85.0±36.2 in males and 46.9±25.4 in females for MIP and 82.4±28.9 in males and 51.2±28.8 in females for MEP. When respiratory pressures were compared with the predicted value, a significant reduction in MIP was observed in men and women[12]. Ramos et al.[13] determined the MIP and MEP responses as 71.85 and 62.28 for men and 57.75 and 49.50 for women. Compared with the values found in the literature, MIP was estimated as 105.41 and MEP as 114.79 for men and MIP as 80.57 and MEP as 78.46 for women[14].

Comparing age-standardized reference values in the literature with data from patients with stroke, Lista Paz et al. found that both MEP and MIP values were significantly lower in the stroke group compared with the control group. In addition, MEP and MIP were <60% of the predicted values (51.56±20.83 and 51.41±20.85, respectively) in the stroke group[8]. Kubo et al. presented changes in respiratory muscle strength in three periods. The mean values of MIP and MEP data were 37.6±19.6, 44.3±24.8, 48.1±25.1 and 46.1±19.8, 55.8±26.5, 63.1±30.1, respectively[2]. Kim found MIP and MEP mean values of 31.17, 33.83 and 26.90, 29.03 in middle-aged and elderly stroke patients, respectively[14]. Jandt et al. found the mean values of MIP data as 36.71±21.22 and MEP data as 47.81±31.15[15].

Our study also calculates reference values for MIP and MEP for stroke patients in relation to age. These reference values show that, on average, stroke patients have significantly lower MIP and MEP values than expected for their age group. By comparing baseline data from the control group with data from patients with stroke available in the literature, Ward et al. found that both MEP and MIP values were significantly lower

in the stroke group compared with the control group[16]. An et al. measured MEP and MIP as 53.08±11.08, 52.50±10.47 and 39.67±5.91, 39.50±5.28 in the experimental and control groups[17]. Jo et al. measured MIP 20.41±3.72 in the intervention group and 18.53±2.47 in the control group and MEP 23.94±4.98 in the intervention group and 21.71±2.73 in the control group[18]. In the study conducted by Anjana in two groups, MIP and MEP values were measured as 45.81, 54.61 and 30.74, 30.33[19].

According to the data of these studies in the literature, the number of studies on respiratory muscle strength in Turkey is limited. According to Boz et al., the MIP was 53.68±20.86 and the MEP was 61.44±22.46 in stroke patients[20]. According to the study conducted by Aydoğan Arslan et al., MIP and MEP values in the experimental group were 58.09±25.59 and 75.81±32.24, respectively, and 61.30±34.48 and 70.90±28.88, respectively, in the control group[21]. Comparison with the data of our study shows that MIP and MEP values are minimally lower. According to the reference values, it is observed that the sum of our female–male percentage data is similar. Due to the low number of people evaluated in both studies, we think that the levels and physical conditions of the patients may have caused the data to be higher.

Studies show that important changes at functional levels are found to be below 40%, which can lead to respiratory problems and recurrent hospitalizations[22]. Like these findings, other studies found a MIP lower than that predicted for individuals after stroke[14,22].

CONCLUSION

This evidence underscores the severe respiratory muscle weakness experienced by stroke patients, and gender-specific differences are also notable. Our results highlight the importance of incorporating respiratory assessments and interventions into stroke rehabilitation protocols to improve the overall health and well-being of stroke survivors. Further research is needed to examine more deeply the factors affecting respiratory muscle function in stroke patients and to develop targeted interventions in this vulnerable population.

ETHICAL APPROVAL

Ethical approval for this study was given by the Istanbul Faculty of Medicine Clinical Research Ethics Committee on April 11, 2017, numbered 409. The study was conducted in accordance with the Declaration of Helsinki.

AUTHORS' CONTRIBUTIONS

AY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **RM:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. **ANB:** Conceptualization, Formal analysis, Investigation, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE

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The role of ultrasound and mitofusin-2 levels to predict pregnancy outcomes in patients with severe preeclampsia: a case–control study

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate mitofusin-2 levels and fetal Doppler ultrasonography effects in patients with severe preeclampsia.

METHODS: This single-center case–control study was conducted in the gynecology service of the university hospital in Van. A total of 90 pregnant women aged 18–40 years were included in the study. Of these, 30 are normal, 30 have mild preeclampsia, and 30 are pregnant with severe preeclampsia. In this study, especially in severe preeclampsia patients, serum mitofusin-2 levels and important fetal Doppler flows such as uterine arterial pressure, umbilical arterial pressure, and 1st and 5th minute Apgar scores, birth weight, and the relationship between postnatal outcomes such as week of birth and the number of patients in the neonatal intensive care unit were investigated.

RESULTS: There was a significant difference between the three groups in terms of mitofusin-2 levels, which was the highest in the group ($p<0.05$). Maternal serum mitofusin-2 levels were positively correlated with uterine arterial pressure ($r=0.543$, $p=0.007$), umbilical arterial pressure ($r=0.238$, $p=0.008$), diastolic blood pressure, and systolic blood pressure ($p<0.001$). Receiver operating characteristic curve of mitofusin-2 in predicting preeclampsia is as follows: optimal cutoff 1.6 ng/mL; area under the curve: 0.861; 95%CI: 0.786–0.917; sensitivity: 83.9%; and specificity: 70.0%, ($p\leq0.001$). A one-unit increase in mitofusin-2 resulted in a statistically significant 4.21-fold increase in preeclampsia risk.

CONCLUSION: This study recommends the use of mitofusin-2 together with fetal Doppler ultrasound findings as a reliable indicator of preeclampsia severity.

KEYWORDS: MFN2 protein. Preeclampsia. Umbilical artery. Uterine artery. Arterial pressure.

INTRODUCTION

Preeclampsia is a disease that manifests itself with hypertension and proteinuria that occurs after the 20th gestational week and can affect many organs. It is one of the important reasons for neonatal and maternal morbidity and mortality. PE can affect 2–8% of pregnant women worldwide[1]. Many factors such as hypoxia, endothelial dysfunction, mitochondrial dysfunction, inflammation, and oxidative stress have been listed among the causes of PE, the etiology of which has not been fully explained[2].

Although not fully understood, the pathophysiology of preeclampsia is likely a multifactorial condition consisting of genetic and environmental factors and abnormal placentation. Current evidence shows that preeclampsia is a two-stage disease. The first stage is the asymptomatic stage of early pregnancy resulting from poor placentation due to abnormal trophoblast invasion and spiral artery remodeling. This results in the second stage of the disease, characterized by placental ischemia/reperfusion injury and maternal immune-mediated response. As a result, there is a release of anti-angiogenic factors and placental debris into the maternal circulation and an inadequate release of pro-angiogenic factors. This leads to angiogenic imbalance, immune-mediated exaggerated inflammatory response, and endothelial cell dysfunction, resulting in increased platelet aggregation, abnormal activation of the coagulation system, and systemic vascular augmentation. The general outcome of this stage is clinical symptoms such as high blood pressure, proteinuria, and other end-organ damage[3].

Poor placentation results in abnormal fetal perfusion. This condition is associated with abnormal uterine artery blood flow and an increased incidence of fetal growth restriction in pregnancies affected by preeclampsia, especially in preterm pregnancies. This abnormal perfusion often appears as notching on uterine artery Doppler evaluation. However, the usefulness of this finding in predicting preeclampsia is limited[4].

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Studies have shown that increased placental hypoxia causes mitochondrial dysfunction and is associated with PE. In addition, it has been determined that there is placental mitochondrial dysfunction in patients with PE and there is a difference in the amount of placental mitochondrial protein[5]. Reactive oxygen species (ROS) occur due to ischemia and hypoxia following inappropriate trophoblastic invasion and placentation. With their participation in the maternal circulation, an increase in the systemic inflammatory response occurs[6].

Mitochondria is a structure in which morphological changes occur through processes called fission (dividing into smaller parts) and fusion (joining parts). There is a mitochondrial fusion protein 2 (Mfn-2) in the outer membrane surrounding the mitochondria inside the cell. Mfn-2 is a protein involved in the regulation of many cellular processes (fusion, morphology and function, energy metabolism, signal transduction, proliferation, and apoptosis)[7].

This is the first study to investigate the effect of maternal serum Mfn-2 levels in patients with sPE.

METHODS

Ethical aspects

Ethics committee approval was obtained for this prospective study (approval number 2022/08-01). The researchers committed to complying with the Declaration of Helsinki guidelines for medical research in humans throughout the study (approval number: 2022/08-01).

Study design

This single-center case–control study was conducted in the gynecology ward of the university hospital in Van. No sample was selected for the study. The study was conducted with a total of 90 patients, aged between 18 and 40 years, including 30 with mild preeclampsia (mPE), 30 with sPE, and 30 normal patients, who met the determined criteria. Mild and severe preeclampsia (sPE) were diagnosed according to the American College of Obstetricians and Gynecologists (ACOG) guidelines[8]. The control group consisted of normotensive pregnant women who applied to our clinic in the same period, had a single pregnancy, and were compatible with the maternal age and gestational age. To avoid selection bias in the study, the case group was determined according to the preeclampsia classification criteria in the ACOG guide. The control group was randomly selected from pregnant women with similar age, gravida, parity, gestational week, miscarriage history, and body mass index (BMI) to the case group.

Data collection tools

Two PE groups were formed: mild and severe. Pregnant women with blood pressure ≥140/90 mmHg, random proteinuria (+), or urine protein ≥300 mg/24 h measured every 4 h after the 20th week of pregnancy were included in the mPE group. Diastolic blood pressure (DBP) >110 mmHg or systolic blood pressure (SBP) >160 mmHg in two separate measurements taken at least 4 h apart, neurological (headache, visual disturbances, or seizures), hepatic (epigastric pain, pain in the right hypochondrium, transaminase more than twice the upper limit of normal), renal pregnant women with hematological (thrombocytopenia, hemolysis), or acute pulmonary edema (serum creatinine elevated >1.1 mg/dL or more than twofold increase in baseline creatinine) were included in the severe preeclampsia group. BMI was obtained by dividing weight (in kg) by the square of height (in m).

The following variables were collected for both groups: age, gravida, parity, history of abortion, mode of delivery (vaginal or cesarean section), birth weight, week of birth, neonatal intensive care unit (NICU), 1st and 5th minute Apgar scores, newborn gender, and UtA PI and UA PI Doppler results.

Exclusion criteria were as follows: chromosomal anomalies, genetic syndromes, major fetal anomalies, multiple pregnancies, fetal death, presence of maternal systemic diseases (chronic liver disease, SLE, diabetes mellitus, renal failure, autoimmune diseases, hypo–hyperthyroidism, cardiovascular diseases, and infections).

Blood samples for the study were collected from the case group after diagnosis of preeclampsia and admission to the hospital, prior to the initiation of any medical treatment such as magnesium sulfate or antenatal corticosteroids. For the control group, blood samples were obtained at the time of presentation to the outpatient clinic for routine check-ups.

To obtain the plasma phase, venous blood samples were taken and centrifuged at 1,000g for 15 min at 2–8°C and stored at -80°C until measurement. Quantitative measurements were made using the Mfn-2 ELISA kit. The detection sequence of the kits was 0.16 ng/mL–10 ng/mL and the sensitivity was 0.055 ng/mL.

Statistical analysis

In this study, the primary outcome measure for patients with preeclampsia was Mfn-2 levels.

Data were analyzed using the SPSS 22.0 statistical program. The distribution of data was analyzed with the Shapiro–Wilk test. Minimum–maximum and median values were used for data that did not fit the normal distribution. Number and percentage values were given for categorical variables. Mann-Whitney

U test was used in paired groups that did not show a normal distribution. ANOVA test was used for normally distributed data in comparison to more than three independent groups. The Kruskal-Wallis test was used for data that were not normally distributed. Tukey and Tamhane T2 tests were used for post-hoc analysis. Spearman's rank test was used in the correlation analysis of the data that did not fit the normal distribution. Categorical variables were appraised with the Pearson chi-square test. Receiver operating characteristic (ROC) analysis was performed to determine the threshold value of Mfn-2 levels in the prediction of preeclampsia. The effect of Mfn-2 level on the development of preeclampsia was assessed by binary logistic regression analysis. The limit of significance was taken as $p \leq 0.05$

RESULTS

The laboratory and clinical results according to the groups are shown in Table 1. In the study, there was no difference between the groups in terms of age, gravida, parity, history of abortion, BMI, and gestational week ($p>0.05$). In terms of SBP and DBP values, all three groups were significantly different from each other. The lowest SBP–DBP values were in the healthy control group, and the highest values were in the severe group ($p<0.05$).

Notably, 24-h urine protein amounts increased from the control group to the sPE group. In terms of protein amounts in 24-h urine, the severe and mPE groups were similar but significantly higher than the control group ($p<0.05$).

UA PI and UtA PIs were similar in the control and mPE groups. It was significantly high in the sPE group than in the other groups ($p<0.05$).

There was a significant differentiation between the three groups in terms of AST and ALT levels. While the AST–ALT levels of the control and mPE groups were similar, the AST–ALT levels of the severe group were higher than the other two groups ($p<0.05$).

The control and mPE groups were similar in terms of platelet counts. Platelet counts of the severe group were lower than in the other groups ($p<0.05$).

In terms of creatinine levels, control 0.5 (0.3–1.0 mg/dL) and mPE 0.5 (0.3–0.8 mg/dL) groups were similar. However, the creatinine level in the sPE group 0.7 (0.3–1.0 mg/dL) was significantly higher than the other two groups ($p<0.05$).

Mfn-2 levels were different in all three groups. Mfn-2 levels rose from the control group to the sPE group ($p<0.05$).

Control and preeclampsia patient groups were statistically different in terms of the week of birth, birth weight, 1st and

Table 1. Demographic and clinical characteristics of the patients grouped according to severity of preeclampsia.

	Groups				
	Total (n=90)	Control (n=30)	Mild PE (n=30)	Severe PE (n=30)	p
Age (years)†	26.4±6.3	25.0±4.1	26.4±5.3	27.7±8.5	0.171*
Gravida‡	3 (1–5)	3 (1–5)	3 (1–4)	2 (1–5)	0.235**
Parity‡	1 (0–4)	1 (0–4)	1 (0–3)	1 (0–4)	0.476**
Abortion story§	44 (36.4)	14 (35.0)	16 (38.1)	14 (35.9)	0.956***
Gestational week (weeks)‡	30.0±1.6	30.1±1.4	29.8±1.4	30.1±2.0	0.549*
BMI (kg/m²)‡	24.9±3.2	24.6±2.6	24.4±2.7	25.9±3.9	0.072*
SBP (mmHg)‡	146 (100–210)	120 (70–100)	146.5 (130–160)	170 (160–210)	0.000**
DBP (mmHg)‡	93 (70–120)	81.5 (70–100)	92 (80–105)	110 (100–120)	0.000**
UA PI‡	0.9 (0.5–1.7)	0.9 (0.6–1.2)	0.8 (0.5–1.7)	1.0 (0.7–1.4)	0.000**
Ut A PI‡	1.1 (0.6–1.1)	0.8 (0.6–1.8)	1.1 (0.7–1.7)	1.6 (0.7–2.1)	0.000**
AST (IU/l)‡	26 (12–120)	22 (12–45)	23 (13–43)	85 (44–120)	0.000**
ALT (IU/l)‡	32 (10–100)	21 (10–37)	23 (13–39)	78 (40–100)	0.000**
Platelets (IU/L)	211.6±69.8	251.3±52.5	242.9±54.1	137.1±31.6	0.000*
Proteinuria in 24 h (mg/dL)	752.1±354	0±0	1,101.9±02	1,132.9±632	0.000*
Creatinine (mg/dL)‡	0.5 (0.3–1.0)	0.5 (0.3–1.0)	0.5 (0.3–0.8)	0.7 (0.3–1.0)	0.000**
Mitofusin-2 (ng/mL)‡	2.22 (0.3–9.9)	1,11 (0.34–2.60)	2.22 (0.30–4.60)	5.1 (2.10–9.90)	0.000**

†: mean±standard deviation, ‡: median (min–max), §: n (%). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate aminotransferase; ALT: alanine aminotransferase; UtA: uterine artery; UA: umbilical artery; PI: pulsatility index. *One-way ANOVA, **Kruskal-Wallis test, ***Pearson chi-square, p-value <0.05 is significant.

5th minute Apgar scores, and NICU (p<0.001). The week of birth, birth weight, and Apgar values of the preeclampsia group were lower than those of the control group, and the NICU was higher (Table 2).

In the correlation analysis, there was no relationship between Mfn-2 levels and age, gravida, and BMI (p>0.001). Mfn-2 levels with SBP (r=0.696, p=0.000) and DBP (r=0.660, p=0.000), UA PI (r=0.238, p=0.008) and UtA PI (r=0.543, p=0.007) had a positive correlation (p<0.001). A relatively weaker association was found with UA compared to UtA PI. Mfn-2 values were negatively related to week of birth (r=-0.733, p=0.000) and birth weight (r=-0.637, p=0.000) and (p<0.001).

The effect of Mfn-2 in the diagnosis of preeclampsia was defined by the ROC curve (Figure 1). Mfn-2 values >1.6 ng/mL were significantly associated with an increased risk of sPE (p≤0.001).

A one-unit increase in Mfn-2 resulted in a statistically significant 4.21-fold increase in preeclampsia risk in logistic regression analysis.

DISCUSSION

There is substantial evidence regarding the risk factors for preeclampsia; however, interpreting them is complex. Preeclampsia is a pregnancy-related heterogeneous disease whose etiology is not fully understood. How angiogenic imbalance occurs, leading to placental insufficiency, abnormal spiral artery remodeling, abnormal placentation, and what causes them are not known, and the molecular mechanism behind the development of preeclampsia remains unclear. There are numerous risk factors, including immunological factors, congenital anomalies, a family history of preeclampsia, chronic hypertension, kidney disease, diabetes, insulin resistance, genetic factors, nulliparity, high BMI, advanced maternal age, hydatidiform mole, and stress, among others. Screening for preeclampsia is challenging due to its asymptomatic nature. Reliable and accurate biomarkers will be necessary to predict the development of preeclampsia in the third trimester. Imaging tests such as uterine artery Doppler ultrasound allow the prediction of only one-third of preeclamptic cases. Since no single test is available to predict preeclampsia, a combination of tests is used to evaluate the condition. The most commonly used biomarkers for preeclampsia are sEng, sFlt-1, PlGF, and VEGF. It has been found that decreased PlGF levels in the first trimester along with increased sFlt-1 and sEng levels are associated with the development of preeclampsia. Studies suggest that the relationship between sFlt-1/PlGF is promising in indicating the imbalance between angiogenic and anti-angiogenic factors[9-11].

In recent years, significant research has been conducted to illuminate the pathophysiology of the disorder, develop methods for identifying women at risk using predictive models, and investigate potential preventive strategies to reduce the incidence of preeclampsia. The ACOG and the International Society for the Study of Hypertension in Pregnancy (ISSHP) recommend screening pregnant women for PE in the first trimester. The primary goal of the first-trimester screening is to identify women at high risk of developing PE in the later stages of pregnancy, thereby enabling the implementation of appropriate preventive strategies. Currently, many centers do not

Table 2. Perinatal outcomes by groups.

	Groups		p-value
	Control (n=30)	Preeclampsia (n=60)	
Birth week (week)‡	39.0 (38.0–40.0)	34.0 (28.0–38.0)	0.000*
Birth weight (g)‡	3,400 (2,890:4,020)	2,500 (1,900–3,910)	0.000*
APGAR 1 min‡	8 (6:8)	8 (4:8)	0.001*
APGAR 5 min‡	10 (8:10)	9 (6:10)	0.001*
NICU§	5 (12.5)	27 (33.3)	0.015**

NICU: neonatal intensive care unit; ‡: Median (min–max); §: n (%), *Kruskal-Wallis test, **Pearson chi-square, p-value <0.05 is significant.

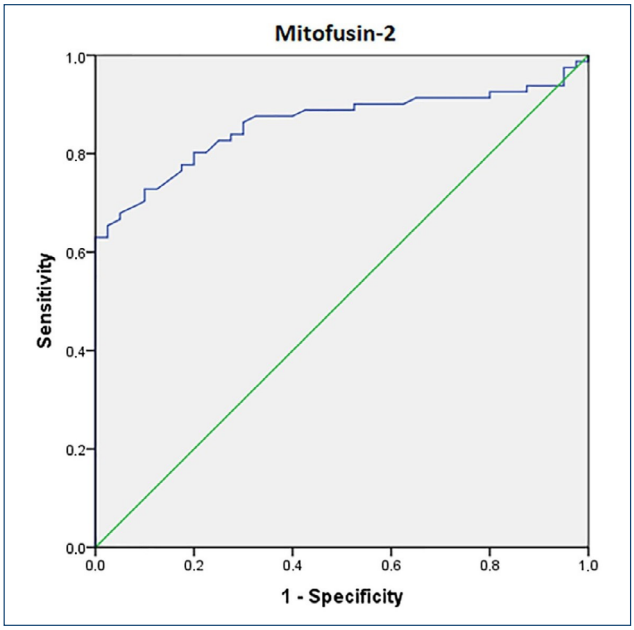

Figure 1. Receiver operating characteristic curve of mitofusin-2 in predicting preeclampsia: optimal cutoff 1.6 ng/mL; area under the curve: 0.861; 95%CI: 0.786–0.917; sensitivity: 83.9%; specificity: 70.0%; p≤0.001.

use a unified first-trimester screening approach. Combining clinical risk factors, maternal blood pressure [mean arterial pressure (MAP), mean uterine arterial pressure (UtA), pulsatility index (PI)], and maternal angiogenic biomarkers (PlGF) in an algorithm may be a more accurate way to identify high-risk women[12,13].

Despite all the studies, the molecules that contribute to the pathophysiology of preeclampsia have not been fully clarified. In this study, we tried to identify a new pathogenic factor that contributes to the development of PE pathogenesis. This is the first study to investigate maternal serum plasma Mfn-2 levels in patients with sPE.

Mfn-2 is a mitochondrial membrane protein that maintains mitochondrial bioenergy and promotes membrane fusion. Mfn-2 plays an important role in the regulation of cell proliferation and oxidative metabolism in many cell types[14]. In recent years, interest in studies related to Mfn-2 has increased, and the role of Mfn-2 in many mitochondria-related diseases has been mentioned[14]. The etiology and pathogenic mechanisms of PE are still unknown. Pathologies in mitochondrial mechanisms play an important role in the early stages of PE[5].

Mitochondrial hypoxia, together with insufficient trophoblast invasion and unsuccessful spiral artery remodeling, is thought to cause the development of PE. Recent evidence suggests that placental mitochondrial problems may increase the development of PE. Oxidative stress caused by ROS that occurs due to mitochondrial dysfunction has been associated with PE. It has been reported that antioxidant protection decreased and ROS production increased in the placental mitochondria of women diagnosed with PE[15].

Leboucher et al., in their studies on the role of Mfn-2 in the activation of mitochondrial apoptosis in cells, stated that mitochondrial dysfunction occurs due to placental hypoxia, and in this case, Mfn-2 levels decrease, which leads to mitochondrial fragmentation and apoptosis[16].

Koziel et al., as a result of their study on the etiopathogenesis of PE patients, stated that placental hypoxia causes maternal endothelial dysfunction. In the study, it was also observed that there were adaptive changes in the mitochondria in the case of hypoxia in maternal endothelial cells[17].

So far, studies on Mfn-2 and preeclampsia seem to be mostly of placental origin. This is the first study in the literature to examine serum maternal Mfn-2 levels in the patient group with sPE. In the study, significant differentiation was observed between sPE, mPE, and control patients in terms of Mfn-2 levels, and the highest values were observed first in the severe group and then in the mild group. Considering the perinatal outcomes between the preeclampsia and control groups, significant differentiation was observed in terms of the week of birth, birth weight, Apgar scores, and NICU. While there was a positive relationship between Mfn-2 levels and SBP and DBP, there was a negative relationship between birth week and birth weight. In this study, it was determined that a 1.6 ng/mL value of Mfn-2 could predict preeclampsia with 83.9% sensitivity and 70% specificity. A one-unit increase in Mfn-2 resulted in a statistically significant 4.21-fold increase in preeclampsia risk in logistic regression analysis.

Significant hemodynamic changes may occur during pregnancy, and the mother's hemodynamic profile is of great importance in treating hypertension in PE[18]. Maternal uterine arterial blood flow, one of the main factors in protecting the intrauterine environment, is necessary for maintaining fetal growth and development and normal placental function. However, hemodynamic ultrasound can predict pregnancy outcomes in PE patients and provide theoretical support to reduce adverse pregnancies. Color Doppler ultrasound can distinguish hemodynamic changes in the middle cerebral artery, UA, UtA, and middle and venous catheters. The PI of the UA and UtAPI are clinical markers of circulation to and from the placenta. Increased PI of the umbilical and uterine arteries and decreased PI of the fetal middle cerebral artery have been associated with fetal growth restriction due to placental insufficiency. Increased PI of the uterine arteries is also used to predict preeclampsia[19].

In a study in which fetal Doppler ultrasound was used with a marker at the molecular level in severe preeclampsia patients, serum adiponectin and UA PI values were examined, and in the sPE group, increased UA PI was observed in parallel with the decreasing adiponectin levels, and a negative correlation was observed between both[20]. In our study, another specific one was observed. We detected increased UtA PI and UA PI in parallel with the serum Mfn-2 molecule. In the study, Mfn-2 levels, UA PI ($r=0.238$, $p=0.008$) and UtA PI ($r=0.543$, $p=0.007$) had a positive correlation ($p<0.001$). A relatively weaker association was found with UA compared to UtA PI.

In PE, vascular invasion is inadequate, leading to reduced placental perfusion, ultimately resulting in chronic hypoxia and intrauterine growth restriction. Oxygen deficiency results in the production of anti-angiogenic factors such as sFlt-1, sEng, TGF-β1, and TGF-β3 by the placenta. These factors enter the maternal circulation, resulting in endothelial dysfunction, hypertension, and proteinuria[21].

Mitochondria, known as the powerhouse of the cell, are vital organelles for energy production and maintaining cellular dynamics. Mitochondria consume the most oxygen in

cells to produce ATP through oxidative phosphorylation. Hypoxia affects mitochondrial function because it disrupts ATP production and increases mitochondrial ROS (mROS). Since mitofusin-2 (Mfn-2) is a mitochondrial fusion protein located on the outer membrane of the organelle, changes in both Mfn-2 and ATP expression in the placenta of preeclamptic patients indicate the relationship between hypoxia and mitochondrial dysfunction[17].

In our study, we also found that levels of Mfn-2 increased in preeclampsia patients parallel to increased anti-angiogenic factors such as sFlt-1 and sEng, indicating increased endothelial dysfunction due to hypoxia.

When looking at the literature, it has been found that the biomarker HIF-1α, which is associated with placental hypoxia and has been the subject of recent studies, plays a crucial role in the pathogenesis of PE. HIF-1α achieves this by facilitating anti-angiogenic activation (VEGF, PlGF) and inhibiting pro-angiogenic factors (sFlt-1, sEng). Additionally, HIF-1α increases the expression of p38MAPK and NLRP3 inflammasomes, which promote placental inflammation and dysfunction[22]. Similar to HIF-1α, Mfn-2 also shows an increase secondary to placental hypoxia, playing a role in the pathophysiology of preeclampsia as a key transcription factor regulating cellular responses to hypoxia and low oxygen tension.

Micronutrients (iron, calcium) and antioxidant deficiencies (vitamins C and E) may contribute to the development of preeclampsia/eclampsia. Iron (Fe) and calcium (Ca) deficiencies have been reported to increase the risk of preeclampsia in women. Studies have suggested that pregnant women with low calcium levels may benefit from daily supplementation of 1.5–2 g of calcium, as it has been shown to reduce the incidence of preeclampsia, maternal death, and serious morbidity. On the contrary, supplementation of antioxidants such as omega-3 vitamins C and E, or selenium does not seem to prevent preeclampsia and is currently not supported by evidence[23].

Aspirin is currently the only medication recommended for the prevention of preeclampsia. Both the US Preventive Services Task Force (USPSTF) and the ACOG recommend the use of aspirin for the prevention of preeclampsia in women at high risk of developing the condition (such as those with chronic hypertension, pregestational diabetes, multiple gestations, kidney disease, and autoimmune disease) between weeks 12 and 28 of pregnancy[24].

The expected management of preeclampsia focuses on reducing the risk of maternal and neonatal complications through the administration of antihypertensive agents (either as a single agent or as a combination of two, such as nifedipine/methyldopa/labetalol/hydralazine) and anticonvulsants (such as magnesium sulfate). Antihypertensive medications reduce maternal complications such as cerebral hemorrhage, eclampsia, and acute pulmonary edema, while anticonvulsants reduce complications of eclampsia for both the mother and the newborn. Depending on the gestational age, the use of betamethasone (two injections of 12 mg each, 24 h apart) aids in fetal lung maturation and reduces the risk of neonatal complications such as hyaline membrane disease, intraventricular hemorrhage, and neonatal mortality. The treatment of preeclampsia depends on the stage of pregnancy. If severe preeclampsia is detected before the 24th week of pregnancy, termination of the pregnancy is recommended due to the high risk of maternal complications and poor neonatal prognosis. Management between weeks 24–34 and 34–37 of gestation depends on the severity of preeclampsia. Expectant management is recommended for mPE, but in the presence of severe preeclampsia or uncontrolled severe hypertension (not responding to dual therapy), symptoms such as acute pulmonary edema, subcapsular hepatic hematoma, placental abruption, or eclampsia, the most effective treatment method is urgent delivery[25].

It is evident that the current study has some potential limitations, and the resulting findings will contribute to future research. Examples of limitations in the study include being a single-center study and having a relatively small sample size. Additionally, in this study, blood samples were collected only at the time of the initial diagnosis of preeclampsia. Therefore, other factors limiting our study include not evaluating the serum Mfn-2 concentrations before the onset of preeclampsia and not monitoring changes in serum concentrations until delivery. A study design could be planned where blood samples are collected at the time of diagnosis and during follow-up. Subsequently, multiple plasma samples could be obtained to determine if there are changes in Mfn-2 levels over time.

In conclusion, we found that serum Mfn-2 concentrations, an important mitochondrial biomarker, are significantly elevated in women with pregnancy complicated by preeclampsia compared to healthy controls, with this elevation being more pronounced in severe preeclampsia. Our study provides a new perspective on the role of Mfn-2 as a novel biomarker for maternal and fetal/neonatal complications in women with suspected or confirmed preeclampsia. It is possible that full elucidation of the pathophysiology may not be achievable with the factor studied. However, this biomarker we investigated is a specific indicator, and further studies are needed to clarify the pathophysiology.

CONCLUSION

The severity of the disease increases due to increased placental hypoxia and endothelial dysfunction in patients with preeclampsia, and it is known that the patient has more advanced pathological results. In this study, we detected more elevated serum maternal Mfn-2 levels in response to increased hypoxia and endothelial dysfunction in sPE. Current management of PE is based on the diagnosis and assessment of the disease and the appropriate timing of delivery. We think that the use of diagnostic tools such as ultrasonographic Doppler findings together with serum plasma Mfn-2 may be promising in predicting diagnosis and treatment. We think that this study is important as it can be a source for studies to be conducted with larger patient groups and to reveal this important relationship between sPE and Mfn-2.

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ETHICAL APPROVAL

In this study, the necessary ethical requirements for human studies determined by the 1964 Helsinki Declaration were fulfilled.

AUTHORS' CONTRIBUTIONS

KU: Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **ÇÖ:** Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **YB:** Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **ÖGE:** Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **İÇ:** Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **HİA:** Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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The role of blood nitric oxide level in predicting return of spontaneous circulation: a prospective case-control study

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SUMMARY

OBJECTIVE: The aim of this study was to investigate whether there is a difference in serum nitric oxide levels between patients who return spontaneously after cardiopulmonary resuscitation and those who do not. We also examined the potential of using serum nitric oxide levels as a marker to make an accurate decision about patient survival.

METHODS: We included 100 consecutive patients who were brought to the emergency clinic due to cardiac arrest. Blood samples were taken from these patients at admission, 30 min after admission, and when resuscitation was terminated.

RESULTS: We found that there was a significant difference in NO1 and NO3 values between the group of patients who did not return after cardiopulmonary resuscitation and the group in which spontaneous circulation returned. The NO1 value was significant in the receiver operating characteristic (ROC) analysis, while the NO3 value was not. A higher NO1 value provided a higher rate of survival.

CONCLUSION: Our findings suggest that nitric oxide may be a useful parameter to support the decision about patient survival. A higher NO1 value is associated with a better prognosis and survival rate. Therefore, serum nitric oxide levels may be a suitable indicator to support the decision-making process regarding patient survival.

KEYWORDS: Cardiopulmonary resuscitation. Nitric oxide. Rosc.

INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide, with 17.9 million people every year[1-3]. In the past 50 years, the survival rates for sudden cardiac deaths have remained low despite the application of cardiopulmonary resuscitation (CPR), electrical defibrillation, and other advanced resuscitation techniques[4]. Resuscitations performed outside the hospital have a survival rate between 1 and 6%[5-7], and those performed by emergency health services have a survival rate between 5 and 10%[7,8]. Ventricular fibrillation is the most common arrhythmia in adult patients who undergo cardiopulmonary arrest[9].

Due to its enlargement, vasomotor tone, and active metabolic state that produces mediators for coagulation and inflammation, the endothelium is an effective area for damage repair in cases of ischemia-reperfusion injury. The endothelium conducts this repair function by releasing nitric oxide (NO), endothelin 1, and prostacyclins[10]. NO activates vasodilation, anti-inflammation, anti-apoptosis, and antioxidant effects and inactivates platelets and leukocytes[11]. Moreover, in cases of the overproduction of NO associated with various nervous system diseases, NO seems to become an important neurotoxin[12].

On the other hand, when giving patients CPR, it is difficult to decide when to stop. There is less information in the literature to guide this decision[3-5], with the most important data available concerning the level of the end-tidal carbon dioxide ($EtCO_2$): an extremely low $EtCO_2$ (<10 mmHg) after prolonged resuscitation (>20 min) is a sign of deficient circulation and a strong predictor of acute mortality[13,14]. Moreover, this decision—which the American Heart Association (AHA) emphasized in its Advanced Cardiac Life Support Guidelines, 2015—should not be solely based on the $EtCO_2$ value, which may be considered only one among other parameters for terminating resuscitation[15].

Therefore, considering the repairing function of NO and the uncertainty regarding when to terminate CPR, in this study, we hypothesize that the blood NO levels of those patients who

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got the return of spontaneous circulation (ROSC) after the standard resuscitation protocols were applied would be different from those who did not get the ROSC. In addition, we aimed to investigate the potential of quantitative serum NO as a marker and tool for the accurate determination of death.

METHODS

Study design

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. All participants or their relatives provided written informed consent before their inclusion in the study. This study was conducted according to a single-center prospective case-control design approved by the local ethics committee (Meeting no. 5, Decision no. 40/2019).

Setting

The study was conducted in a tertiary emergency department (ED). The study was conducted prospectively between July 2019 and February 2021. Patients who had a heart attack in the ED, whether brought in by ambulance or by their relatives, and patients who developed a heart attack during their follow-up in the ED were included.

Blood samples were taken from these patients (NO1), and resuscitation was performed according to the AHA 2015 Advanced Life Support Guidelines. Blood samples were taken again when ROSC was provided or when the decision of death was made (NO3). In patients whose resuscitation took longer than 30 min, one more blood sample was taken at the 30th minute, resulting in a total of three blood samples taken from these patients (NO2).

Participants

Patients aged 18 years and over who underwent resuscitation (defined as cessation of heartbeat and breathing) in the emergency department were included in the study. Patients with trauma, intracerebral lesion, brain hematoma, cerebral hemorrhage, intracranial tumors, terminal malignancy, end-stage lung fibrosis, and chronic systolic heart failure with an ejection fraction less than 20% were excluded.

The study included 100 consecutive patients who underwent resuscitation in the emergency department. Patients not included in the study are: 21 patients with trauma, 4 with intracerebral lesion, 7 with cerebral hemorrhage, 15 with terminal malignancy, and 9 patients with chronic systolic heart failure with an ejection fraction less than 20%.

Variables

The serum NO levels of the patients were analyzed using the Nitrate/Nitrite Colorimetric Assay Kit and the spectrophotometric method. The coefficient of variation of 84 samples was 2.7%, and that of five samples was 3.4%, according to the package insert of the kit.

Measurements

From each patient, a 5 mL blood sample was taken in a gel biochemistry blood tube. The blood samples were collected in a centrifuge at 3,500 rpm for 10 min. After centrifugation, the serum phase at the top of the tube was transferred to Eppendorf tubes by aliquoting. All the samples were stored in a deep freezer at -80°C until the day of NO analysis. In March 2021, all the serum samples were thawed at +4°C, and the NO levels were measured using the Nitrate/Nitrite Colorimetric Assay Kit.

Statistical analysis

Data were presented as mean, standard deviation, median, minimum, maximum, percentage, and number. The normal distribution of quantitative variables was evaluated using the Shapiro-Wilk W-test. The Pearson chi-square test was used to compare categorical variables. Independent sample t-tests were used to compare quantitative variables between the survivors and deceased groups when the normal distribution condition was met, and the Mann-Whitney U test was used when it was not. The repeated measures ANOVA test was used to compare the quantitative variables of more than two dependent groups when the condition of normal distribution was met, and the Friedman test was used when it was not.

The predictive estimators were investigated using receiver operating characteristic (ROC) analysis to determine whether the quantitative variables of the survivors and deceased had distinguishing features. The validity of diagnostic test results was checked by calculating sensitivity, specificity, positive predictive value, negative predictive value, prevalence, positive likelihood ratio, negative likelihood ratio, and accuracy. The power of the variable to distinguish between the deceased and survivors was also determined. All analyses were performed using the IBM SPSS 22 version. A statistical significance level of $p<0.05$ was accepted.

Sample size calculation

The sample size calculation was based on a previous study[16] that reported the mean NO value of non-survivors and survivors as 42.53 µmol/L and 77.09 µmol/L, respectively. With a power of 80% and an alpha level of 0.05, a total of 100 patients (50 in each group) were needed to detect a significant difference between the two groups.

RESULTS

A total of 100 patients were included in the study, with 64% (64) being male and a mean age of 69±13 years (minimum 32, maximum 91). The demographic data are summarized in Table 1.

The relationship between categorical variables and prognosis was analyzed and presented in Table 1. There was a significant relationship between the patients' arrival rhythm and prognosis, but no significant relationship was found between the location of the arrest, the manual or mechanical application of compression, and the gender of the patient and prognosis.

The NO1 and NO3 data were normally distributed, while the NO2 data were not. The results in Table 2 show a significant correlation between prognosis and the NO1 and NO3 variables ($p<0.05$).

The change in NO values over time (initial, second, and last measurements) for survivors and deceased are compared and given in Figure 1. No significant difference was found between the changes in NO values over time in both groups.

ROC analysis was used to investigate whether NO1 and NO3 variables could be used in estimation. While NO1 was

Table 1. Demographic data of the study and analysis of categorical variables affecting prognosis among groups.

Demographic data		Survivor (n=40)	Deceased (n=60)	p-value	Total
Age mean±SD (min–max)		65.52±15.1 (32–91)	71.13±11.33 (42–88)	0.037	68.89±13.2 (32–91)
Gender (male)%		65% (26)	63.3% (38)	0.87	64% (64)
Compression (mechanical)		50% (30)	35% (14)	0.14	44% (44)
Initial rhythm		Asystole 60% (24) VF 30% (12) PEA 10% (4)	Asystole 85% (51) VF 1.7% (1) PEA 13.3% (8)	<0.001	Asystole 74.7% VF 13.1% PEA 12.1%
Place		OHCA 70% (28) iHCA 30% (12)	OHCA 80% (48) iHCA 20% (12)	0.25	OHCA 75.8% iHCA 24.2%
Variables		**Survivors/(survivors+deceased) %**		**Chi-square**	**p-value**
Rhythm	VF	12/13 (92.3%)		17.043	<0.001
	PEA	4/12 (33.3%)			
	Asystole	24/75 (32%)			
Place	OHCA	28/76 (36.8%)		1.316	0.251
	iHCA	12/24 (50%)			
Compression	Mechanical	14/44 (31.8%)		2.192	0.139
	Manual	26/56 (46.4%)			
Gender	Male	26/64 (40.6%)		0.029	0.865
	Female	14/36 (38.9%)			

SD: standard deviation; VF: ventricular fibrillation; PEA: pulseless electrical activity; OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest.

Table 2. Comparison of nitric oxide levels.

Prognosis	Deceased			Survivor			t, Z	p
	Valid, n	Mean±SD	Median (min–max)	Valid, n	Mean±SD	Median (min–max)		
NO1	59	12.77±8.52	10.69 (1.74–52.33)	39	21.68±14.47	18.91 (2.32–70.65)	3.470	0.001
NO2	26	12.52±7.43	11.97 (2.89–30.1)	8	19.9±13.44	15.95 (8.15–50.03)	1.584	0.113
NO3	56	12.22±7.11	9.94 (2.32–30.57)	39	16.78±11.79	13.73 (0.76–44.86)	2.157	0.035

Cutoff value for NO1	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Accuracy ratio
14.96	0.68	0.74	0.80	0.60	2.64	0.43	0.70
16.97	0.78	0.67	0.78	0.67	2.34	0.33	0.73
18.12	0.81	0.59	0.75	0.68	1.98	0.32	0.72

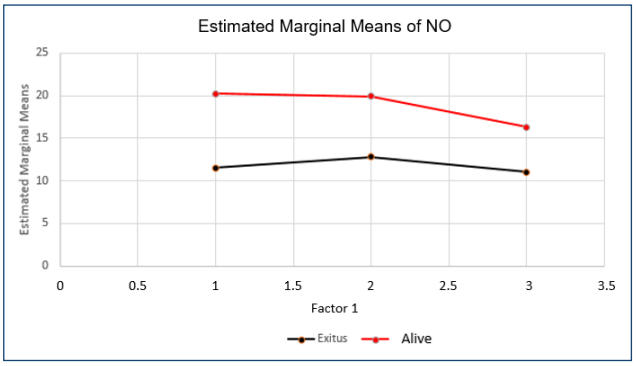

Figure 1. Averages of NO1, NO2, and NO3 values.

found to be statistically significant (p=0.001), NO3 was not (p=0.163). The NO1 cutoff value was determined using the Youden index, and the calculated value was 16.9754. Table 2 presents the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and accuracy ratio for the validity of the diagnostic test results for the two cutoff values with a high Youden index.

DISCUSSION

In our study, the NO1 value was observed to be significantly different in patients who died after CPR and those with ROSC. This confirms the hypothesis that there would be a difference between the blood NO quantitative levels of patients with ROSC and those without. Although results supporting our finding are available in animal studies[11,17], this is the first time this difference has been demonstrated in a study on humans. This study also demonstrates that ROSC is more likely in patients with a high NO1 value. Moreover, a significant difference was found between the two groups in terms of their NO3 values, reinforcing the idea that there is a significant difference between the exitus patient group and the group with ROSC and that NO level is an effective factor in determining whether to end resuscitation. In contrast, no significant difference in NO2 values was found between the deceased group and the group with ROSC, suggesting that patients with high NO1 values might have ROSC in less than 30 min at a high rate and that patients whose resuscitation lasted longer than 30 min might generally have a low initial NO1 value. While only eight patients with low NO1 values survived, 26 of them died, indicating that there may not be a significant difference between the groups in terms of the NO2 value and that NO is an effective factor for ROSC but not the only one. In future studies on this subject, determinative factors other than NO should be considered.

ROC analysis was used to examine the potential of the NO1 and NO3 values as markers for supporting the death decision, and the NO1 value was found to be statistically significant (p=0.001) unlike the NO3 value (p=0.163). The NO value's sensitivity and specificity for the cutoff value of 16.97 were 78 and 67%, respectively. The accuracy rate was determined to be 73%. Also, when we accepted the cutoff value as 18.12, the patients who would survive were indicated with an accuracy of 81%. Moreover, when we accepted the cutoff value as 14.96, the specificity rate became 74%. Thus, consistent with the results in animal studies, it was found that the NO value has the potential to be a parameter to support the death decision in humans[11,17,18].

In conclusion, the NO value at the time of cardiopulmonary arrest is an important factor for ROSC; patients with a high baseline NO seem to have a significantly higher chance of ROSC. However, this study is limited: its results cannot be generalized as it had only 100 participants and was conducted at a single center. Therefore, more detailed and multi-centered studies that focus on subgroup analyses—such as patients' admission rhythm and age range—may provide more useful and generalizable results. However, nitric oxide levels may be different depending on the initial rhythm and age of the patient. These changes may affect the interventions that need to be made.

AUTHORS' CONTRIBUTIONS

AB: Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – review & editing. **ET:** Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – review & editing. **EK:** Conceptualization, Investigation, Methodology, Visualization. **KK:** Formal Analysis, Writing – review & editing. **NK:** Investigation, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE

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Comparison of two different frailty screening scales for predicting mortality due to all causes in older inpatients

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SUMMARY

OBJECTIVE: This study examines the relationship between two frailty screening tools and 90-day all-cause mortality in geriatric inpatients.

METHODS: The study included patients aged ≥60 years who were admitted to the geriatrics unit of a university hospital between June 2021 and August 2022 and whose mortality status and duration of hospitalization data were obtained from the Health Ministry System. During hospitalization, the patients were screened using two different frailty scales: the Simpler Modified Fried Frailty Scale (sMFS) and the Clinical Frailty Scale (CFS). Patients scoring ≥5 on the CFS and ≥3 on the sMFS were considered frail.

RESULTS: A total of 84 participants with a mean age of 78.3±7.6 years were included in this study, of which 36.9% were male. Of the total, 60.7% and 89.3% were considered frail according to the CFS and sMFS, respectively, and the prevalence of all-cause mortality within 90 days was 19%. A univariate analysis using the Kaplan-Meier survival method revealed CFS scores to be statistically significantly related to 90-day all-cause mortality ($p<0.001$), while sMFS scores were not found to be statistically significant ($p=0.849$). Furthermore, a statistically significant relationship was identified between CFS score and all-cause mortality in multivariate analysis with Cox regression analysis [($p<0.001$), hazard ratio (HR): 3.078; (95% confidence interval: 1.746–5.425)].

CONCLUSION: An evaluation of frailty in hospitalized older adults using two different scales revealed the CFS to be superior to the sMFS in predicting all-cause mortality within 90 days.

KEYWORDS: Frailty. Mortality. Comparison. Older adults.

INTRODUCTION

The general health status of older adults can range from completely healthy and independent in daily activities to being completely dependent and bedridden[1,2]. The approaches to the health management of older adults and the potentially wide spectrum of health conditions that may be encountered thus necessitate different approaches[1,2]. Overdiagnosis in older adults whose mortality is expected within a few months should be avoidable through scientific approaches. This has led to the definition of the concept of "frailty"[1,2]. Frail older adults are the most complex patient group to follow up due to the difficulties encountered in the management of chronic diseases, the different treatment goals, and the presence of multiple comorbidities and their associated problems[3]. The frailty concept is adopted to identify people at greater risk of adverse health outcomes associated with, for example, falls, recurrent hospitalizations, placement in a nursing home, dependency, and mortality[1-4].

Numerous frailty screening tools have been developed for the assessment of frailty, such as the Fried Physical Frailty Scale, the Frailty Index, the Rockwood Clinical Frailty Scale (CFS), and the FRAIL Scale[1]. The Fried Physical Frailty Scale was one of the first such assessment scales to be introduced to the field[3,5-7]. The Fried Scale is based on a formal and detailed assessment of the patient's self-reported kilocalorie per week expenditure[5,7]. However, This assessment approach takes a lot of time and relies on the cognitive function of the responding older adult. Likewise, hand grip strength requires evaluation with a hydraulic hand dynamometer, while walking speed is a formal evaluation measured in meters/second. For all the above reasons, the Fried Frailty Scale can be considered an impractical screening tool for use in clinical practice as most patients hospitalized in geriatric units are unable to stand or may have sequelae symptoms[8].

Based on an evaluation of responses to five questions asked to the patient or close caregiver, frailty determined using the Simplified Modified Fried Frailty Scale (sMFS) has been shown to predict mortality in nursing home residents[5]. The five questions relate to involuntary weight loss, feelings

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of exhaustion-burnout, weakness (hand grip strength), slow walking speed, and low physical activity[5,6].

The Clinical Frailty Scale (CFS), which was created by Rockwood et al., is based on the observation of the patient by a physician[9]. It is a practical tool for frailty screening in geriatric service settings, where care plans for older adults with multiple problems need to be devised quickly, due to the easy applicability of the nine items[9].

The intention of this study is to meet a need of physicians in the geriatric care of older adults, the management of which can be difficult and complex, through the identification of the optimum frailty screening tool in terms of speed, ease of application, and ability to predict mortality. To this end, we compare the ability of the sMFS and the CFS to predict all-cause mortality within 90 days of discharge.

METHODS

Patients aged 60 years and over who were admitted to the geriatric service between June 2021 and August 2022 were included in this retrospective study. Prior to hospitalization, all patients were tested for COVID-19 in the emergency room or COVID-19 polyclinics, and those with positive or suspected COVID-19 results were admitted to separate COVID-19 services. Patients who died during hospitalization, those whose hospitalization continued, and those who were transferred to surgical services were excluded from the study. Approval for the study was obtained from the ethics committee of a local university (Reference number/1083), and all procedures in the study were carried out in accordance with the principles defined by the Declaration of Helsinki. The data of all participants admitted to the geriatric service were recorded by a responsible internal medicine doctor other than the attending physician. All information was obtained within the first 2 days of the patient's admission. The demographic characteristics of the patients (age, gender), presence of chronic diseases, activities of daily living (ADL), instrumental activities of daily living (IADL), presence of geriatric syndromes (falls, frailty, malnutrition, urinary incontinence, sleep disorders), presence of frailty fracture in the last 1 year, and duration of hospitalization were recorded. The risk of malnutrition was assessed using the Mini Nutritional Test-Short Form (MNA-SF). Patients with an MNA-SF score of <11 were considered at risk of malnutrition[10]. Polypharmacy was identified as four drugs[11].

Frailty screening using the sMFS is based on an evaluation of the responses to five questions asked to the patient or close caregiver[5]. The five questions are related to involuntary weight loss, fatigue/feelings of burnout, weakness (hand grip strength), slow walking speed, and low physical activity[5,6]. In this study, patients scoring ≥3 on the sMFS scale were evaluated as frail.

The CFS is based on physician observations, for which patients are evaluated on a scale of 1–9 in which 1 indicates very fit and 9 indicates terminally ill[9]. Patients scoring ≥5 on the CFS scale are considered frail[9]. Details of the patients who were discharged from the hospital were obtained from the hospital records.

Statistical analysis

Following the evaluation of data distribution using a Kolmogorov-Smirnov test. The association between the data distribution by gender and the other study variables was evaluated with chi-square, Mann-Whitney U, and independent-sample t-tests, depending on the characteristic properties of the data. The Kaplan-Meier method was used to evaluate the relationships between the length of stay, 90-day all-cause mortality data, and frailty scales. The Cox regression model was used to examine the associations between the frailty scales and 90-day all-cause mortality, for which hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

RESULTS

A total of 84 participants with a mean age of 78.3±7.6 years were included in this study, of which 36.9% were male. The application of the CFS and sMFS revealed 60.7 and 89.3% of the sample to be frail, respectively, and all-cause mortality within 90 days was 19%. The median length of hospitalization of the study population was 15.5 (1–158) days.

In univariate analyses, age, presence of dementia as a chronic disease, urinary incontinence, number of chronic diseases, number of chronic drugs, ADL, IADL, length of stay, and mortality were all identified as statistically significant factors, as identified by the CFS frailty screening tool (p-values, respectively, p=0.001, p=0.002, p=0.007, p <0.001, p=0.017, p <0.001, p<0.001, p<0.001, and p<0.001) (Table 1).

In the univariate analyses, the factors associated with the sMFS frailty screening tool were determined as age, ADL, and IADL (p=0.004, p=0.008, and p<0.001, respectively) (Table 2).

A statistically significant correlation was found between the CFS and sMFS frailty screening tools (r=0.602, p<0.001).

In univariate analyses using the Kaplan-Meier survival method, the CFS was statistically significantly related to 90-day all-cause mortality (p<0.001), while in univariate analyses of the sMFS, it was found not to be statistically significant (p=0.849). A statistically significant relationship was revealed between the CFS and all-cause mortality after adjusting for age, sex,

Table 1. Relationship between CFS frailty screening scale in univariate analyses with demographic characteristics, chronic diseases, geriatric syndromes, 90-day all-cause mortality, and length of stay.

	CFS≥5 (n=51) 60.7%	CFS<5 (n=33) 39.3%	Total (n=84) 100%	p-value
Age	80.4± 6.8	75 ±7.7	78.3±7.6	0.001ᵠ
Gender				
Male	17 (33.3%)	14 (42.4%)	31 (36.9%)	0.399
Female	34 (66.7%)	19 (57.6%)	53 (63.1%)	
Chronic disease (n, %)				
CHF	16 (31.4%)	7 (21.2%)	23 (27.4%)	0.308
CKF	10 (19.6%)	9 (27.3%)	19 (22.6%)	0.412
COPD	6 (11.8%)	3 (9.1%)	9 (10.7%)	0.699
DM	23 (45.1%)	12 (36.4%)	35 (41.7%)	0.428
Dementia	18 (35.3%)	2 (6.1%)	20 (23.8%)	0.002ᵠ
Depression	11 (21.6%)	3 (9.1%)	14 (16.7%)	0.134
HT	40 (78.4%)	23 (69.7%)	63 (75%)	0.367
Geriatric syndromes (n, %)				
Falls	28 (54.9%)	17 (51.5%)	45 (53.6%)	0.761
Undernutrition (MN+MNR)⊥	48 (96%)	33 (100%)	81 (97.6%)	0.245
Frailty fracture in last year⊥	8 (15.7%)	3 (9.1%)	11 (13.3%)	0.409
Urinary incontinence	44 (86.3%)	20 (60.6%)	64 (76.2%)	0.007ᵠ
Sleep disordersˣ	32 (64%)	17 (53.1%)	49 (59.8%)	0.327
Polypharmacy (n, %)	50 (98%)	29 (87.9%)	79 (94%)	0.055
Number of chronic drugs	11.3 ±3.5	7.9± 3.5	10±3.9	<0.001ᵠ
Number of chronic diseases	4.8 ±2.3	3.7±1.5	4.3±2.1	0.017ᵠ
ADL*	1 (0–6)	6 (5–6)	5 (0–6)	<0.001ᵠ
IADL*	1 (0–8)	8 (3–8)	4 (0–8)	<0.001ᵠ
Length of stay*	18 (4–158)	12 (1–50)	15.5 (1–158)	<0.001ᵠ
90-day mortality (days)	11 (21.6%)	5 (15.2%)	16 (19%)	<0.001ᵠ

ADL: activities of daily living; CHF: congestive heart failure; CKF: chronic kidney failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HT: hypertension; CFS: Clinical Frailty Scale; IADL: instrumental activities of daily living; MN: malnutrition; MNR: malnutrition risk. *Given data as median. ᵠSignificant p-values. ⊥Marked data include 83 participants. ˣmarked data include 82 participants.

undernutrition, number of diseases, and falls in the evaluation of the screening tools in multivariate analysis with Cox regression analysis [(p<0.001), HR: 3.078; 95%CI: 1.746–5.425]. Although not significant in the univariate analyses, the sMFS tool and all-cause mortality association remained statistically insignificant after adjusting for age, sex, malnutrition risk, number of drugs, and falls (Table 3).

DISCUSSION

This study of 84 geriatric service patients aged 60 years and older assessed and compared the capacity of the CFS and sMFS frailty scales to predict 90-day all-cause mortality. A moderate correlation was noted between the CFS and sMFS in the results of the study; although a significant statistical relationship was noticed between all-cause mortality and CFS, no such relationship was identified with the sMFS. Neither the CFS nor sMFS results showed statistical significance with duration of hospitalization.

Frailty was identified in 60.7% of the geriatric inpatients based on the CFS, while the sMFS identified 89.3% of the participants as frail. All-cause mortality within 90 days was 19%.

There are studies comparing the ability of various frailty scales to predict mortality in different patient groups. In a

Table 2. Relationship between sMFS frailty screening scale in univariate analyses with demographic characteristics, chronic diseases, geriatric syndromes, 90-day all-cause mortality, and length of stay.

	sMFS≥3 (n=75) 89.3 %	sMFS<3 (n=9) 10.7%	Total (n=84) 100%	p-value
Age	79.2 ±7.5	71.5 ± 5.1	78.3±7.6	0.004ᵠ
Gender				
Male	25 (33.3%)	6 (66.7%)	31 (36.9%)	0.050
Female	50 (66.7%)	3 (33.3%)	53 (63.1%)	
Chronic disease (n, %)				
CHF	22 (29.3%)	1 (11.1%)	23 (27.4%)	0.247
CKF	14 (18.7%)	5 (55.6%)	19 (22.6%)	0.012ᵠ
COPD	8 (10.7%)	1 (11.1%)	9 (10.7%)	0.968
DM	32 (42.7%)	3 (33.3%)	35 (41.7%)	0.592
Dementia	20 (26.7%)	0 (0%)	20 (23.8%)	0.076
Depression	14 (18.7%)	0 (0%)	14 (16.7%)	0.156
HT	57 (76%)	6 (66.7%)	63 (75%)	0.541
Geriatric syndromes (n, %)				
Falls	42 (56%)	3 (33.3%)	45 (53.6%)	0.198
Undernutrition (MN+MNR)⊥	72 (97.3%)	9 (100%)	81 (97.6%)	0.618
Frailty fracture in last year⊥	10 (13.5%)	1 (11.1%)	11 (13.3%)	0.841
Urinary incontinence	56 (74.7%)	8 (88.9%)	64 (76.2%)	0.344
Sleep disorders×	44 (58.7%)	5 (55.6%)	49 (59.8%)	0.785
Polypharmacy (n, %)	71 (94.7%)	8 (88.9%)	79 (94%)	0.489
Number of chronic drugs	10.2 ±3.8	7.6 ±3.7	10±3.9	0.058
Number of chronic diseases	4.4±2.2	3.7± 1.5	4.3±2.1	0.367
ADL*	5 (0–6)	6 (5–6)	5 (0–6)	0.008ᵠ
IADL*	3 (0–8)	8 (7–8)	4 (0–8)	<0.001ᵠ
Length of stay*	15 (1–158)	16 (4–50)	15.5 (1–158)	0.862
90-day mortality (days)	16 (21.3%)	0 (0%)	16 (19%)	0.849

ADL: activities of daily living, CHF: congestive heart failure, CKF: chronic kidney failure, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, HT: hypertension, IADL: ınstrumental activities of daily living, MFS: Simpler Modified Fried Scale, MN: malnutrition, MNR: malnutrition risk. *Given data as median. ᵠSignificant p-values. ⊥Marked data include 83 participants. ×Marked data include 82 participants.

Table 3. Relationship of CFS and sMFS screening tools with 90-day all-cause mortality after adjustment in Cox regression.

	Age	Gender	Undernutrition risk⊥	Number of chronic diseases	Dementia	Falls	CFS≥5
p	0.062	0.558	1	0.222	0.743	0.854	<0.001ᵠ
HR	1.033	0.867	1	0.932	1.115	1.047	3.078
95%CI							
-Lower	0.998	0.539	0.209	0.832	0.582	0.641	1.746
-Upper	1.069	1.396	4.790	1.044	2.134	1.710	5.425
	Age	**Gender**	**Undernutrition risk⊥**	**Number of chronic diseases**	**Dementia**	**Falls**	**MFS≥3**
p	0.609	0.588	0.713	0.366	0.312	0.756	0.900
HR	1.008	0.877	0.749	0.950	1.376	1.079	1.050
95%CI							
-Lower	0.976	0.547	0.161	0.849	0.741	0.667	0.491
-Upper	1.042	1.408	3.490	1.062	2.557	1.745	2.246

CFS: Clinical Frailty Scale; CI: confidence ınterval; HR: hazard ratio; MFS: Simpler Modified Fried Scale. ᵠSignificant p-values. ⊥Marked data include 83 participants.

study comparing the ability of the Fried Scale and the CFS to predict 90-day mortality among the older adults admitted to the emergency department, an association was identified between mortality and CFS, concurring with the results of the present study[12], which may be due to the similarity of the patient population. In addition, as symptoms such as decreased physical activity and fatigue may be common in all patients with acute illnesses, the effectiveness of the Fried scale or the scales derived from it may be limited. Future studies may come up with revisions to the sMFS allowing its application in acute situations. In a further study assessing the ability of the FRAIL Scale, Fried Scale, and CFS to predict 28-day mortality and re-hospitalization in emergency older patients, none of the scales was found to predict rehospitalization, while all three were able to predict mortality, with the predictions based on the Fried Scale being more accurate[13]. These results conflict with the findings of the present study, which may be attributable to the different accompanying comorbidities of the patients, the level of objectivity of the responses of patients or their relatives, and the more objective nature of the present study due to the observations being made by a single physician.

There are also studies of patients undergoing geriatric rehabilitation comparing the ability of different frailty scales to predict adverse clinical outcomes[14,15]. In a study by Soh et al. of patients undergoing geriatric rehabilitation, the ability of the Frailty index laboratory, modified Frailty index laboratory, and CFSs to predict 1-year mortality was evaluated[14], and the authors found all three scales to be poor predictors of mortality in elderly patients undergoing geriatric rehabilitation[14]. This difference may be due to the longer mortality period assessed in this study and the different patient populations.

Bahat et al. found that sMFS was able to predict mortality after 4 years in their study of 224 nursing home residents to a statistically significant degree[5]. While the validity and reliability of the sMFS have been established[6], studies comparing the relationship with predicting mortality of sMFS in geriatric service patients with other studies are not yet available in the literature.

In a prospective study comparing four different scales, namely, the FRAIL, the Tilburg Frailty Indicator, the CFS, and the Frailty Index, in terms of their ability to predict loss of functionality, institutionalization, length of hospital stay, and mortality during hospitalization in the geriatric patient population, CFS was found to better predict loss of functionality and length of stay[16]. These results differ from those of our study in two ways. First, the ability of the scales to predict loss of functionality was not assessed in this study, which may be due to the difference in the definition of mortality, and second, the duration of hospitalization differed from those reported in this study, which may be due to the difference in the definition of frailty.

CONCLUSION

This is the first study to compare the ability of the sMFS and CFS to predict 90-day all-cause mortality in a hospitalized geriatric patient population. The CFS was found to predict mortality in geriatric hospitalized patients, and the results reveal that physician observations are more consistent than those reported by the patients and their relatives. Further observational prospective studies are required to assess the ability of the sMFS to predict adverse clinical outcomes in geriatric inpatients.

ETHICS APPROVAL

We obtained ethical approval from the ethical board of Istanbul University Medical School (Approval number: 2023/1083).

CONSENT TO PARTICIPATE

We received informed consent from all participants.

CONSENT FOR PUBLICATION

We received informed consent from all participants.

AUTHORS' CONTRIBUTIONS

MEB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **TE:** Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CK:** Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **HO:** Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **GO:** Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **EA:** Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ZF:** Project administration, Resources, Software,

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ORIGINAL ARTICLE

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A study on obese patients' participation in cancer screening programs: an example from Turkey

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SUMMARY

OBJECTIVE: Obesity is associated with many types of cancers. Despite this, the participation of obese individuals in cancer screenings is limited. The aim of this study was to evaluate the cancer screening-related attitudes of obese patients.

METHODS: The study included 185 obese patients who presented to the obesity center (OC) and 191 obese patients who presented to the family medicine outpatient clinic from October to December 2019. The participants in both groups were first asked whether or not they had ever undergone any cancer screening tests and then provided with relevant training. After 3 months, the participants were contacted again and their attitudes toward cancer screening tests were re-evaluated.

RESULTS: Patients who followed in the OC were found to have higher awareness of and compliance with cancer screening tests than the obese patients admitted to the outpatient clinic. The factors of being female, being followed in the OC, and residing in an urban area were positively associated with participation in cancer screening tests.

CONCLUSION: Monitoring obese patients in target-oriented facilities such as an OC increases the chance of success in the fight against obesity and related health problems.

KEYWORDS: Cancer screening. Obesity. Patient participation. Prevention.

INTRODUCTION

Today, obesity is one of the leading causes of preventable death. According to the World Health Organization, in 2016, more than 1.9 billion adults were overweight, of which over 650 million were obese[1].

In addition to affecting disease-related mortality, obesity has been associated with many diseases[2,3]. Studies also have found that obesity is a risk factor for many cancer types and the rate of cancer attributable to obesity in the world constituted 3.6% of all cancer cases[4,5]. Despite the fact that obesity and cancer are related, research shows that obese people's attitudes toward cancer screening tests appear to be limited and a significant negative correlation has been reported to exist between obesity and participation in cancer screening programs[6-8].

In the literature, studies investigating the tendency of participation of obese patients in cancer screening tests remain very limited, and likewise, those investigating the participation of such patients followed up in a private center are very few. Therefore, the aim of this study was both to assess the cancer screening status of obese people and to evaluate the possible differences in the attitudes toward cancer screening tests between obese individuals followed up by private centers and those who were not followed up in any center.

METHODS

Study design and participants

This is a observational and prospective study and was conducted in a single center. The research population consisted of people who presented to the Family Medicine Outpatient Clinic of the Health Sciences University, Antalya Training and Research Hospital (HSUATRH) between March and May 2020, and those who were followed up in the Health Sciences University Antalya Training and Research Hospital Obesity Center (OC) between October and December 2019. This study included patients having a BMI ≥30 kg/m^2, being at the age of 18 years and over, having no previous diagnosis of malignancy, not being pregnant or in the postpartum period, and agreeing to participate in the research for both groups.

While determining the number of those to be included in the study in the outpatient group, the fact was that the

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prevalence of obesity in adults in Turkey was reported to be approximately 30%[9]. In this regard, the sample size was calculated as 244 people (the confidence interval was 95%, and the sampling error was 5% EpiInfo™, 7.2.0.1; sample size and power). However, as the data collection period in the outpatient clinic group overlapped with the COVID-19 pandemic, when many restrictions were imposed on patient admission to outpatient clinics, the data collection process was terminated when 191 participants were included in the study sample.

The study included all of the patients who were followed up at the OC from October to December 2019, and no sampling was done. The number of patients followed at the OC until the end of the study was 198. Because 13 patients had previous diagnoses of malignancy, 185 patients were included in the OC group.

After this process, the cancer screening status of the individuals in the two groups was compared and investigated whether or not the patients followed in the OC developed positive health-related behavior in terms of cancer screening tests.

Health Sciences University Antalya Training and Research Hospital Obesity Center

The Center started its operations on November 1, 2018, within the HSUATRH. In the OC, weight loss is targeted to achieve a state of health in those with obesity, and thus, such individuals are informed about health problems caused by obesity through various educational activities: one of these is the relationship between obesity and cancer and the importance of cancer screening.

Measurement tools

Sociodemographic data form

After receiving the written consent of the participants, the researcher asked the research questions through face-to-face interviews with the participants.

The height and weight of the participants were measured by the researchers and their body mass indexes were calculated. The cancer screening programs in Turkey include those for breast, cervical, and colon cancer types, regarding which the participants were questioned.

In our questionnaire, patients were asked questions about their demographic data and whether or not they ever had cancer screening tests done in conformity with age and gender, upon which the patients' responses were noted. Afterward, they were informed about obesity-related cancer risks in detail, provided with appropriate guidance for any possible missing cancer screening tests and given the prepared information brochure as a print-out. At least 3 months later, the patients were contacted by phone and asked whether or not they got the screenings done as included in the national cancer screening program, upon which their answers were recorded in the research form.

Ethical approval

Approval for this study was obtained from the Clinical Research Ethics Committee of the UHSATRH with decision number 21/7 (dated 26.09.2019). The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Table 1 presents the detailed demographic characteristics of the patients included in the study comparatively.

Table 2 presents the findings regarding the availability of the patients' cancer screening tests before training.

Table 3 presents the findings regarding the status of patients undergoing cancer screening tests after the training.

The rate of patients who presented to the family medicine clinic with no cancer screening at all or who only had it before the training was higher when compared with those who followed in the OC. Likewise, those who had cancer screening both before and after the training among the OC patients ($p<0.001$) was higher as a rate. While no significant change was observed in the rates of cancer screening tests before and after the training in the OC patients ($p=0.652$), 33 (30%) of the outpatients who got screening tests done prior to the training were found not to have received any of the relevant screenings after the training ($p=0.049$).

As a result of the multivariate logistic regression analysis performed to determine the factors that independently affect the status of getting at least one cancer screening done after training in patients who were supposed to get them done, it was found that being a woman (OR: 68.697; 95%CI: 9.01–523.761; $p<0.001$), being followed at the OC (OR: 2.353; 95%CI: 1.248–4.437; $p=0.008$), and living in an urban area (OR: 2.507; 95%CI: 1.019–6.166; $p=0.045$) positively affected the cancer screening status after the training.

DISCUSSION

This study evaluated a total of 376 patients, including 185 obese patients followed in the OC and 191 obese patients admitted to the outpatient clinic. The obese patients followed in the OC were found to have higher awareness of and compliance with

Table 1. Demographic characteristics of the patients.

Demographic characteristics		All patients (n=376)	Patients followed at the OC (n=185)	Outpatients (n=191)	P
Age		50.33±10.89 (19-79)	52.23±9.82 (21–73)	48.49±11.57 (19–79)	**0.001**
Gender	Female	308 (81.9)	174 (94.1)	134 (70.2)	**<0.001**
	Male	68 (18.1)	11 (5.9)	57 (29.8)	
Marital status	Single	40 (10.6)	13 (7)	27 (14.1)	0.082
	Married	291 (77.4)	149 (80.5)	142 (74.3)	
	Separated/divorced	45 (12)	23 (12.4)	22 (11.5)	
Educational background	Illiterate	8 (2.1)	1 (0.5)	7 (3.7)	0.369
	Primary school	168 (44.7)	85 (45.9)	83 (43.5)	
	Secondary school	40 (10.6)	18 (9.7)	22 (11.5)	
	High school	91 (24.2)	46 (24.9)	45 (23.6)	
	University	61 (16.2)	32 (17.3)	29 (15.2)	
	Master's degree/PhD	8 (2.1)	3 (1.6)	5 (2.6)	
Occupation	Unemployed	18 (4.8)	10 (5.4)[a]	8 (4.2)[a]	**<0.001**
	Housewife	181 (48.1)	105 (56.8)[a]	76 (39.8)[b]	
	Worker	81 (21.5)	14 (7.6)[a]	67 (35.1)[b]	
	Civil servant	26 (6.9)	7 (3.8)[a]	19 (9.9)[b]	
	Retired	70 (18.6)	49 (26.5)[a]	21 (11)[b]	
Place of residence	Urban area	344 (91.5)	172 (93)	172 (90.1)	0.310
	Rural area	32 (8.5)	13 (7)	19 (9.9)	
With social security		354 (94.1)	171 (92.4)	183 (95.8)	0.163

OC: obesity center. Results are shown as mean±SD (min–max) or n (%) values. Student's t-test, Pearson chi-square test, and Fisher's exact test. Different lowercase letters in a row indicate statistically significant differences between groups. Bold: Of all the 376 patients included in the study, 81.9% were female and 18.1% were male, with a mean age of 50.33±10.89 years (min.: 19; max.: 79). The ratio of female patients (p<0.001) and mean age (p=0.001) were found to be higher in patients followed in the OC compared with those followed in the outpatient clinic. The housewife and retired rates in OC (p<0.001) and the worker and civil servant rates in the outpatient clinic (p<0.001) were found to be statistically higher.

Table 2. The status of patients undergoing cancer screening test prior to the training.

Screening tests*	All patients	Patients followed at the OC	Outpatients	P
Receiving cancer screening (n=376)	254 (67.6)	144 (77.8)	110 (57.6)	**<0.001**
PAP smear/HPV DNA tests (n=308)	158 (51.3)	92 (52.9)	66 (49.3)	0.529
Breast self-exam (n=308)	160 (51.9)	89 (51.1)	71 (53)	0.749
Mammography (n=308)	122 (39.6)	79 (45.4)	43 (32.1)	**0.018**
Colonoscopy/sigmoidoscopy (n=376)	44 (11.7)	23 (12.4)	21 (11)	0.665
Fecal occult blood test (n=376)	42 (11.2)	19 (10.3)	23 (12)	0.586

*The number of patients (n) who needed to have screening tests was specified according to the indication by gender. OC: obesity center. Findings are shown with n (%) values. Pearson chi-square test and Fisher's exact test. Bold: The rate of having cancer screening tests (p<0.001) as well as mammography (p=0.018) and PSA test (p=0.004) prior to the training in patients followed in the OC was found to be statistically significantly higher than that of the outpatients.

cancer screening tests after the training than the obese patients admitted to the outpatient clinic. Our study revealed that the factors of being female, being followed in the OC, and residing in an urban area were positively associated with participation in cancer screening tests.

In Turkey, the prevalence of obesity in women is approximately twice that of men[10]. Our study revealed that the female gender ratio was statistically significantly higher among the patients followed in the OC compared with those who presented to the outpatient clinic. We consider that this situation

Table 3. The status of patients undergoing cancer screening after the training.

Types of screening tests*	All patients	Patients followed in the OC	Outpatients	p
Cancer screening (n=376)	241 (64.1)	146 (78.9)	95 (49.7)	**<0.001**
PAP smear/HPV DNA tests (n=308)	12 (3.9)	8 (4.6)	4 (3)	0.468
Breast self-exam (n=308)	233 (75.6)	144 (82.8)	89 (66.4)	**0.001**
Mammography (n=308)	14 (4.5)	10 (5.7)	4 (3)	0.249
Colonoscopy/sigmoidoscopy (n=376)	2 (0.5)	1 (0.5)	1 (0.5)	0.999
Fecal occult blood test (n=376)	4 (1.1)	2 (1.1)	2 (1)	0.999

*The number of patients (n) who needed to have screening tests was specified according to the indication by gender. OC: obesity center. Findings are shown with n (%) values. Pearson chi-square test and Fisher's exact test. Bold: The rate of having cancer screening done (p<0.001) and breast self-exam (p=0.001) after the training in patients followed up in the OC was found to be statistically higher than those of outpatients.

was rooted in the fact that the majority of those who presented to the OC were women because the prevalence of obesity was higher in women. Yildirim and Eryilmaz evaluated the profile of patients who presented to the OC in their study conducted in Konya/Turkey and stated that 91.3% of the patients were female and 8.7% were male[11]. These rates seem to be compatible with our study.

In this study, 67.6% of the patients stated that they had at least one cancer screening test done prior to the training. This rate was found to be 77.8% in the patients followed in the OC, whereas it was 57.6% in the patients admitted to the outpatient clinic. The rate of getting cancer screening tests done after receiving relevant training was found to be 64.1% in all patients, 78.9% in those followed in the OC, while it was 49.7% in patients admitted to the outpatient clinic, indicating a significant difference between the two groups. This significant difference between the patients followed in the OC and those admitted to the outpatient clinic in terms of the tendency of getting cancer screening tests done may result from the fact that the health-seeking behavior of the patients followed up in the OC is more advanced, and trainings on "obesity and cancer" and "cancer screenings" are given as a standard procedure in the third module in the OCs[12].

It is stated that obesity most likely is a barrier to screening for breast and cervical cancers, particularly among white women[13]. The detailed analysis of the cancer screenings shows us that the percentage of women who were supposed to do breast self-exam but never did so was 18.6% in total. This rate was 13.8% for women followed in the OC, while it was 24.8% for those admitted to the outpatient clinic, indicating a significant difference between the two groups. In addition, those who did breast self-exam after training were significantly higher in the patients followed in the OC. In our study, the rate of having mammography in patients who needed that was found to be 49% in total. Bussiere et al. examined the impact of obesity on patients' access to breast cancer screening tests. That study included women between the ages of 40 and 75 years and reported that the rate of mammography in the last 2 years was 63.3% in obese women and 69.8% in non-obese women[6]. This result supports that obesity is a barrier to breast cancer screening. In obese individuals, reasons such as low self-esteem and poor body perception, as well as fear of humiliation, concern about lack of respect from healthcare providers, and unwillingness to hear weight loss advice may have exerted a negative impact on the desire to seek healthcare.

Our study found that 58% of the patients who were supposed to have a Pap smear screening test actually had it. Also, the rate of those who had a Pap smear screening test after training was higher in the patients followed up in the OC in comparison with those admitted to the outpatient clinic, yet this difference was not statistically significant.

According to the study conducted by Bussiere et al. in France, the rate of having a Pap smear in the last 3 years was found to be 61% in obese patients and 74% in non-obese patients[6]. Richard et al. examined the impact of lifestyle and health-related factors on participation in cervical cancer screening in a population-based study of Swiss women. The study that was conducted with 7,319 women aged 20–69 years revealed that the rate of receiving cervical cancer screening tests in the last 3 years was 72.9%. When multiple variables were adjusted, the odds ratio of participation in cervical cancer screening tests in obese women was found to be significantly lower (OR=0.64; 95%CI)[14]. This study is a good example of the negative impact of obesity on cancer screening participation.

It is known that overweight and obesity are associated with an increased risk of colorectal cancer[15]. In this study that included obese patients, we found the rate of those who got the FOB test done was 16.1% among those who needed to

get it done. We also revealed that the rate of those who underwent colonoscopy/sigmoidoscopy in the last 10 years among those who needed that was only 15.4%. A recent study states that colorectal cancer screening starting at 45 or 40 years of age instead of at 50 years of age, or shortening screening intervals, in women and men with obesity appears cost-effective[16]. For this purpose, it can be said that developing special approaches for obese individuals in cancer screening programs can produce cost-effective results.

In this study, the rates of undergoing cancer screening tests and mammography before the training were found to be statistically higher in patients followed up in the OC compared to those of the outpatients, a situation that may be attributed to the positive effect of being followed up in a center on health awareness in general or to the participation of obese individuals with higher health awareness in the OC.

Our study also has some limitations. First of all, the patients followed in the OC were predominantly female, and those who were admitted to the outpatient clinic were different from those in the OC in terms of gender ratios. Second, due to the COVID-19 pandemic, which started in December 2019 with the first case seen in our country in March 2020, our patients' behavior patterns were affected and their interactions with the outside world decreased accordingly, which may have influenced our patients' behaviors to participate in cancer screening programs.

CONCLUSION AND RECOMMENDATIONS

Monitoring obese patients in target-oriented facilities such as an OC increases the chance of success in the fight against obesity and related health problems. In this regard, OCs that prove beneficial in the fight against obesity should be expanded across our country and the world with increased service capacity. We hope that the findings of our study will benefit future research to be conducted in a more comprehensive manner as a multi-center study.

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AUTHORS' CONTRIBUTIONS

ST: Conceptualization, Data curation, Formal Analysis, Supervision, Writing – original draft, Writing – review & editing. **MÖ:** Conceptualization, Data curation, Formal Analysis, Supervision, Writing – original draft. **RNE:** Data curation, Formal Analysis, Supervision, Writing – original draft. **ABA:** Formal Analysis, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Contributing role of metabolic genes *APOE*, *FTO*, and *LPL* in the development of atrial fibrillation: insights from a case-control study

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SUMMARY

OBJECTIVE: The aim of the study was to examine the expression profile of genes (*APOE*, *FTO*, and *LPL*) associated with metabolic syndrome (MetS) in subjects with concomitant atrial fibrillation (AF).

METHODS: A total of 690 subjects were categorized into control, AF without MetS, and AF with MetS.

RESULTS: The expression profiles of the *APOE*, *FTO*, and *LPL* genes were decreased in AF subjects and AF subjects with MetS as compared to the controls. In AF without the MetS group, an inverse relationship was found between the expression of the *LPL* gene with body mass index (BMI) and a positive relationship with creatine kinase-MB, whereas expression of the *FTO* gene was inversely associated with fasting blood glucose and positively with cardiac troponin I in AF suffering from MetS. Expression of the *LPL* gene was directly linked with systolic blood pressure (SBP) and high-density lipoprotein-cholesterol (HDL-C), whereas an inverse correlation with heart rate and expression of the *FTO* gene in AF with MetS were shown. The expression of the *LPL* gene was inversely related to BMI in subjects with AF. The expression of the *LPL* gene was positively correlated with SBP and HDL-C and negatively correlated with heart rate, while the expression of the *FTO* gene was an important predictor of AF with MetS.

CONCLUSION: The decreased expression of *APOE*, *FTO*, and *LPL* genes in AF with and without MetS indicates their potential contributing role in the pathogenesis of AF.

KEYWORDS: Gene expression profile. Atrial fibrillation. Metabolic syndrome.

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent, sustained heart arrhythmia. Globally, more than 37 million people are affected by AF, which accounts for 0.51% of the world's population, while the prevalence of AF has increased by 33% over the past two decades. Future projections suggest that the absolute burden of AF could increase by more than 60% by the year 2050[1].

Metabolic syndrome (MetS) diagnosis requires the presence of at least three out of five specific medical conditions, namely elevated fasting blood glucose (FBG), elevated blood pressure (BP) levels, elevated plasma levels of triglycerides (TG), low plasma levels of high-density lipoprotein cholesterol (HDL-C), and central obesity. The presence of MetS increases the risk of developing type 2 diabetes and cardiovascular disease[2]. It is well established that MetS and its components are linked to the development of AF[3,4]. It has been shown that the occurrence and development of AF may be influenced by a combination of various genes and/or environmental factors[5].

The Apolipoprotein E (*APOE*) gene is situated on chromosome 19q13 and is responsible for producing the primary apolipoprotein that is present in the central nervous system. *APOE* is a protein consisting of 299 amino acids with a molecular mass of approximately 34 kDa[6]. The enzyme *FTO* (fat mass and obesity-associated), also known as alpha-ketoglutarate-dependent dioxygenase, is encoded by the *FTO* gene located on chromosome 16 in humans[7]. The *LPL* gene, situated on chromosome 8p22, is responsible for the metabolism and transport of lipoproteins in humans[8,9]. However, the exact mechanisms underlying this association remain unclear, and effective prevention of AF in patients with MetS is a clinical challenge. The key pathogenic factor involved in AF development in MetS is yet to be determined. The objective of this study was to determine the expression of *APOE*, *FTO*, and *LPL* genes in AF patients at the Punjab Institute of Cardiology, Lahore. Additionally, the study aimed to examine the relationship between the expression of these genes and other clinical parameters in AF patients.

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METHODS

This case-control study was conducted in the Department of Zoology, Lahore College for Women University, Lahore. Participants were recruited from the Punjab Institute of Cardiology, Lahore, Pakistan, from July 2021 to June 2022. Subjects were enrolled after providing written informed consent. The study was approved by the Ethical Review Committee (ref. no.: RTPGME-Research-179) of the Punjab Institute of Cardiology and Lahore College for Women University, Lahore, Pakistan.

RNA isolation and cDNA synthesis

Blood samples were collected for mRNA isolation within 2–4 h of collection, and the Trizol method was used to extract mRNA (Refrigerated Centrifuge Machine HARRIER 18/80, UK). The quality and quantity of mRNA were determined using a Nanodrop (Multiskan SkyHigh Microplate spectrophotometer, UK). The Maxima® First Strand cDNA Synthesis Kit (Thermo Scientific) was used to convert mRNA to cDNA for gene expression (Programmable Thermal Cycler Ptc-06 UK) (Thermo Scientific RevertAid First Strand cDNA Synthesis Kit, cat # K1622). Gel electrophoresis was performed to confirm the cDNA.

Expression analysis by real-time PCR

To perform real-time PCR (Applied Biosystems Step One™ Real-Time PCR system, Thermo Scientific Fisher Inc., USA), oligonucleotide primers were designed using Primer 3 software. The primer was created by a readily available commercial industry. *APOE* (F: CGGACATGGAGGACGTGT, R: CTGGTACACTGCCAGGCG), *FTO* (F: TGGTGTCCCAAGAAATCGTG, R: TGCAGGCCGTGAACCAC), and *LPL* (F: CCCGAGATGGAGAGCAAAG, R: CCCCTTCCAACTTCCTTCTT) genes' relative expression was evaluated using the Thermo Scientific Maxima SYBER Green/ROX qPCR Master Mix (CAT # k0221). The Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene (F: ATCCCATCACCATCTTCCAGGA, R: CAAATGAGCCCCAGCCTTCT) was used as a reference to normalize the expression of the target gene. One cycle of 94°C for 4 min, followed by 30 cycles of 94°C for 30 s, 59°C for 20–30 s, and 72°C for 45 s, made up the RT-PCR condition. The final extension lasted 5 min at 72°C.

Statistical analysis

The statistical analysis was carried out using SPSS version 22.0 software. An ANOVA test was utilized to compare mean values among the control group, AF without MetS, and AF with MetS groups. Bivariate Pearson correlation analysis was employed to identify any association between the expression of *APOE*, *FTO*, and *LPL* genes and the clinical parameters of AF. Stepwise multiple regression was conducted to examine the impact of the expression of *APOE*, *FTO*, and *LPL* genes on the clinical parameters of AF. The expression of genes was presented as a fold change, and relative gene expression levels were measured using comparative CT ($2\text{-}\Delta\Delta^{CT}$-). A p-value of ≤0.05 was considered significant, whereas a p-value of <0.001 was regarded as highly significant.

RESULTS

Demographic and biochemical characteristics of subjects

Table 1 presents the mean±SD values of the studied variables in the control, AF without MetS, and AF with MetS groups.

Assessment of expression of *APOE*, *FTO*, and *LPL* genes

The expression profile of the *APOE* gene was decreased by ~0.66-fold in AF without the MetS group and by ~1.59-fold in AF with the MetS group as compared to an increase by ~3.41-fold in the control group, representing a significant difference (Table 1).

The expression profile of the *FTO* gene was decreased by ~1.37 fold in AF without the MetS group and by ~1.14-fold in AF with the MetS group as compared to an increase by ~3.84-fold in the control group, also representing a significant difference (Table 1).

The expression profile of the *LPL* gene was decreased by ~0.01-fold in AF without the MetS group and by ~0.24-fold in AF with the MetS group, as compared to an increase by ~2.41-fold in the control group, representing a significant difference as well (Table 1).

Pearson correlation analysis

In the AF without MetS group, a highly significant inverse relationship was found between the expression of the *LPL* gene and BMI (body mass index; r=-0.180, p=0.006) and a positive, significant correlation with creatine kinase-MB (CK-MB; r=0.137, p=0.037). In AF with MetS group a significant, inverse relationship was found between the expression of the *FTO* gene with FBG (r=-0.168, p=0.011), the expression of the *LPL* gene (r=-0.163, p=0.013), and a positive relationship with cTnI (r=0.139, p=0.035). In addition, a significant, positive correlation was found between the expression of the *LPL* gene with systolic blood pressure (SBP; r=0.136, p=0.039), HDL-C (r=0.137, p=0.038),a negative association with heart rate (r=-0.307, p=0.001), and the expression of the *FTO* gene (r=-0.163, p=0.013) (Table 2).

Table 1. Clinical parameters of atrial fibrillation in the control group, atrial fibrillation without the metabolic syndrome group, and atrial fibrillation with the metabolic syndrome group.

Clinical parameters	Control group (n=230)	AF without the MetS group (n=230)	AF with the MetS group (n=230)
Age (years)	57.86±11.32	58.40±11.23	58.40±11.23
Gender, n (%)			
Male	108 (47)	120 (52)	106 (70)
Female	122 (53)	110 (48)	124 (54)
SBP (mmHg)	112.43±8.10	126.45±21.42	134.30±36.52**
DBP (mmHg)	85.34±5.80	83.22±13.48	93.04±18.07**
Heart rate (*bpm*)	68.08±6.79	121.45±30.60	116.80±30.83**
BMI (kg/m^2)	23.37±2.12	29.29±5.55	28.22±10.33**
FBG (mg/dL)	89.60±8.77	122.39±38.56	140.77±50.15**
WHR	0.81±0.05	0.80±0.05	0.93±0.06**
TC (mg/dL)	179.34±18.57	189.29±166.35	187.73±58.73
HDL-C (mg/dL)	56.66±12.53	39.84±23.29	10.68±1.72**
TG (mg/dL)	84.14±66.169	135.01±68.13	156.94±55.99**
LDL-C (mg/dL)	167.88±43.18	185.82±167.82	189.43±74.17
cTnI (ng/mL)	6.40±3.45	0.93±2.19	1.08±3.03**
CK-MB (U/L)	19.49±2.41	55.60±78.81	79.11±84.02**
CPK (U/L)	118.68±28.64	1136.52±4325.53	675.18±3096.93**
Expression of *APOE* gene (arbitrary units)	3.41 fold	0.66 fold	1.59 fold**
Expression of *FTO* gene (arbitrary units)	3.84 fold	1.37 fold	1.14 fold**
Expression of *LPL* gene (arbitrary units)	2.41 fold	0.01 fold	0.24 fold**

p<0.01** is considered a highly significant difference among the groups. SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute; BMI: body mass index; FBG: fasting blood glucose; WHR: waist:hip ratio; TC: total cholesterol; HDL-C: high-density lipoprotein-cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein-cholesterol; cTnI: cardiac troponin I; CK-MB: creatine kinase-MB; CPK: creatine phosphokinase; *APOE*: apolipoprotein E; FTO: fat mass and obesity-associated; *LPL*: lipoprotein lipase.

Table 2. Correlation analysis of gene expression of *APOE*, *FTO*, and *LPL* genes with the clinical parameters of atrial fibrillation in studied groups.

Clinical parameters	r-value of Exp APOE gene			r-value of Exp FTO gene			r-value of Exp LPL gene		
	Control group	AF without MetS group	AF with MetS group	Control group	AF without MetS group	AF with MetS group	Control group	AF without MetS group	AF with MetS group
Age (years)	-0.004	0.020	0.071	0.072	0.089	-0.015	0.025	0.042	-0.041
SBP (mmHg)	-0.109	-0.073	-0.013	0.043	-0.013	-0.021	-0.092	0.024	0.136*
DBP (mmHg)	-0.029	0.026	-0.022	-0.067	0.033	0.044	-0.029	0.048	-0.038
Heart rate (bpm)	0.092	0.119	0.028	-0.007	-0.025	0.097	-0.125	0.086	-0.307**
BMI (kg/m^2)	-0.075	-0.005	-0.046	-0.047	0.044	0.015	0.002	-0.180**	0.014
FBG (mg/dL)	0.014	-0.010	-0.056	-0.017	0.007	-0.168*	-0.044	-0.024	0.041
HDL-C (mg/dL)	-0.035	0.033	0.110	0.089	-0.065	0.009	-0.158*	0.047	0.137*
TG (mg/dL)	0.013	0.058	-0.034	0.032	-0.045	0.070	-0.014	0.051	-0.046
cTnI (ng/mL)	-0.252**	0.039	0.106	-0.041	-0.001	0.139*	-0.347**	-0.015	-0.001
CK-MB (U/L)	-0.099	0.028	-0.118	-0.114	-0.089	-0.029	-0.036	0.137*	0.015
CPK (U/L)	-0.102	-0.023	0.001	-0.092	-0.050	-0.039	-0.062	0.118	-0.015
Expression of APOE gene	–	–	–	0.015	0.043	0.004	0.381*	-0.037	-0.108
Expression of FTO gene	0.015	0.043	0.004	–	–	–	-0.020	-0.102	-0.163*
Expression of LPL gene	0.381**	-0.037	-0.108	0.020	-0.102	-0.163*	–	–	–

*Correlation is significant at 0.05 level (two-tailed). **Correlation is significant at 0.01 level (two-tailed).

Stepwise regression analysis in the subjects

While for AF without the MetS group, no models were computed with an expression of *APOE* and *FTO* genes as dependent variables, only one model was computed with *LPL* as a dependent variable, where BMI (β=-0.180, p=0.006) was identified as an important predictor of AF. In AF with the MetS group, no model was computed when stepwise multiple regression was employed, considering the expression of the *APOE* gene as a dependent variable. When expression of the *FTO* gene was employed as the dependent variable, three models were computed, indicating FBG (β=-0.168, p=0.011), expression of the *LPL* gene (β=-0.157, p=0.016), and cTn (β=0.153, p=0.018) as important determinants of AF subjects suffering with MetS. Whereas when expression of the *LPL* gene as a dependent variable, three models were computed with heart rate (β=-0.307, p=0.001), expression of the *FTO* gene (β=-0.135, p=0.033), and SBP (β=0.132, p=0.035) as important determinants of AF subjects suffering with MetS (Table 3).

DISCUSSION

This study aimed to investigate the expression patterns of metabolic genes (*APOE*, *FTO*, and *LPL*) in individuals with AF. Results showed that there was a deceased expression of the *APOE*, *FTO*, and *LPL* genes. This is the first study to report a negative correlation between the expression of the *FTO* gene and FBG, as well as the expression of the *LPL* gene, and a positive correlation between the expression of the *FTO* gene and cardiac troponin 1 in AF subjects with metabolic syndrome. The expression of the *LPL* gene was positively correlated with

Table 3. Stepwise linear regression of atrial fibrillation without and with metabolic syndrome groups.

Variable	B	95% CI		SE B	β	p-value	R^2	ΔR^2	Sig. F change
		LL	UL						
AF without MetS group (Expression of LPL gene)									
Model 1							0.033	0.033	0.006
Constant	0.057	0.030	0.083	0.013		0.000			
BMI	-0.001	-0.002	0.000	0.000	-0.180	0.006			
AF with MetS group (Expression of FTO gene)									
Model 1							0.028	0.028	0.011
Constant	1.941	1.301	2.582	0.325		0.000			
FBG	-0.006	-0.010	-0.001	0.002	-0.168	0.011			
Model 2							0.053	0.025	0.016
Constant	2.121	1.470	2.771	0.330		0.000			
FBG	-0.005	-0.010	-0.001	0.002	-0.162	0.013			
Exp of *LPL* gene	0.869	-1.576	-0.163	0.359	-0.157	0.016			
Model 3							0.076	0.023	0.018
Constant	2.086	1.442	2.731	0.327		0.000			
FBG	-0.006	-0.010	-0.002	0.002	-0.174	0.007			
Exp of *LPL* gene	-0.866	-1.565	-0.166	0.355	-0.158	0.016			
cTnI	0.084	0.015	0.154	0.035	0.153	0.018			
(Expression of LPL gene)									
Model 1							0.094	0.094	0.001
Constant	0.592	0.446	0.739	0.074		0.000			
Heart rate	-0.003	-0.004	-0.002	0.001	-0.307	0.000			
Model 2							0.112	0.018	0.033
Constant	0.605	0.459	0.751	0.074		0.000			
Heart rate	-0.003	-0.004	-0.002	0.001	-0.294	0.000			
Exp of *FTO* gene	-0.024	-0.047	-0.002	0.011	-0.135	0.033			
Model 3							0.129	0.017	0.035
Constant	0.458	0.259	0.658	0.101		0.000			
Heart rate	-0.003	-0.004	-0.002	0.001	-0.293	0.000			
Exp of *FTO* gene	-0.024	-0.046	-0.002	0.011	-0.132	0.035			
SBP	0.001	0.000	0.002	0.001	0.132	0.035			

Analysis of data was done using stepwise linear regression. BMI: body mass index; FBG: fasting blood glucose; *FTO*: fat mass and obesity-associated; *LPL*: lipoprotein lipase; cTnI: cardiac troponin I; Exp: expression; SBP: systolic blood pressure.

CK-MB and negatively correlated with BMI in AF subjects. In AF subjects with MetS, the expression of the *LPL* gene was negatively correlated with heart rate and *FTO* gene expression and positively correlated with SBP and HDL-C. The decreased expression of these genes might be influenced by various factors, including environmental and genetic factors.

Our study revealed a positive correlation between the expression of the *LPL* gene and SBP in AF subjects with MetS, as indicated by both correlation and stepwise analysis. This finding is consistent with previous studies that suggest the involvement of the *LPL* gene or nearby genes in BP regulation. For instance, the *LPL* gene and nearby genetic loci have been found to contribute to the variation of BP in the Chinese population. Moreover, the initial association of the *LPL* gene with diastolic blood pressure (DBP) in the Chinese population provides a valuable basis for investigating its role in other populations and races[10].

In our study, we only used cTnI, CKMB, and CPK as cardiac markers, which have not been reported before. It is also speculated that cardiac markers are linked to the expression of the *APOE* gene, the *FTO* gene, and the *LPL* gene. Cardiac Tn is an intracellular molecule that is involved in heart muscle contraction. Even in healthy individuals, the heart releases small amounts of Tn, but a high concentration of Tn in the blood is a sensitive indicator of myocardial injury[11]. The control group in our study had elevated levels of cTnI, whereas the other groups had decreased levels. Through our correlation analysis and stepwise regression analysis, we discovered a significant association between cTnI and the expression of the *FTO* gene in the group of AF subjects with MetS. Our study investigated the relationship between the expression of the *FTO* gene and cTnI, but we did not provide details on the precise mechanism underlying this association. It is possible that myocardial ischemia due to a rapid heart rate, alterations in microvascular blood flow, inflammation, and fibrosis in both the atrial and ventricular myocardium may play a role[12-16].

Our findings indicated that the levels of CK-MB were higher in the group of individuals with AF and MetS compared to those with AF subjects and the control group. The results of our correlation analysis revealed a positive association between the expression of the *LPL* gene and CK-MB levels in individuals with AF. Currently, there is no available data on the mechanism underlying the link between the expression of the *LPL* gene and CK-MB.

Our findings showed a decreased expression of the *APOE* gene in both AF subjects and those with metabolic syndrome compared to the control group. This study is the first to report on the expression of the *APOE* gene in atrial fibrillation. However, the specific mechanism of the gene's involvement in AF has not yet been determined. Previous studies have suggested that *APOE* polymorphisms may affect the occurrence of AF and that the *APOE*4 phenotype may be sensitive to AF[17].

Our study showed a reduction in the expression of the *FTO* gene in both AF with MetS and without MetS groups when compared to the control group. However, it is still unclear how diabetes and obesity impact *FTO* gene expression in the liver. Studies have shown conflicting results, with some suggesting that obese mice with high blood sugar and insulin levels have lower levels of *FTO* mRNA in the liver due to the harmful effects of these conditions[18,19]. Carnevali et al. have concluded that a lack of *FTO* in mice results in an imbalance of autonomic neural modulation of the heart's function towards a sympathetic direction, and it could lead to potentially proarrhythmic remodeling of the heart's electrical and structural properties[20].

A present study found decreased expression of the *LPL* gene in AF with the MetS group and AF without MetS as compared to a control group. Overall, these studies suggest that the mechanisms behind decreased *LPL* gene expression in humans are complex and might be involved in multiple regulatory pathways, including transcriptional regulation, epigenetic modifications, and post-transcriptional regulation. *LPL* gene expression can also be regulated at the post-transcriptional level through various mechanisms such as mRNA stability, splicing, and translation efficiency. For example, certain microRNAs might inhibit *LPL* expression by targeting the *LPL* mRNA for degradation[21].

The current study has some limitations, as it only focuses on a few metabolic genes and does not explore the potential mechanisms underlying the association between the expression of *APOE*, *FTO*, and *LPL* genes and AF in subjects with MetS. Thus, further studies are needed to better understand the molecular mechanisms that underlie the relationship between these genes and AF in patients with MetS.

CONCLUSION

This study concludes that there is decreased expression of the *APOE*, *FTO*, and *LPL* genes in AF subjects and AF subjects suffering from MetS as compared to the control group. The decreased expression of these genes might be influenced by various factors, including environmental and genetic factors. Decreased expression of the *APOE*, *FTO*, and *LPL* genes can have a significant impact on health and disease risk, and further research is needed to fully understand the mechanisms behind these associations. It is suggested that therapeutic intervention targeting the genetic and molecular mechanisms of

atrial arrhythmia might help prevent cardiovascular events by reducing the incidence of atrial arrhythmias and their associated complications.

ETHICAL APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethical Review Committee of Lahore College for Women University, Lahore, and was approved by the ethical review committee (ref. no.: RTPGME-Research-179) of Punjab Institute of Cardiology, Lahore, Pakistan.

CONSENT TO PARTICIPATE

Prior to their participation, all of the participants gave their informed consent, and the data were either pseudo-anonymized or anonymized, depending on the circumstance.

AUTHOR CONTRIBUTIONS

SR: Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. SS: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – review & editing. SN: Data curation, Resources. DP: Writing – review & editing. AK: Writing – review & editing.

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ORIGINAL ARTICLE

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Expression of sirtuins 1 in placenta, umbilical cord, and maternal serum of patients diagnosed with placenta accreta spectrum

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SUMMARY

OBJECTIVE: Placenta accreta spectrum (PAS) is defined as the attachment of the placenta to the uterine wall in varying degrees. However, the studies have explored that the underlying molecular mechanisms of the PAS are very limited. Sirtuins 1 (SIRT1) is associated with placental development by controlling trophoblast cell invasion and remodeling of spiral arteries. We aimed to determine the expression level of SIRT1 in placentas, and maternal and umbilical cord serum of patients with PAS.

METHODS: In total, 30 individuals in control, 20 patients in the placenta previa group, and 30 patients in the PAS group were included in this study. The expression levels of SIRT1 in the placentas were determined by Western blot and immunohistochemistry. Serum levels of SIRT1 in maternal and umbilical cord blood were determined by ELISA.

RESULTS: SIRT1 was significantly lower in placentas of the PAS. However, maternal and umbilical cord serum samples were not significantly different between groups.

CONCLUSION: SIRT1 may play an important role in the pathogenesis of the PAS.

KEYWORDS: Umbilical cord. Serum. Placenta accreta. Sirtuin 1.

INTRODUCTION

The placenta accreta spectrum (PAS) refers to the excessive trophoblast invasion of part or all of the placenta into the uterine wall's myometrium[1]. It is histopathologically categorized into placenta accreta, placenta increta, and placenta percreta based on the degree of attachment to the myometrium[2]. The frequency of PAS has increased about eight times since the 1970s[3], and the overall proportion of PAS in recent times had indeed reached 0.91%[4]. PAS is associated with significant maternal morbidity because the post-delivery placenta of the fetus does not spontaneously separate and can lead to severe hemorrhage, frequently leading to an exigency hysterectomy, blood transfusion, and critical care unit admission[5]. Uterine scar, cesarean history, and presence of placenta previa (PP) are the main clinical risk factors[2]. Accreta placentation is the consequence of implantation and placental development in a uterine scar (mainly post C-section in the lower segment) where the myometrium has been replaced by scar tissue and is often extremely thin with loss of the decidua, junctional zone, and spiral artery circulation. Hence, it is recently defined as a disorder of defective decidua and uterine scar dehiscence, and not as a disorder of destructive trophoblast invasion[6]. However, the molecular mechanism underlying PAS is not fully understood.

Sirtuins (SIRT) are a highly conserved NAD^+-dependent histone deacetylase family and regulate different important cellular pathways such as DNA repair, transcriptional regulation, metabolism, and aging[7,8]. They also have complex roles in either promoting or suppressing epithelial-mesenchymal transition (EMT), and their functional features may largely depend on the cellular context[8]. Sirtuins 1 (SIRT1) is a member of the sirtuins family. It is extensively expressed in the human and mouse placenta and decreased following labor[9]. In the last trimester of pregnancy, the SIRT1 level of the trophoblasts of both the patients with preeclampsia[10], and in the placenta of the obese mice is decreased[11]. It is also downregulated in advanced maternal age pregnancies[12]. In addition, it has been shown that SIRT1 may be related to placental development by controlling EVT invasion and spiral artery remodeling through modulation of

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EMT[13]. However, there are no studies on the role of SIRT1 in PAS. Therefore, in this study, we aimed to investigate the expression of SIRT1 in placenta, maternal serum, and umbilical cord serum samples of PAS patients.

METHODS

Study design and population

The study includes 30 individuals in control, 20 patients in the PP group, and 30 patients in the PAS group. Patients who applied to the Dicle University Faculty of Medicine, Department of Obstetrics and Gynecology, were included in our study. This study protocol was approved by the Inonu University, Clinical Research Ethics Committee (2020/51), and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all the participants. Three groups of patients were formed. The first group consists of patients with no history of cesarean section, uterine intervention, or uterine surgery but who were diagnosed with PP without invasion were included, and this group was called the PP group. In the second group, patients who had at least one previous cesarean section and had PP and invasion were included, and this group was called the PAS group. The third group was the control group, and those with similar demographic features with PP and PAS groups and with no known disease were included. The patients in the control group were formed from patients who delivered by cesarean section. Patients with PP marginalis or inferior placenta, those who underwent surgery before the 24th week of pregnancy, individuals under the age of 18 years, multiple pregnancies, patients with pregnancy complications in the past, thyroid dysfunction, hypertension, epilepsy, those with gestational diabetes mellitus, and those with type 1 and type 2 diabetes mellitus were not included in the study. For preoperative diagnosis, abdominal, transvaginal, and Doppler ultrasonography were used. PAS or PP was defined according to current FIGO consensus guidelines[5]. PAS was diagnosed with the pathology results. Age, number of pregnancies, and gestational weeks of the patients were compatible with the control group.

Collecting placental and serum samples

Placental tissues containing villous and extravillous trophoblasts, the fibrinoid layer, and the basal plate layer were obtained in all groups. They were collected after cesarean section and flash frozen using liquid nitrogen and stored at -80° until Western blot analysis. For ELISA, maternal peripheral venous blood was drawn before the administration of anesthesia in patients who underwent general anesthesia and before spinal anesthesia in patients who underwent spinal surgery. Umbilical cord blood was taken from the umbilical artery after the umbilical cord was clamped and cut.

Immunohistochemistry

Placenta samples from the maternal region were immersed in a 10% neutral formaldehyde solution. About 4–6 m paraffin slices were cut according to the standard paraffin process. The antigen retrieval procedure was carried out twice in citrate buffer solution (pH: 6.0). Endogenous peroxidase activity was inhibited in a 10% hydrogen peroxide solution for 7 min. Before the application of primary antibodies overnight, Ultra V block was applied for 8 min. Then, a secondary antibody was used. The sections were exposed to streptavidin peroxidase for 20 min. The chromogen utilized was diaminobenzidine. The slides were mounted following counterstaining with hematoxylin, washing in tap water for 3 min, and mounting for 2–3 min.

Western blot analysis

The placenta was ground into a fine powder in a chilled mortar in the presence of liquid nitrogen. Then, cold RIPA buffer containing protease-phosphatase inhibitor cocktail and nuclease was added to milled sample. Also, 20 μg of protein were separated by 10% SDS-PAGE gel and transferred into polyvinyl difluoride membrane (Santa Cruz). Membranes were blocked with 5% skim milk/PBS-T, prior to overnight incubation with anti-SIRT1 (Biolegend) and anti-β-actin (Biolegend) antibodies in 2% skim milk/PBS-T. A suitable HRP-conjugated secondary antibody (Advansa) was utilized to visualize the specific bands. β-Actin was used as a loading control.

ELISA

The whole blood was gathered and blood was left to clot at 20-25°C for 15–30 min for ELISA. The clot was skimmed by centrifuging at 1,000–2,000 x g for 10 min at +4°C. Separated serums were stored at -80°C. Serum levels of SIRT1 were determined by a human ELISA according to the manufacturer's instructions (SunRed bio, Shanghai, PR China).

Statistical methods

The statistical analyses were performed using SPSS statistical programming. Data are presented as mean±sd. Normally distributed data in the comparisons between multiple groups were analyzed with a one-way ANOVA. p-value <0.05 was considered to be statistically significant.

RESULTS

Protein levels of sirtuins 1 in maternal and umbilical cord serums

A total of 30 individuals in control (30 maternal and 30 umbilical cord serums), 20 patients in the PP group (20 maternal and 20 umbilical cord serums), and 30 patients in the PAS group (30 maternal and 30 umbilical cord serums) were included in this study. Our result showed that there was no statistical difference between SIRT1 levels in both maternal serum samples of control (n=30, mean: 3.8 ng/mL,±sd: 2.0), PP (n=20, mean: 4.4 ng/mL,±sd: 0.6), and PAS (n=30, mean: 4.4 ng/mL,±sd: 3.0) (p=0.299) (Table 1) and umbilical cord serum samples of control (n=30, mean: 6.3 ng/mL,± sd: 3.5), PP (n=20, mean: 6.1 ng/mL,±sd: 2.2), and PAS (n=30, mean: 8.0 ng/mL, ±sd: 4.7) (p=0.135) (Table 1).

Total protein levels of sirtuins 1 in placenta samples

The presence of SIRT1 was examined by Western blot analysis in the placental tissues of the three groups via using anti-SIRT1 primary antibodies. Our result showed that SIRT1 expression levels were significantly decreased in PAS patients compared to the control and PP groups (*p<0.037, p<0.05) (Figure 1).

Sirtuins 1 localization in placenta samples

It was observed that SIRT1 expression was weak positive in cytotrophoblast of the control, PP, and PAS groups (Figures 2A, B, C, respectively) in immunohistochemically stained sections. It was also observed that SIRT1 expression was increased specifically in fetal capillary endothelium and syncytiotrophoblast cells in the PAS group but weak positive in villus mesenchyme (Figure 2C). In addition, there was positive expression of SIRT1 in both syncytiotrophoblast and villus mesenchyme but weak positive expression in fetal capillary endothelium of the PP group (Figure 2B). In the control group, weak positive expression in syncytiotrophoblast cells, positive expression in villus mesenchyme, and negative expression in fetal capillary endothelium were observed (Figure 2A).

DISCUSSION

The increasing number of cases, blood losses, and maternal mortality rates related to PAS reveal the need for urgent diagnosis and treatment methods for PAS. Although uterine scar, cesarean history, and presence of PP are among the clinical risk factors[2], studies on molecular mechanisms responsible for

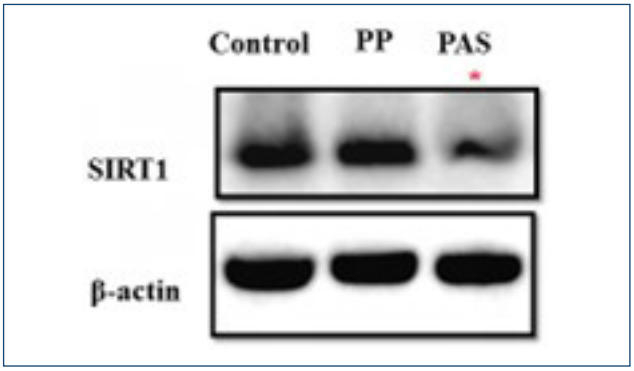

Figure 1. Expression level of sirtuins 1 in placentas of control, placenta previa, and placenta accreta spectrum. Protein levels of sirtuins 1 were determined by Western blotting in the control (n=10), placenta previa (n=10), and placenta accreta spectrum (n=10) groups. β-Actin was used as a loading control. The image indicates a single representative example of experiments (*p<0.05).

Table 1. Demographic characteristics, and maternal and fetal serum levels of sirtuins 1 in control, placenta previa, and placenta accreta spectrum groups.

	Control	PP	PAS	p-value
Age (years)	33.3±4.8	33.4±6.0	33.9±4.9	0.883
Gravidity	4.7±1.9	3.2±2.3	5±1.8	*0.009
Parity	3.2±1.4	1.45±1.5	3.3±1.7	**0.0002
Previous cesarean section	2.7±1.1	0	2.3±1.0	–
Birth weight (g)	3076±420	2954±574	2788±430	0.062
Interpregnancy interval (months)				
≤9	2	0	1	
>9	28	20	29	
Birth week	37.2±1.2	36.5±2.4	36.3±1.2	0.106
Maternal serum level of SIRT1 (ng/mL)	3.8±2.0	4.4±0.6	4.4±3.0	0.299
Umbilical cord serum level of SIRT1 (ng/mL)	6.3±3.5	6.1±2.2	6.3±3.5	0.135

One-way ANOVA was used for comparison of the three groups. *p<0.05, **p<0.01.

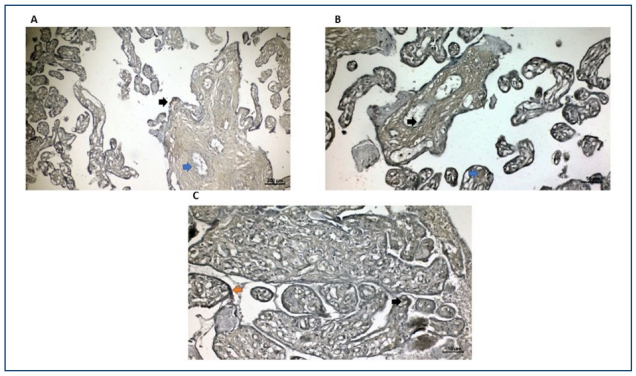

Figure 2. SIRT-1 immunohistochemical staining in the placenta structure of the control (A), placenta previa (B), and placenta accreta spectrum (C) groups. (A) Weakly positive SIRT-1 expression in syncytiotrophoblast cells (black arrow) and negative SIRT-1 expression in fetal capillary endothelium (blue arrow) were observed (bar: 200 µm). (B) Weakly positive SIRT-1 expression in fetal capillary endothelium (black arrow) and positive SIRT-1 expression in villus mesenchyme (blue arrow) were observed (bar: 50 µm). (C) Positive SIRT-1 expression in fetal capillary endothelium (black arrow) and positive SIRT-1 expression in syncytiotrophoblast cells (orange arrow) were observed (bar: 50 µm).

pathophysiology of PAS are very limited. A few studies have shown that EMT is effective in PAS[14]. Although negative regulation of cell migration was downregulated[15] and EMT markers are high in PAS[16-18], there are no studies on the role of SIRT1, which has proven efficacy in cell migration and EMT, in the pathogenesis of the disease. Therefore, we aimed to investigate SIRT1 expression level in PAS.

EMT is a process of molecular and phenotypic epithelial cell replacement that supports invasiveness, resulting in the transformation of immobile epithelial cells into migrant mesenchymal cells[16]. It is activated by epigenetic regulators and shows that abnormally aggressive EMT that continues throughout pregnancy plays a significant role in PAS development[14]. Duzyj et al. observed the co-expression of cytokeratin-7 and vimentin in the PAS group that implies EVTs show their EMT characteristics in the third trimester[16]. Increasing expressions of matrix metalloproteinases (MMP-9 and MMP-2), which play an important role in the penetration of trophoblast cells, were found in samples with PAS[17]. The best characterized event occurring in EMT is the loss of the basic cell–cell adhesion protein E-cadherin. In accretated placenta, the expression of E-cadherin was lower in the chorionic villi of the invasive part, whereas the expression of Snail and TGF-β in the decidual cells of the invasive part increased[19]. In another study, the expression level of ZEB1, the EMT promoter, was found to be high in PAS[9]. It has also shown that methyl-CpG-binding domain protein 2 (MeCP2) regulated by SIRT1, podocin (PODN), and apolipoprotein D (ApoD), which participate in negative regulation of cell migration, were downregulated at the mRNA and protein levels in the PAS group[15].

SIRT1 governs a variety of cellular processes. In particular, it has been shown to affect epithelial plasticity by reprogramming transcription at the epithelial–mesenchymal transition, leading to invasion and metastasis. SIRT1 controls trophoblast cell invasion. It has been found that SIRT1 knockdown induces a more invasive phenotype in Swan 71 cells accompanied by reduction in proliferation and enhancement of MMP-2 and MMP-9[13], which overexpressed in PAS, thereby promoting invasion and migration. Moreover, increased invasion resulted from the induction of EMT markers such as N-cadherin, Snail, and ZEB1 and activation of Akt /p38MAPK signaling pathways[13] as shown in PAS[18]. In addition, a recent study showed that heat shock 70 kDa protein 4 (HSPA4) regulated by SIRT1[19] is elevated in PAS[20].

CONCLUSION

Reduced expression of the SIRT1 in placenta of PAS may be effective in the pathophysiology of PAS. However, further studies need to be conducted to clarify the role of SIRT1 in PAS.

AUTHORS' CONTRIBUTIONS

IIT: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **SG:** Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. **MSI:** Data curation, Resources, Writing – original draft. **DCD:** Resources, Writing – review & editing. **FMF:** Data curation, Resources. **ED:** Methodology, Resources.

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ORIGINAL ARTICLE

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Comparison of obstetric and perinatal complications in intracytoplasmic sperm injection cycles with autologous oocytes and donated oocytes

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SUMMARY

OBJECTIVE: The aim of this study was to compare the obstetric and perinatal complications in women who became pregnant with autologous oocytes and those who received donated oocytes (DO) in intracytoplasmic sperm injection cycles (ICSI).

METHODS: A retrospective cohort study was carried out by collecting data from medical records between 2019 and 2022. Only patients who underwent ICSI in an induced cycle using their own or freshly DO, with male infertility factor and tubal factor, were included.

RESULTS: A total of 120 patients were assessed, comprising 51 cases utilizing their own oocytes (control group) and 69 cases employing DO (study group). Patients receiving DO (n=69) exhibited a significantly higher mean age compared to those utilizing their own oocytes (n=51) (41.96±2.16 vs 38.54±1.42 years, p<0.001). There was no significant association between the source of oocytes and gestational age at delivery (p=0.296), birth weight (p=0.836), admission to neonatal intensive care unit (ICU) (p=0.120), or maternal admission to adult ICU (p=0.767). Additionally, the origin of oocytes did not demonstrate any significant association with the risk of pre-eclampsia (p=0.357), gestational diabetes mellitus (p=0.187), premature rupture of membranes (p=0.996), uterine atony (p=0.996), placenta previa (p=0.393), oligohydramnios (p=0.393), or gestational hypertension (p=0.393)."

CONCLUSION: An increase in obstetric and perinatal complications was not observed in pregnancies with DO compared to pregnancies with autologous oocytes in women undergoing ICSI without prior comorbidities. Further studies with larger sample sizes are required to validate our findings.

KEYWORDS: ICSI. Oocyte donation. Pregnancy outcomes. Neonatal intensive care units.

INTRODUCTION

According to the World Health Organization (WHO), infertility is defined as the failure of a couple to achieve pregnancy after 1 year of consistent, unprotected sexual intercourse. Globally, infertility impacts around 17.5% of couples in their reproductive years, as reported by the WHO. It is noteworthy that infertility can stem from factors originating from both males and females[1-3].

Even with the assisted reproductive techniques (ARTs) currently available in reproductive medicine, it remains challenging to counteract the decline in fertility linked to maternal age, particularly beyond the age of 35 years[1]. Nevertheless, in 1% of women, premature ovarian failure (POF) occurs, characterized by disrupted menstrual cycles, elevated serum levels of follicle-stimulating hormone, and diminished anti-Müllerian hormone prior to the age of 40 years. POF can arise from various factors, including genetic predisposition, environmental influences, infections, autoimmune disorders, as well as chemotherapy and ovarian surgery, exerting a significant impact on fertility even among younger women[4].

With the goal of increasing the chances of pregnancy for women with diminished ovarian reserve or even those

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experiencing POF, the use of oocytes donated by younger donors for women with reduced ovarian reserve or POF began in the 1980s. Consequently, donated oocytes (DO) have emerged as a viable alternative to autologous oocyte use in ART, yielding good live birth rates in this group[5]. The pregnancy rate among women who receive DO remains more stable, even with advanced maternal age, *compared to women who use their own oocytes*, where the decline in live birth rate with age is much greater[6]. Overall, the live birth rate with DO is equivalent to 19.3% of all live births with ART[7].

In pregnancies involving DO, the fetus is completely allogeneic, that is, it has a completely distinct genetic composition from the mother who received the oocyte. This is because the fetus inherits genes from both the father and the oocyte donor. Conversely, in spontaneous pregnancies or pregnancies with the mother's own oocyte, the fetus is semi-allogenic to the pregnant woman. During pregnancies with DO, the maternal immune system requires additional adaptations to support the allogeneic nature of the pregnancy[8]. It is believed that the genetic condition of the fetus conceived through DO may trigger immunological responses and placental alterations in the recipient[9]. These alterations can affect the presence and functionality of macrophages, depending on the type of pregnancy, whether spontaneous, ART with or without DO[10].

There are several reports comparing pregnancies achieved through ART using autologous oocytes versus those using DO. It appears that DO is independently associated with high rates of placental abnormalities, such as pre-eclampsia[11]. When DO was added to the ART, the risk of pre-eclampsia ranged from 4 to 7.94 times higher than in spontaneous pregnancies[12,13].

Previous research on the obstetric and perinatal risks associated with DO in Brazilian patients was lacking. Conducting a study of these risks within Brazilian patients is imperative given the increasing importance and use of this technique in reproductive medicine in Brazil. Identifying and evaluating these risks is crucial for improving regulations and clinical guidelines related to DO. Our hypothesis is that Brazilian patients who have used DO have a higher risk of adverse perinatal outcomes compared to the group of women who use their own oocytes in ICSI cycles.

The aim of this study was to compare the obstetric and perinatal complications of women who became pregnant with autologous oocytes with those who received DO in ICSI cycles.

METHODS

A retrospective cohort study was carried out by collecting data from patients at the Profertil Reproductive Medicine Clinic in Niterói, RJ, southeast of Brazil from medical records between 2019 and 2022. This study was approved by the Ethic Committee of Fluminense Federal University (CAAE: 65041422.8.0000.5243).

Only patients who underwent ICSI in an induced cycle using their own or freshly DO, with male infertility factor and tubal factor, were included. Pregnant women with twin pregnancies, regardless of the origin of the oocyte, and pregnant women with pre-existing comorbidities that could negatively impact pregnancy (such as diabetes mellitus, chronic hypertension, and benign or malignant degenerative diseases) were excluded.

A total of 120 patients were evaluated, comprising 51 cases with own oocytes (control group) and 69 cases with DO (study group). Obstetric information (gestational age, type of delivery, presence of diseases during pregnancy, placental abnormalities, and obstetric complications) and perinatal information [birth weight and neonatal intensive care unit ICU admission] were obtained.

The data were transferred to an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and Prisma GraphPad version 7.0 (GraphPad Software, San Diego, CA, USA). Shapiro-Wilk normality tests were used to analyze whether the values were Gaussian distributed. Parametrically distributed values were presented as medians and standard error (SE) or standard deviation (SD). To carry out the analyses, the following variables were initially considered dependent variables: age, ethnicity, type of delivery, gestational age at delivery, race, obstetric and perinatal complications, birth weight, and admission to neonatal and maternal ICU.

Given that we did not observe a normal distribution of ages between the groups, the age factor was then included in the model as an independent variable due to its physiological importance. Women under 40 years of age use their own oocytes more often and women over 40 years of age use DO. Therefore, treatments (own and DO) and age (<40 years and ≥40 years) were considered independent variables. Two-way ANOVA (with Tukey's post-test) and the Kruskal-Wallis test (with Dunn's post-test) were carried out to compare dependent variables between the treatment groups and age. Categorical variables were described as absolute and percentage frequencies and are presented in tables. Binary logistic regression was used to calculate the odds ratio (OR) for adverse pregnancy and neonatal outcomes. Stepwise binary logistic regression with maternal age as a covariate was used to adjust the model and calculate the adjusted OR. The level of significance for all tests was $p<0.05$.

RESULTS

From April 2019 to September 2022, 120 patients undergoing ICSI were evaluated. The final statistical analysis included 51 cases of own oocytes (control group) and 69 cases of DO (study group).

Patients who received DO were significantly older than those who received their own oocytes (41.96±2.16 vs 38.54±1.42 years, p<0.001). There was no significant association between the origin of the oocyte and gestational age at delivery (p=0.296) or birth weight (p=0.836). There was also no significant association between the origin of the oocyte and white (p=0.119), mixed (p=0.818), Black (p=0.071), vaginal delivery (p=0.399), cesarean section (p=0.399), presence of obstetric and perinatal complications (p=0.366), admission to neonatal ICU (p=0.120), and maternal admission to adult ICU (p=0.767) (Table 1).

The origin of the oocyte did not show association and no significant increase in the risk of pre-eclampsia (p=0.357), gestational diabetes mellitus (p=0.187), premature rupture of ovular membranes (p=0. 996), uterine atony (p=0.996), placenta previa (p=0.393), oligohydramnios (p=0.393), and gestational hypertension (p=0.393), even after maternal age was included as a covariate in the model (Table 2).

DISCUSSION

This study examined obstetric and perinatal outcomes among Brazilian pregnant women who underwent ICSI using either autologous or DO. In contrast to most studies, an increase in obstetric and perinatal complications was not observed in pregnancies with DO compared to pregnancies with autologous oocytes.

DO is a widely employed ART technique, particularly in cases of female infertility related to oocyte quality due to advanced maternal age, POF, early menopause, or even treatments or medical conditions affecting ovarian reserve, such as chemotherapy and genetic disorders. Currently, DO is utilized in at least 7% of all in vitro fertilization (IVF/ICSI) cycles in Europe. However, this number of cycles is likely to be higher, as not all countries report their DO data[8]. DO from younger donors exhibit a significantly higher IVF/ICSI success rate compared to autologous oocytes from women over 40 years of age. This underscores the critical role of oocyte quality in successful fertilization and subsequent embryo development[2,7].

In this study, 120 patients were evaluated, 51 cases of own oocytes (control group) and 69 cases of DO (study group). The mean maternal age was higher in the DO group (41.96 years) than in the control group (38.54 years). While only 33.3% of the controls were over 40 years of age, 82.6% of the DO group were over 40 years of age. As has been reported in the literature, DO patients are usually older than those who use their own oocytes, as the procedure is indicated for cases of advanced maternal age[8,14].

Studies assessing the impact of donor ethnicity have indicated that Black race appears as a risk factor for unsuccessful pregnancy outcomes following DO, in contrast to the higher likelihood of pregnancy observed in White recipient women. According to Bodri et al.[15], the explanation for this is that Black women have more tubal infertility, uterine myomas, and a

Table 1. Maternal characteristics and perinatal outcomes of both included groups.

	Donated oocytes (N=69)	Own oocytes (N=51)	p
Age (years ± SD)	41.96 ± 2.16	38.54 ± 1.42	<0.001¥
Ethnicity			
White	59.4% (41/69)	74.5% (38/51)	0.119∂
Mixed	20.3% (14/69)	17.6% (9/51)	0.816∂
Black	20.3% (14/69)	7.8% (4/51)	0.072∂
Type of delivery			
Vaginal	2.9% (2/69)	7.8% (4/51)	0.399∂
Cesarean section	97.1% (67/69)	92.2% (47/51)	0.399∂
Gestational age at delivery (weeks±SE)	37.8±0.38	37.69 ± 0.35	0.296¥
Obstetric and perinatal complications	43.5% (30/69)	35.3% (18/51)	0.366∂
Birth weight (g±SE)	3182.68±98.73	3036.43 ± 92.33	0.836¥
Admission to neonatal ICU	8.7% (6/69)	2.0% (1/51)	0.120∂
Maternal ICU admission	7.2% (5/69)	5.9% (3/51)	0.767∂

ICU: intensive care unit; SE: standard error; SD: standard deviation. Mann-Whitney: median (minimum-maximum) ¥, Chi-squared: % (n/N) ∂. p<0.05.

Table 2. Association between oocyte type and obstetric and perinatal complications.

Obstetric and perinatal complications	Donated oocytes (N=69)	Own oocytes (N=51)	OR (95%CI)	aOR (95%CI)
Preeclampsia	17.4% (12/69)	15.5% (8/51)	1.32 (0.42–3.06), p>0.999	1.74 (0.53–5.65), p=0.357
Gestational diabetes mellitus	10.1% (7/69)	3.9% (2/51)	2.76 (0.56–13.55), p=0.298	3.51 (0.54–22.69), p=0.187
Premature rupture of ovular membranes	1.4% (1/69)	2.0% (1/51)	0.73 (0.03–14.23), p>0.999	0.00 (0.0-infinite), p=0.996
Uterine atony	1.4% (1/69)	2.0% (1/51)	0.73 (0.03–14.23), p>0.999	0.00 (0.0-infinite), p=0.996
Placenta previa	1.4% (1/69)	3.9% (2/51)	0.36 (0.02–3.19), p=0.574	0.22 (0.008–6.72), p=0.393
Breech presentation	1.4% (1/69)	0.0% (0/51)	*	
Polycystic kidneys	1.4% (1/69)	0.0% (0/51)	*	
Oligohydramnios	1.4% (1/69)	3.9% (2/51)	0.36 (0.02–3.19), p=0.574	0.22 (0.008–6.72), p=0.393
Gestational hypertension	1.4% (1/69)	3.9% (2/51)	0.36 (0.02–3.19), p=0.574	0.22 (0.008–6.72), p=0.393
Eclampsia	1.4% (1/69)	0.0% (0/51)	*	
HELLP syndrome	0.0% (0/69)	0.0% (0/51)	*	
Polyhydramnios	1.4% (1/69)	0.0% (0/51)	*	
Chorioamnionitis	1.4% (1/69)	0.0% (0/51)	*	
Respiratory distress	1.4% (1/69)	0.0% (0/51)	*	

Binary logistic regression; OR: odds ratio; aOR: odds ratio adjusted for maternal age; CI: confidence interval; Chi-square: % (n/N); *It was not possible to use a statistical test due to the absence of at least one case in each group. p<0.05.

higher body mass index than other races. In addition, a retrospective study by Liu et al.[16] described that the Black recipient who received an oocyte from a Black donor appeared to have a lower likelihood of achieving a live birth compared to White donor–recipient pair. In this study, both the DO and control groups were ethnically homogeneous, with no statistically significant difference observed. Furthermore, the absence of Black recipients who did not conceive or did not carry the pregnancy to term with a live birth might explain the lack of racial disparity between the groups.

There are several reports on the prevalence of cesarean section in cases of DO compared to pregnancies with autologous oocytes, showing at least twice the risk of occurrence, regardless of whether the embryo transfer was fresh or frozen. While the cesarean section rate in our study ranged from 92 to 97%, it is notably higher than the average rate reported in the literature, which stands at around 45%[17,18]. The exception was a German study in which the frequency of cesarean section in the group of women with oocyte receptors in a singleton pregnancy was 83.9%[19]. The high cesarean section rates observed in our study are consistent with the high rates observed in Brazil, especially in private services[20].

In our study, despite observing a higher numerical frequency of preterm births in women with DO, no statistically significant relationship was found between preterm births and oocyte origin. In the study by Elenis et al.[21], there was also no statistically significant relationship between prematurity and DO, with only a trend toward prematurity in the DO group.

In this study, pregnant women>40 years of age had more obstetric complications compared to pregnant women<40 years of age, and DO patients also exhibited a higher incidence of obstetric complications compared to pregnant women with their own oocytes. However, no statistically significant difference was observed, possibly due to the limited number of patients evaluated. A higher incidence of obstetric and perinatal complications among patients receiving DO has been previously described in the literature[17,18]. Obstetric complications are known to be more frequent in older pregnant women[14,22], particularly when DO is performed after the age of 45 years[14].

In a meta-analysis of 23 studies, DO was associated with a higher risk of hypertensive disorders of pregnancy, pre-eclampsia, severe pre-eclampsia, and pregnancy-induced hypertension. The meta-analysis also found a 1.27 times higher risk of gestational diabetes mellitus in DO patients[5]. In a retrospective cohort study that compared pregnant women from DO (n=78) and pregnant women with own oocytes (n=112), the authors observed that pregnancy-induced hypertension and gestational diabetes mellitus were significantly higher in DO patients[23].

In this study, the newborns of DO patients had a relatively higher mean birth weight than the control group; however, the difference was not significant. In the study of Rodriguez-Wallberg et al.[24], as in our study, no difference in birth weight was observed between DO and ART patients. A meta-analysis

of 23 studies also found no increased risk of low birth weight when adjusting for the presence of pre-eclampsia[5].

Obstetric and perinatal complications are known to increase the likelihood of maternal and neonatal ICU use during the postpartum period. In this study, DO patients had a numerically higher rate of ICU admission for both neonates and mothers, although there was no statistical significance. Malchau et al.[25] compared patients who underwent DO with IVF or ICSI and spontaneous pregnancy and found a statistically significant difference in terms of longer ICU stay in DO patients compared to patients who underwent ICSI with their own oocyte or spontaneous pregnancy. On the contrary, patients who underwent IVF with their own oocytes had the same length of stay as DO patients.

A limitation of this study was the sample size, particularly in the control group, attributed to the difficulty in recruiting patients over the age of 40 years who utilized their own oocytes in an ICSI procedure. Nevertheless, this study marks the first exploration in Brazil of obstetric and perinatal data among patients who underwent DO.

Thus, according to our data, DO can be considered a safe alternative for patients with low ovarian reserve due to advanced age or other factors. However, it is important to note that there may be a higher risk of DO in certain aspects, especially in patients over the age of 40 years, with pre-existing chronic diseases and with poor access to prenatal care. Thus, obstetric follow-up needs to be individualized with strategies to reduce the risk of complications, with special attention to hypertensive disorders during pregnancy.

CONCLUSION

No increase in obstetric and perinatal complications was observed in DO pregnancies compared with autologous oocyte pregnancies in women undergoing ICSI without prior comorbidities. Further studies with larger sample sizes are needed to validate our findings.

AUTHORS' CONTRIBUTIONS

VCDH: Data curation, Investigation. **RAMS:** Supervision. **MAPL:** Data curation, Investigation. **RaDH:** Methodology. **LGLM:** Resources. **ABP:** Formal Analysis. **EAJ:** Writing – original draft. **RDH**: Data curation, Investigation, Validation.

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ORIGINAL ARTICLE

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The usefulness of anti-HCV signal to cut-off ratio in predicting hepatitis C viremia and the effect of genotype differences on signal to cut-off ratio

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SUMMARY

OBJECTIVE: In the hepatitis C virus (HCV) diagnostic algorithm, an anti-HCV screening test is recommended first. In countries with low HCV prevalence, anti-HCV testing can often give false-positive results. This may lead to unnecessary retesting, increased costs, and psychological stress for patients.

METHODS: In this study, the most appropriate S/Co (signal-cutoff) value to predict HCV viremia in anti-HCV test(+) individuals was determined, and the effect of genotype differences was evaluated. Of the 96,515 anti-HCV tests performed between 2020 and 2023, 934 were reactive. A total of 332 retests and 65 patients without HCV-ribonucleic acid (RNA) analysis were excluded. Demographic data were calculated for 537 patients, and 130 patients were included in the study.

RESULTS: The average age of 537 patients was 55±18 years, and 57.1% were women. The anti-HCV positivity rate was 0.62% (602/96,515), and the actual anti-HCV positivity rate was 0.13% (130/96,515). Anti-HCV levels were higher in HCV-RNA(+) patients than in HCV-RNA-negative individuals ($p<0.0001$) (Table 1). Receiver operating characteristic curve analysis identified the optimal S/Co value to be 10.86 to identify true positive cases. Sensitivity was 96.1%, specificity was 61.2%, positive predictive value (PPV) was 44.2%, and negative predictive value (NPV) was 98% (Figure 2). A total of 107 (82.3%) of the patients were identified as GT1, and the most common subtype was GT1b (n=100).

CONCLUSION: If anti-HCV S/Co is ≥10.86, direct HCV RNA testing may be recommended; However, the possibility of false positivity should be considered in patients with a S/Co value below 10.86.

KEYWORDS: Hepatitis C virus. Genotype. Hemodialysis. Ribonucleic acid.

INTRODUCTION

Hepatitis C virus (HCV) is a virus that can lead to acute and chronic hepatitis[1]. In the HCV diagnosis algorithm for HCV, the process starts with an anti-HCV screening test, and if the result is reactive, an HCV-ribonucleic acid (RNA) test is recommended for a definitive diagnosis[2,3]. As a reactivity threshold in anti-HCV tests, a value of S/Co≥1 is considered positive based on the manufacturer's recommendation[4]. In countries with low HCV prevalence, anti-HCV tests often give false positive results and slightly exceed the cutoff value[5]. Obtaining a false-positive result in anti-HCV testing may lead to unnecessary test repetitions in laboratories, increased costs due to the need for confirmatory testing, and psychological stress for patients[4].

In this study, the primary objectives were to determine the most appropriate S/Co value for predicting HCV viremia in individuals with positive anti-HCV results and to evaluate the impact of HCV genotype differences on this prediction.

METHODS

This study was conducted with the approval of the Health Sciences University Hamidiye Clinical Research Ethics Committee (15.02.2023/14772).

This is a retrospective descriptive study comparing the results of anti-HCV, HCV-RNA, and HCV genotype tests requested at Sultan 2. Abdulhamid Han Training and Research Hospital

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between 2020 and 2023. The study included patients aged ≥18 years with anti-HCV(+) results and simultaneous testing of HCV-RNA. Patients under the age of 18 years with an anti-HCV(–) result and those without simultaneous testing for HCV-RNA and genotyping were excluded.

A total of 96,515 anti-HCV tests were performed during the 3-year study period. As a result of exclusions, anti-HCV and HCV-RNA tests were performed simultaneously in 537 patients. Demographic data were calculated for these 537 patients. Among these patients, 130 were diagnosed with chronic HCV infection based on the detection of HCV-RNA positivity, and genotyping was performed for all of them (Figure 1).

Anti-HCV tests were performed using the "Electrochemiluminescence immunoassay" (ECLIA) method using the fourth-generation "Elecsys Anti-HCV II" kit (Roche Diagnostics, Germany), following the manufacturer's recommendations.

For the detection of HCV-RNA, viral nucleic acid isolation was conducted using the "QIAsymphony DSP virus/pathogen midi kit" (Qiagen, Germany) on the "QIAsymphony SP/AS" system, while the polymerase chain reaction (PCR) was performed using the "Artus HCV QS-RGQ" kit (Qiagen, Germany) on the "Rotor-Gene Q" system, following the manufacturer's guidelines.

In the determination of HCV genotyping, the "Geno Sen's HCV RG Genotype 1/2/3/4" qualitative real-time PCR kit (Corbett Research, Australia) and the "GEN-C 2.0 reverse hybridization strip assay" kit (NLM Diagnostics, Italy) were utilized.

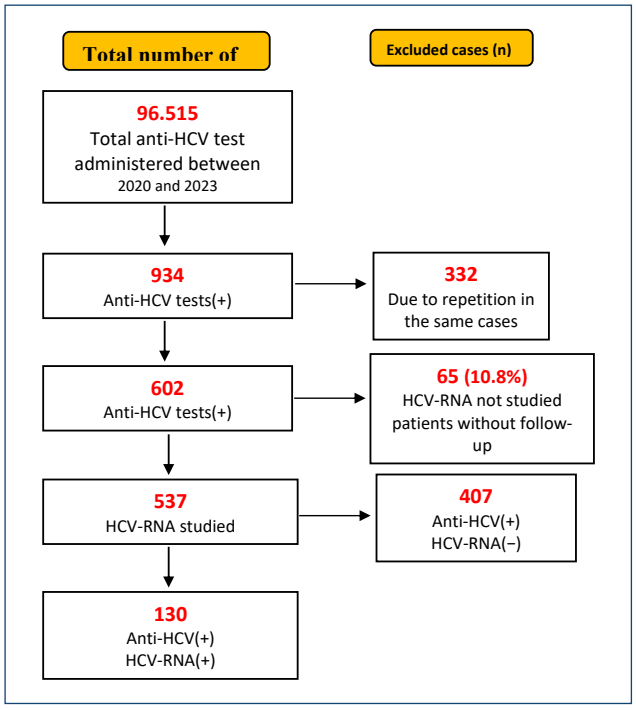

Figure 1. A schematic flowchart describing the inclusion and exclusion design.

Statistical analysis

Statistical analysis was conducted using IBM SPSS version 22. The normal distribution of the data was assessed using the Shapiro–Wilks test. For difference analysis, the chi-square test was used for categorical data, the Student's t-test and ANOVA were employed for continuous data that met parametric assumptions, and Mann-Whitney U and Kruskal–Wallis tests were used for those not meeting parametric assumptions. Diagnostic accuracy was evaluated through receiver operating characteristic (ROC) curve analysis, and the cutoff values were determined using the Youden's Index. Statistical significance was investigated at a confidence level of 95% ($p<0.05$).

RESULTS

The average age of the 537 patients included in the study was 55 years, with 301 (57.1%) being female (Table 1).

The anti-HCV positivity rate was 0.62% (602/96,515), and the actual anti-HCV positivity rate was 0.13% (130/96,515) (Figure 1).

The average age of patients in the HCV-RNA(+) group was found to be higher than that of the HCV-RNA(–) group, and this difference was statistically significant ($p=0.023$). When examining gender distribution, no statistically significant difference was found between the two groups of patients ($p=0.234$) (Table 1).

The anti-HCV levels of patients with HCV-RNA(+) results were statistically significantly higher than those with HCV-RNA(–) results ($p<0.0001$) (Table 1). Quantitative analysis of HCV-RNA was conducted, and a significant correlation was found between the anti-HCV S/Co ratio and HCV-RNA levels (Spearman correlation coefficient: 0.218; $p=0.013$).

In the ROC curve analysis, HCV-RNA was considered the gold standard to determine the best threshold value, and the most suitable S/Co value was found to be 10.86. The sensitivity was 96.1%, specificity was 61.2%, and positive predictive value (PPV): 44.2% and negative predictive value (NPV): 98% were calculated (Figure 2).

HCV genotype analysis was conducted for the entire cohort of 130 patients. Genotype-1 was identified in 107 patients (82.3%), with the most common subtype being 1b (n=100). Genotypes 5/6/7 were not detected. There were 16 patients (12.3%) with Genotype-3, one patient with Genotype-2, and four patients (3.07%) with Genotype-4. There was no statistically significant difference in the mean values of anti-HCV

and HCV-RNA between those with Genotype-1 and other genotypes (p=0.759 and p=0.333). Patients with Genotype-1 were found to be older, and this difference was statistically significant (p<0.001).

DISCUSSION

HCV infection is prevalent in all regions of the world, with the highest disease burden found in the Eastern Mediterranean and European regions[1]. While Pakistan (5.8%), Uzbekistan (4.4%), and Thailand (1.7%) have significantly higher prevalence rates, Austria (0.4%), Sweden (0.7%), Canada (0.8%), and Iran (0.4%) report lower rates[6]. Turkey is considered one of the countries with low HCV prevalence worldwide. Various studies conducted in Turkey have reported anti-HCV positivity rates ranging from 0.5 to 1.85%[5,7-9]. In our study, the anti-HCV positivity rate was found to be 0.62% (602/96,515), which is consistent with other studies.

The CDC recommends universal HCV screening, advising HCV screening at least once in a lifetime for all adults aged 18 years and older, except in settings where the prevalence of HCV infection is less than 0.1%, and for all pregnant individuals during each pregnancy[10]. Besides this recommendation, in our country, HCV screening is conducted before blood donation, before surgery, before marriage, during employment entry, and during periodic check-ups. The anti-HCV test is used for screening HCV infection, and if anti-HCV positivity is detected, a confirmatory test, the HCV-RNA test, is performed for a definitive diagnosis[8]. In countries with low HCV prevalence, individuals without symptoms of HCV infection often encounter false-positive anti-HCV test results in screening. The false positivity may be associated with other viral diseases genetically identical to the original infection-causing HCV strain, underlying autoimmune hepatitis, and a history of resolved or treated HCV disease. To reduce false-positive anti-HCV test results in populations with low HCV prevalence, the CDC has expanded the HCV diagnostic algorithm by providing anti-HCV S/Co values reflecting true antibody positivity for several manufacturers, allowing laboratories to create their own HCV diagnostic algorithms[2]. In this study, the relationship between anti-HCV and HCV-RNA positivity was retrospectively examined, aiming to determine the most suitable S/Co value for identifying true patients in anti-HCV testing.

In studies conducted in our country and worldwide, the most accurate S/CO value in anti-HCV ROC curve analysis has been found to be between 7.13 and 12.27[11-14]. In these studies, it has been suggested that a positivity below the S/CO value determined by ROC analysis may be a false positive, and it is recommended to repeat the anti-HCV test with a new sample at least 2 weeks later. In case of reactivity, it is further recommended to perform an HCV-RNA test.

In a retrospective study conducted in the United States, three different anti-HCV S/CO values were determined: 3, 8, and 20. The study recommended considering samples with an anti-HCV S/CO value <3.0 as true negatives, performing RIBA for those with an anti-HCV S/CO value between 3.0 and 19.9, conducting HCV RNA testing for RIBA-positive samples, and directly performing HCV RNA testing for samples with an anti-HCV S/CO value >20.0[15].

In our study, the anti-HCV S/Co value was determined to be ≥10.86 in ROC curve analysis. No case with an S/CO value <3 was a true positive. Among cases with S/CO values between 3 and 7, two true patients had decompensated liver

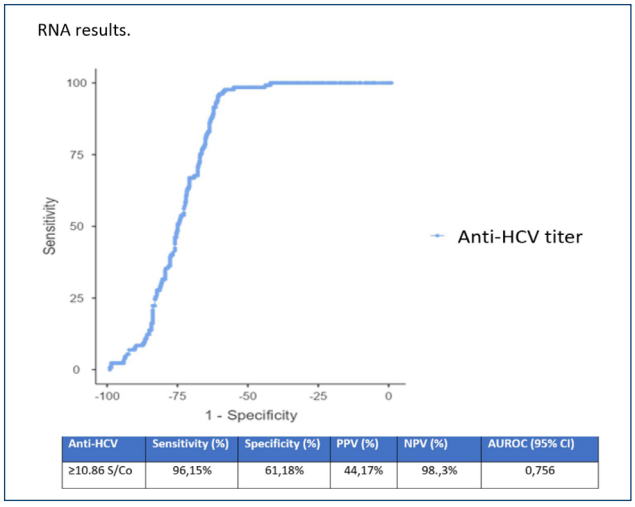

Figure 2. Receiver operating characteristic analysis of anti-hepatitis C virus S/Co values according to HCV RNA results.

Table 1. Baseline characteristics of patients according to HCV RNA.

	All patients (n=537)	HCV-RNA(+) (n=130)	HCV-RNA(−) (n=407)	p-value
Female, n (%)	301 (57.1%)	67 (51.5%)	234 (57.5%)	0.234
Age, SD	55±18	58±17	54±19	0.023
Anti-HCV S/Co ratio	32±42	47±37	28±42	<0.0001

n: number of patients; SD: standard deviation; HCV: hepatitis C virüs; S/Co ratio: signal to cutoff ratio.

cirrhosis, and one of these patients had co-infection with HBV and HCV. It was considered that the low-titer level of anti-HCV could be secondary to HBV co-infection and/or decompensated liver cirrhosis. For patients with anti-HCV S/CO values between 7 and 10.86, false positives could be due to other viral diseases genetically identical to the HCV strain, and accordingly, we recommend repeating the anti-HCV test with a new sample at least 2 weeks later and, in case of reactivity, performing an HCV-RNA test. For patients with anti-HCV S/CO ≥10.86, it is considered appropriate to directly conduct an HCV-RNA test.

Furthermore, in our study, our recommendation is reinforced by the significantly higher anti-HCV levels in patients with positive HCV-RNA results compared to those with negative HCV-RNA results ($p<0.0001$) (Table 1), and by the significant correlation found in the Spearman correlation test between the anti-HCV S/Co ratio and HCV-RNA levels ($p=0.013$). We believe that an anti-HCV S/Co value ≥10.86 would be beneficial in detecting true patients.

In our study, the average age of patients was higher compared to other studies. Additionally, the average age of patients in the HCV-RNA positive group was statistically significantly higher than that of the HCV-RNA negative group ($p=0.023$)[4,12,13]. We believe that the presence of numerous elderly care centers in the location of our hospital and the conduct of pre-admission health screenings for these centers at our hospital may be the reason for this. Additionally, in other studies, foreign national patients were reported to be younger, and we consider this as another possible reason for the observed difference.

The hepatitis C virus has 8 main genotypes and 86 subtypes[16]. Genotype-1 is the most widespread globally. It is estimated that over one-third of genotype 1 cases are in East Asia, while three-quarters of genotype 3 cases are in South Asia. Genotype-4 is known to be prevalent in North Africa and Central Asia[17].

In HCV genotyping studies conducted in our country, GT1 has been identified most frequently, with prevalence rates ranging from 65.1 to 88.4%[7,9,18]. Before 2010, GT1 rates were at their highest, but studies conducted after 2010 indicate a decline in GT1 rates. In studies conducted in our country over the past decade, an increase in GT3/4 and mixed genotypes has been emphasized, attributed to the higher inclusion of foreign national patients. Additionally, it has been highlighted that GT4 was first detected in Turkey in 2011, being the dominant genotype in Syria, and with the influx of refugees to Turkey, GT4 rates may have increased in recent years[7].

The genotype distribution rates of the patients in our study are similar to the results of studies conducted in Turkey before 2010. Our GT3 rates were considerably lower compared to data from our neighboring country, Greece. GT4 was identified in four patients (3.07%), which is quite low compared to recent genotype study data in Turkey. Two patients of foreign nationality had a mixed genotype. The variation in genotype distribution in our study compared to other studies may be attributed to the location of our hospital on the Asian continent in Istanbul. The majority of residents in the vicinity of our hospital are typically local, while foreign national refugees tend to reside more on the European side of Istanbul. Recent HCV genotype studies in Turkey have mostly included data from hospitals on the European side of Istanbul, and these studies have particularly emphasized the inclusion of a high number of foreign national patients. In our study, patients with GT1 were found to be older, which was statistically significant. However, the younger age of foreign national patients and the predominance of GT3/GT4 patients could explain this age difference.

The retrospective nature of our study and the inability to evaluate transmission routes and risk groups are important limitations. Additionally, despite the large sample size, since the data represent the experience of a single center, the genotype distribution may not fully reflect the entire country. Some studies indicate that the sensitivity of the anti-HCV test is lower in patients undergoing hemodialysis due to low viral loads. Considering the possibility of patients with occult HCV infection among those undergoing hemodialysis and testing negative for anti-HCV, the prevalence of HCV found in our study might actually be higher.

CONCLUSION

The study revealed a prevalence of 0.62% for HCV antibody positivity and a viremia prevalence of 0.13%. This rate was lower than the worldwide HCV viremia rate. In this study, if anti-HCV S/Co≥10.86 is detected, direct HCV RNA testing is recommended. For patients with S/Co values below 10.86, it should be considered that false positives may occur due to other viral diseases genetically identical to the HCV strain. In cases where high clinical suspicion for HCV persists, it is suggested to repeat the anti-HCV test with a new sample at least 2 weeks later, and if reactivity is confirmed for the second time, HCV RNA testing is recommended.

AUTHORS' CONTRIBUTIONS

BS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original

draft, Writing – review & editing. **İDY:** Conceptualization, Data curation, Validation, Writing – original draft. **SY:** Data curation, Investigation, Project administration, Software, Supervision, Writing – original draft. **YT:** Conceptualization, Data curation, Methodology, Visualization. **VAS:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **RAÇ:** Conceptualization, Data curation, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **DK:** Conceptualization, Methodology, Project administration, Software, Writing – original draft.

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ORIGINAL ARTICLE

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The effect of preoperative embolization rate on surgical outcomes for carotid paraganglioma resection

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SUMMARY

OBJECTIVE: Preoperative embolization of paragangliomas decreases tumor volume and reduces intraoperative blood loss. This study aimed to evaluate the effect of the rate of devascularization achieved by preoperative embolization of carotid body tumors on surgical outcomes.

METHODS: Patients with carotid body tumors who underwent preoperative transarterial embolization between 2013 and 2024 were included in this retrospective study. The Shamblin classification of all patients was carried out using radiological imaging. Devascularization rates obtained after the embolization of carotid body tumors were determined from angiographic images. Patients were divided into two groups: near-complete embolization (devascularization rate >90%) and incomplete embolization (devascularization rate <90%). Hemoglobin loss was calculated with blood tests before and immediately after surgery. Tumor volume loss was calculated by preoperative radiological tumor volume and postoperative surgical specimen volume. Hemoglobin loss, tumor volume loss, and postoperative complication rates of the two groups were compared.

RESULTS: A total of 31 patients with carotid body tumors who underwent surgery were included in the study. Near-complete embolization was achieved in 21 patients (67.74%), while incomplete embolization was achieved in 10 patients (32.25%). Shamblin classification was statistically similar (p>0.05) between the two groups. The vascular complication rate in the near-complete embolization group was significantly lower than in the incomplete embolization group (p=0.027). However, no significant difference was observed in neurological complication rates, hemoglobin loss, and tumor volume loss parameters between the two groups (p>0.05).

CONCLUSION: The preoperative devascularization rate should be at least 90% to minimize the risk of vascular complications.

KEYWORDS: Carotid body tumor. Vascular complication. Artery embolization.

INTRODUCTION

Carotid body tumors are the most common head-neck paraganglioma tumors. They are highly vascular, rare, and generally benign tumors[1,2]. The predicted incidence of carotid body tumors is 1:30,000 and accounts for 3% of paragangliomas[3]. They often present as a painless, slow-growing lateral neck lump.

Treatment options include conservative management, resection, and radiotherapy. The only curative treatment for these tumors is surgical resection. Multiple difficulties arise in the surgical treatment of carotid body tumors, which are mostly due to their complex anatomical location and high vascularity. The Shamblin classification is used to evaluate the extent of difficulty in the surgical resection of the tumor. Involvement of the internal carotid artery (ICA) and external carotid artery (ECA) in the tumor can also be evaluated with the intraoperative Shamblin classification. Preoperative prediction of the Shamblin classification can be achieved by assessing the angle of ICA to tumor contact in radiological imaging (group I: <180°, group II: <180–270°, and group III: >270°)[4].

Preoperative carotid body tumor embolization is a standard step in treatment management. However, there is still disagreement in the field on the benefits of the procedure. Three different meta-analyses carried out on preoperative embolization in carotid body tumor surgery have reported different and controversial results[5-7]. According to two of the meta-analyses, surgical resection of the tumor after preoperative embolization appeared to shorten the duration of surgery and reduce blood loss compared with surgery without preoperative embolization[5,7]. However, the third meta-analysis reported that preoperative embolization did not provide sufficient benefit[6]. Cobb et al. have also reported that embolization was not beneficial[8]. Upon the publication of these studies, some institutions carried out surgical resections without preoperative embolization; however, there was significant blood loss in these patients[9].

Several studies have examined the efficacy of preoperative embolization. Some studies have demonstrated that preoperative embolization decreases blood loss during surgery and provides easy dissection of the tumor from the internal/external carotid arterial wall[10]. However, other studies have reported

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that preoperative embolization is ineffective[11-13]. Therefore, it is imperative to understand the reasons for the differences in the effectiveness of preoperative embolization in the different studies. Shiga et al. reported that the timing of pre-embolization may affect surgical outcomes[14]. Katagiri et al. reported that same-day preoperative embolization significantly decreased blood loss and surgery time[15].

Another reason for the different outcomes observed in the different studies could be the success rate of embolization and the experience of the interventional radiologist. The percentage of devascularization after embolization may also affect surgical outcomes. However, to the best of our knowledge, none of the studies in the published literature have evaluated this. Therefore, the purpose of this study was to determine the effect of the percentage of tumor devascularization achieved by preoperative embolization on surgical outcomes.

METHODS

Study population

Ethical approval for this retrospective and cross-sectional study was obtained from the local ethics committee (approval number: 2024/03-54). A total of 31 consecutive patients who were diagnosed with histopathological carotid body tumors between 2013 and 2024 were identified from the hospital database. All patients underwent preop embolization and subsequent surgical resection. Notably, 31 patients with 31 carotid body paragangliomas were included in the study.

Shamblin classification

The Shamblin classification of carotid body tumors in all patients was carried out using preoperative contrast-enhanced neck computed tomography (CT) images. The classification was carried out according to the circumferential contact angle of the tumor with the ICA with group I: <180°, group II: <180–270°, and group III: >270° encasement[4].

Preoperative embolization

For preoperative embolization, the right femoral artery was punctured, and a 5-Fr sheath was inserted. A 5-Fr diagnostic catheter was next inserted into the common carotid artery (CCA), followed by selective angiography of the ECA and CCA. A microcatheter and a 0.018-inch guide wire were used to carry out super-selective catheterization of the arteries supplying the tumor. Polyvinyl alcohol (PVA) was used as an embolizing agent. PVA particles were mixed with a contrast agent in a 1:1 ratio and injected via the microcatheter. A final angiogram was carried out to assess the degree of embolization and patency of the ICA. The percentage of devascularization was determined by comparing the angiograms before and after embolization by a vascular interventional radiologist (HY). A devascularization rate greater than 50% was accepted as technical success. A devascularization rate of >90% was considered a near-complete embolization (Figures 1 and 2). A devascularization rate of <90% was considered incomplete embolization.

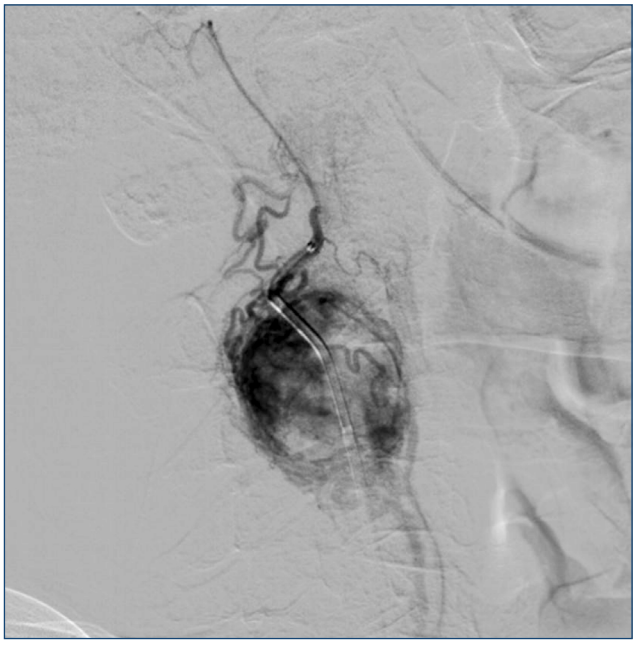

Figure 1. Vascularization of the carotid body tumor before embolization procedure.

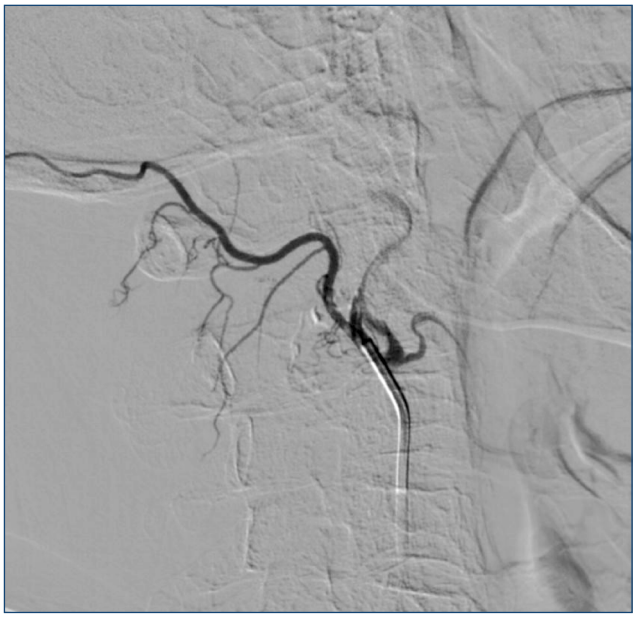

Figure 2. Near-complete devascularization achieved after the embolization procedure in the same patient.

Surgical resection

Surgery was planned within 24 h after the embolization. The surgical procedure was performed by an ear, nose, and throat specialist under general anesthesia.

Intraoperative and postoperative complications were determined from the hospital database. Hemoglobin loss in blood tests performed immediately before and after the surgery provided information about the amount of blood lost during the surgery.

Tumor volume

The volume of the paraganglioma was calculated using neck CT images preoperatively. The volume of the carotid body tumor was measured using longitudinal (a), transverse (b), and thick diameter (c). The postoperative volume of the paraganglioma was predicted using surgically resected specimens. Preoperative and postoperative tumor volumes were calculated with the formula: $a \times b \times c \times 0.523$. Following this, the percentage reduction in tumor volume after surgery was calculated.

Statistical analysis

After the embolization procedure, patients were divided into two groups: patients with near-complete embolization (devascularization rate >90%) and patients with incomplete embolization (devascularization rate <90%). The demographic and surgical outcomes of the two groups were compared statistically using IBM SPSS, version 25.0. The Kolmogorov-Smirnov test was applied to evaluate whether the distribution was normal. A student t-test was used for normally distributed parameters. A chi-square test was used to compare complication rates.

RESULTS

A total of 31 patients were included in this retrospective study. With preoperative embolization, 29 patients had a devascularization rate of more than 50%. The technical success rate of preoperative embolization was 93.54%. The devascularization rate achieved in 21 patients (67.7%) was greater than 90%, and these patients were included in the near-complete embolization group. The devascularization rate was less than 90% in 10 patients (32.2%), and these patients were included in the incomplete embolization group. No significant difference was observed between the two groups in terms of age, gender, tumor location (right vs. left), Shamblin classification, and preoperative tumor volume ($p>0.05$) (Table 1).

In the near-complete embolization group, the average volume loss of tumors after surgery was 51.45%. In the group with incomplete devascularization, the average volume loss of the tumor was 50.55%. Regarding tumor volume loss, there was no significant difference between the two groups ($p=0.488$). However, tumor volume loss was greater in the near-complete embolization group than in the incomplete embolization group.

The mean hemoglobin loss of all patients after surgery was 1.50±1.13. The mean hemoglobin loss after surgery was 1.32±1.13 in patients with near-complete embolization and 1.71±1.16 in patients with incomplete embolization. No significant difference was observed in hemoglobin loss between the two groups. However, hemoglobin loss in the near-complete embolization group was less than in the incomplete embolization group.

Major vascular complications were detected in a total of three patients (9.67%). No major vascular complications were detected in patients with near-complete embolization. In the group with incomplete devascularization, two patients had intraoperative carotid artery injury, and one patient had postoperative hematoma. The complication rate was significantly lower in the group with near-complete embolization ($p=0.027$). The carotid artery injury in two patients was repaired by a

Table 1. The comparison of demographic data and tumor features of the two groups.

	Near-complete embolization (n=21)	Incomplete embolization (n=10)	p
Age	53.73±14.43	56.80±14.75	0.58
Gender (M/F)	6/15	3/7	1.000
Tumor location (right/left)	13/8	7/3	1.000
Preoperative tumor volume (mL)	26.80±24.97	29.50±16.99	0.761
Shamblin classification			
Group I (n)	6	3	0.995
Group II (n)	13	6	
Group III (n)	2	1	

cardiovascular surgeon, while the patient with a postoperative hematoma underwent surgical drainage.

Postoperative neurological complications developed in seven patients (22.58%). Vagus paralysis occurred in four patients, and hypoglossal paralysis occurred in three patients. Temporary nerve paralysis occurred in five patients, and permanent nerve paralysis occurred in two patients. Neurological complications occurred in five patients (23.80%) in the near-complete embolization group and in two patients (20%) in the incomplete embolization group. No significant difference was observed in terms of neurological complications between the two groups (p=0.813).

DISCUSSION

Carotid body tumors require surgical resection due to the possibility of growth and local invasion. Because of the high-grade vascularization of the tumor, surgical resection carries a considerable risk of blood loss. Thus, preoperative embolization is a useful approach to reduce the risk of bleeding[10]. In this study, all patients underwent preoperative embolization. No vascular complications were observed in the group with near-complete embolization (devascularization rate >90%). The vascular complication rate was 30% in the incomplete embolization group (devascularization rate <90%). In the near-complete embolization group, the vascular complication rate was significantly lower. According to our study, the preoperative devascularization rate should be at least 90% to minimize the risk of vascular complications.

Presurgical embolization for highly vascular tumors has been used for the past 30 years[16]. Preoperative embolization of paragangliomas is widely implemented as it reduces intraoperative blood loss, decreases tumor volume, increases intraoperative tumor visualization, and facilitates tumor dissection[17]. In our study, vascular complications developed in three patients with incomplete embolization. Of these, two patients had intraoperative carotid artery injuries, while postoperative hematoma was detected in one patient. Our data suggest that nearly complete embolization can improve visualization of the tumor and reduce the risk of carotid artery injury.

Patients with preoperative embolization were shown to have a shorter duration of surgery and less blood loss compared with patients without embolization[5]. However, another study reported no intraoperative or postoperative advantage to patients undergoing preoperative embolization[6]. The reason for this difference may be related to the devascularization rates achieved with embolization. We observed significantly lower rates of vascular complications when almost complete devascularization was achieved. However, there was no significant difference in tumor volume decrease, hemoglobin loss, or postoperative neurological complications between the near-complete embolization group and the incomplete embolization group. In this study, the mean hemoglobin loss after surgery was 1.50±1.13. None of the patients required a blood transfusion after surgery.

Embolization with PVA particles provides capillary occlusion to achieve complete or near-complete embolization in cases with prominent arterial feeders. However, sometimes the embolization procedure can be incomplete and time-consuming. The reasons for this are the multiplicity, tortuosity, and small caliber of the feeding arteries. Additional factors include vascular spasticity caused by catheter manipulation and blood supply from the ICA and vertebral artery[18].

We observed that complete or nearly complete embolization was necessary to minimize the risk of vascular complications. However, total devascularization cannot be achieved with an angiographic embolization procedure in every case. We achieved near-total devascularization in 21 patients (67.7%) and incomplete devascularization in 10 patients (32.2%). In addition, the transarterial embolization procedure has a potential risk of stroke due to the migration of the embolizing agent into the intracranial circulation via collaterals[19]. Due to these disadvantages of the intravascular approach, embolization of paragangliomas with direct puncture is being used at some institutions.

Ozyer et al. used an ultrasound-guided intratumoral injection of n-butyl cyanoacrylate to achieve complete devascularization in patients with incomplete devascularization achieved by transarterial embolization[20]. Pérez-García et al. carried out preoperative embolization of carotid body tumors in six patients by direct puncture using the Squid® embolizing agent. These authors reported near-complete embolization in all cases[21]. A meta-analysis by Schartz et al. showed that the rate of total devascularization was higher in the direct percutaneous puncture approach compared with transarterial embolization[22]. Therefore, the direct puncture approach may be more effective than transarterial embolization in reducing vascular complications. Large-scale and prospective studies are needed to evaluate this.

The limitations of this study include the small number of patients and its retrospective design.

Overall, this study showed that preoperative embolization of carotid body tumors can be effective in preventing complications. Preoperative total or near-total devascularization should be achieved to minimize the risk of vascular complications.

ETHICAL APPROVAL

This retrospective study was approved by the local ethics committee (Protocol number: 2024/02-24).

AUTHORS' CONTRIBUTIONS

MY: Data curation, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **HY:** Methodology, Validation, Visualization. **YD:** Formal Analysis, Investigation, Methodology.

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ORIGINAL ARTICLE

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Identification of sexual myths of university students in health-related departments and affecting factors

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SUMMARY

AIM: The research aimed to determine the attitudes of students studying in health-related departments toward sexual myths and the factors affecting them.

METHODS: The study is descriptive research involving 287 students enrolled in health-related departments. The data were collected using a "Descriptive Information Form" and the "Sexual Myths Scale (SMS)" and analyzed using the SPSS 22.0 software package. The SPSS 22.0 package program was used to evaluate the data. In statistical analysis, Spearman correlation analysis was employed to determine the relationship between continuous variables and the SMS score, and the statistical significance level was accepted as $p<0.05$.

RESULTS: The total score was found to be 53.57±17.54 (min: 28.00 to max: 140.00), reflecting a moderate level. There was a statistically significant difference between the total score of SMS according to gender, family type, maternal employment status, and paternal education level ($p<0.05$). It was also determined that male students, students whose mothers were unemployed, who lived in extended families, and whose fathers had low education had lower SMS scores.

CONCLUSION: Despite students studying in health-related departments and receiving relevant courses, their level of sexual myths remains at a moderate level, indicating the presence of knowledge gaps and misconceptions in the subject matter. Therefore, it is crucial to implement comprehensive education and counseling services on reproductive and sexual health for all university students.

KEYWORDS: Belief. Health occupations students. Sexuality. Sexual health.

INTRODUCTION

It encompasses sexual orientation, eroticism, intimacy, and reproduction, with gender playing a central role and significantly influencing an individual's quality of life[1]. Perspectives on sexuality are influenced by multiple factors, including personal meanings, beliefs, attitudes, values, and experiences with sexual roles and relationships, as well as the broader social structure and culture in which individuals reside[2]. The influence of social and cultural structures contributes to the formation of beliefs about sexuality that may lack truth but are accepted nonetheless. Although lacking scientific validity, these beliefs and information permeate society as integral components of the culture, shaped and mythologized by the collective imagination of individuals. Frequently, these beliefs manifest as exaggerated notions and thoughts regarding sexuality, commonly known as sexual myths[3]. Such sexual myths hinder individuals from openly expressing and discussing matters related to sexuality[4]. It is acknowledged that the university education period, during which young individuals socialize, develop their individual identities, and engage in sexual activity, has a significant impact on sexual myths and attitudes[5]. In particular, the perspectives of students studying in health-related fields regarding sexuality hold great importance. Given that sexuality is influenced by various factors throughout the lifespan, sexual health services are recognized as vital components of general healthcare and health promotion programs. However, research indicates that, despite having adequate knowledge, students often refrain from discussing patients' sexual histories due to concerns regarding the reactions of patients, their families, and healthcare professionals[6,7]. Numerous studies have highlighted that nursing students who hold moderate levels of sexual myths encounter increased perceived barriers when

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it comes to evaluating and providing sexual care, leading to difficulties in delivering comprehensive care[6,8,9]. Given that these students are future healthcare professionals, their sexual myths carry substantial significance as they directly impact the effective provision of care and the overall health of society. Therefore, this study was conducted to examine the attitudes of students pursuing careers in healthcare toward sexual myths and identify the factors influencing these attitudes.

METHODS

Study setting: Between February and June 2022, this descriptive research was conducted among students enrolled in health-related departments at a foundation university.

Population and sample: The target population consisted of 2,167 students studying various health-related disciplines at a private university in Turkey during the Spring Term of the academic year 2021–2022. The sample size was determined using the formula established by Salant and Don[10]. Using the sampling formula, the required sample size was calculated as n=221 with a 95% confidence interval and±5% sampling error for this population, which is not homogenous. In the post hoc power analysis, comparing the scale score averages according to gender, one of the factors affecting the Sexual Myths Scale (SMS), the effect size was found to be 1.167 and the power of the study was determined to be 0.99.

Ethical approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee (Date 15. 03.2022/No: 2022035). Before the study, written consent was obtained indicating that they agreed to participate in the study. It was specifically stated to the students that this study did not have any grade impact.

Data collection and data collection tools: For this study, the researchers collected the data using a face-to-face interview technique when the students were not attending classes. Two data collection tools were utilized: the "Introductory Information Form" and the "SMS."

Descriptive information form: Developed by the researchers based on the existing literature, this form consists of 15 questions to evaluate the students' sociodemographic characteristics, education-related attributes, and perspectives on sexuality[6,8,9]. The student's level of knowledge about sexuality and their comfort level when discussing sexuality is assessed through questions where they subjectively rate themselves on a scale ranging from 0 to 10 (0: Strongly Disagree to 10: Strongly Agree).

The SMS: Created by Golbası et al. in 2016, the SMS is a 5-point Likert-type scale, with responses such as "completely agree" (5), "somewhat agree" (4), "not sure" (3), "disagree" (2), and "completely disagree" (1). The minimum and maximum scores on the scale are 28 and 140. The scale measures the extent to which individuals believe in sexual myths, with a higher score indicating a higher probability of belief[11]. The Cronbach's alpha coefficient for the SMS was determined to be 0.91, and the coefficient for the test–retest reliability study was found to be 0.814. In this study, Cronbach's alpha value for the scale was calculated to be 0.93.

Data analysis

The SPSS 22.0 package program was employed for data analysis. The conformity of the variables to the normal distribution was evaluated with the Shapiro-Wilk test. Percentages, mean±standard deviation, and median (min–max) were used to represent descriptive statistics. The distribution of scale scores in independent groups was evaluated with the Mann-Whitney U test and the Kruskal-Wallis test. Median (min–max)/Mean rank was used for descriptive data that were not normally distributed. The relationship between continuous variables and scale scores was evaluated using Spearman's correlation analysis. The statistical significance level was accepted $p<0.05$.

RESULTS

For students with a mean age of 20.59±1.58 years, 84.7% of participants expressed their belief that there should be a course on sexuality. The average level of knowledge about sexuality was found to be 7.01±1.91. The average comfort level score was 7.60 ±2.42 when discussing sexuality within the family and 4.37±2.22 when talking about sexuality among friends. Table 1 shows the data related to the level of knowledge about sexuality and feeling uncomfortable while talking about sexuality.

Characteristics related to the mean scores of the SMS and subscales are as follows: SMS total score 53.57±17.54, 51.00 (28.00–140.00); Sexual orientation sub-dimension scale score 12.61±4.93, 12.00 (5.00–25.00); Gender subscale score 9.56±4.22, 8.00 (6.00–30.00); Age and Sexuality subscale score 7.45±3.30, 7.00 (4.00–20.00); Sexual Behavior subscale score 4.67±2.26, 4.00 (3.00–15.00); Masturbation subscale score 4.32±2.15, 4.00 (2.00–10.00); Sexual Violence subscale score 6.13±2.56, 5.00 (4.00–20.00); Sexual Intercourse subscale score 4.50±2.05, 4.00 (2.00–10.00); and Sexual satisfaction subscale score 4.33±1.87, 4.00 (2.00–10.00). Table 2 shows the characteristics related to the mean scores of the SMS and

subscales. In addition, Table 2 shows the correlation findings of the SMS. No statistically significant correlation was found between the SMS score and age, level of knowledge about sexual issues, or comfort level when talking about sexual issues in the family ($p>0.05$). There was a negative, weak, statistically significant correlation between the level of comfort when talking about sexual issues with friends ($p<0.05$). As the SMS score increased, the level of comfort when talking about sexual issues with friends decreased (Table 2).

Table 3 shows the relationship between the SMS and some variables. The SMS score of male students was found to be statistically significantly higher than that of female students, and those in extended family structures were statistically significantly higher than those in nuclear family structures. While there was no difference between the groups in terms of marital status, maternal education, paternal employment status, place of residence, and class ($p>0.05$), the SMS score was statistically significantly higher in those whose mothers were unemployed than those whose mothers were employed; in those whose fathers were secondary school graduates than those whose fathers were primary school graduates; in those whose fathers were unemployed than those whose fathers were employed; and in those who were medical faculty students than midwifery students ($p<0.05$).

DISCUSSION

In Turkey, sexuality is seen as a taboo due to cultural and religious reasons, and topics related to sexuality are avoided from being discussed[11]. However, it is generally observed that young people do not receive science-based education about sexual health throughout their education life. It is observed that only students studying in health-related departments take courses on sexual health[12]. For this reason, students studying in health-related departments are considered to have very good knowledge of sexual health. Additionally, they are thought not to have many sexual myths[12]. Contrary to what is thought, in the study of Junior et al., it was reported that adolescents' knowledge about STIs was not sufficient[13]. Lack of knowledge about sexuality may cause sexual myths to be more common in young people. Lack of information also paves the way for reproductive and sexual health problems. Studies report that the sexuality of women with gynecological problems is affected to certain degrees[14,15]. The relationship between sexuality, sexual health, and sexual myths can be thought of as a circle that affects each other. According to the findings of this study, unfortunately, the sexual health knowledge and sexual myths of students studying in health-related departments are not at the desired level. For this reason, determining the attitudes and influencing factors of university students studying in health-related departments

Table 1. Level of knowledge about sexuality and feeling comfortable when talking about sexuality.

	N (287)	% (100.0)
Should there be a sexual health course?		
Yes	243	84.7
No	14	4.9
No idea	30	10.5
Level of knowledge about sexuality and feeling uncomfortable talking about sexuality	Mean ±SD	Med (Min–Max)
Sexual knowledge level	7.01±1.91	7 (1–10)
Comfort level when talking about sexuality in the family	4.37±2.22	4 (1–10)
Comfort level when talking with friends about sexuality (same sex)	7.60±2.42	8 (1–10)

Mean: average; SD: standard deviation; Med: median; Min: minimum; Max: maximum.

Table 2. Total and subscale score averages of the Sexual Myths Scale and correlation findings of the Sexual Myths Scale score and some variables.

Sexual Myths Scale	Mean±SD	Med (Min–Max)
Sexual Myths Scale total score	53.57±17.54	51.00 (28.00–140.00)
Sub-dimensions		
Sexual orientation	12.61±4.93	12.00 (5.00–25.00)
Gender	9.56±4.22	8.00 (6.00–30.00)
Age and sexuality	7.45±3.30	7.00 (4.00–20.00)
Sexual behavior	4.67±2.26	4.00 (3.00–15.00)
Masturbation	4.32±2.15	4.00 (2.00–10.00)
Sexual violence	6.13±2.56	5.00 (4.00–20.00)
Sexual intercourse	4.50±2.05	4.00 (2.00–10.00)
Sexual satisfaction	4.33±1.87	4.00 (2.00–10.00)
Some variables	Sexual Myths Scale	
Age	ρ=–0.026	p=0.662
Level of knowledge on sexuality	ρ=–0.078	p=0.190
Comfort level when talking about sexuality in the family	ρ=–0.101	p=0.088
Comfort level when talking with friends about sexuality (same-sex)	ρ=-0.162	p=0.006

SD: standard deviation; ρ: Spearman's rho correlation coefficient.

Table 3. The relationship of Sexual Myths Scale with some variables.

Sociodemographic characteristics	Sexual Myths Scale		Analysis
	n	Med (min–max)/M.Rank	
Gender			
Male	46	69.50 (40–104)/219.21	z=-6.709 p=0.000
Female	241	49.00 (28–140)/129.65	
Marital status			
Married	4	52.50 (33–80)/149.38	z=-0.130 p=0.896
Single	283	51.00 (28–140)/143.92	
Family type			
Nuclear	246	49.00 (28–140)/137.43	z=-3.284 p=0.001
Extended	41	60.00 (28–116)/183.40	
Maternal education			
Illiterate	2	59.50 (49–70)/186.50	χ^2=2.411 df=5 p=0.790
Literate	5	54.00 (28–96)/136.00	
Primary school	61	54.00 (30–140)/150.39	
Secondary school	50	54.00 (29–91)/151.98	
High school	85	49.00 (28–106)/134.96	
University and above	84	50.00 (28–116)/143.21	
Maternal employment			
Yes	97	47.00 (28–96)/1236.58	z=-2.542 p=0.011
No	190	54.00 (28–140)/152.89	
Paternal education			
Primary school	25	43.00 (28–80)/114.96	χ^2=8.539 df=3 p=0.036 a–b
Secondary school	40	58.00 (30–104)/169.95	
High school	85	48.00 (28–140)/133.94	
University and above	137	52.00 (28–116)/147.97	
Paternal employment			
Yes	246	50.00 (28–140)/138.91	z=-2.543 p=0.011
No	41	62.00 (28–116)/174.51	
Permanent place of residence			
City	228	50.00 (28–140)/142.21	χ^2=0.620 df=2 p=0.734
District	51	54.00 (28–93)/149.52	
Town/village	8	56.50 (28–89)/159.75	
Department			
Faculty of Medicine	80	59.00 (33–116)/176,62	χ^2=21.783 df=7 p=0.003 (a–d)
Nutrition and Dietetics	10	59.00 (28–73)/173.30	
Speech and Language Therapy	14	46.00 (32–75)/124.14	
Midwifery	157	49.00 (28–140)/129.71	
Ergotherapy	3	56.00 (39–62)/148.33	
Physiotherapy and Rehabilitation	8	54.50 (31–72)/143.38	
Nursing	12	38.50 (28–89)/106.17	
Vocational School Departments	3	59.00 (34–90)/165.83	
Year			
1	84	49.00 (28–106)/136.08	χ^2=6.097 df=3 p=0.107
2	108	54.00 (28–140)/158.19	
3	70	51.00 (28–96)/140.00	
4	25	48.00 (28–73)/120.48	

M.Rank: mean rank; ρ: Spearman's rho correlation coefficient; z: Mann-Whitney U test; χ^2: Kruskal-Wallis test. Statistically significant values are indicated in bold.

regarding sexual myths, which will shape the health of the society, is important for raising and educating healthy individuals in the society.

Awareness, education, and maintenance of sexual health are crucial factors in promoting the well-being of individuals concerning sexuality and sexual health[16]. It is noteworthy that 84.7% of the students who took part in our study expressed the need for a comprehensive sexuality course to be included in their education curriculum. Furthermore, when asked to rate their average level of knowledge on sexual issues on a scale from 1 to 10, the students reported an average score of 7.01±1.91, indicating a perceived high and satisfactory level of knowledge. Notably, 65.54 and 79.3% of university students considered their knowledge about sexuality to be sufficient in a study conducted by Örüklü et al. and Doğan et al., respectively[17,18]. As in other societies worldwide, sexual behaviors and attitudes in Turkish society are significantly influenced by religious regulations, prejudices, taboos, customs, and traditions[19]. Specifically, within the context of Turkish society, individuals tend to feel more comfortable discussing sexuality with their peers than with their families[20]. Our study's results support this notion, as the comfort level score of the participating students was 4.37±2.22 when discussing sexuality within the family, whereas it increased to 7.60±2.42 when talking with friends.

Numerous factors, such as family dynamics, cultural influences, physiological aspects, religious beliefs, and psychological conditions, contribute significantly to the development of an individual's sexual attitude[21]. Recognizing the significance of understanding personal sexual misconceptions, it is crucial for students pursuing health-related disciplines to explore their own sexual beliefs before engaging in the assessment of others' sexuality and delivering effective sexual counseling[6]. In our research, the average score for sexual myths was determined to be 53.57±17.54. A study by Örüklü et al. examining the perspectives of university students regarding sexual myths reported a mean score of 61.02±19.10[17]. Similarly, Öz et al. found a score of 56.77±17.8 among nursing students in a comparable study, while Evcili and Demirel reported a score of 76.43±17.09 among nursing and midwifery students[6,19]. Along with existing literature, our study reveals that students generally hold moderate myths about sexuality. Research indicates that students with moderate levels of sexual myths face increased perceived barriers when addressing sexuality in caregiving and encounter difficulties in providing appropriate care[6,8,9].

Notably, the perspective on sexuality is influenced by various factors, including gender[17]. A study conducted among

Turkish students demonstrated that sexual myths were more prevalent among male students[21]. Likewise, our study revealed higher levels of sexual myths among male students compared with their female counterparts. These differences in beliefs and attitudes between genders may be attributed to the distinct societal values associated with male and female sexuality in Turkish culture.

In our study, marital status did not significantly influence the score of sexual myths. However, previous studies conducted with different populations have reported higher sexual myth scores among married individuals compared with those who are single. This difference is believed to stem from variations in sexual knowledge and experiences[22,23].

The nuclear family structure is considered a significant reflection of modernization[24]. In our study, we speculate that the lower sexual myths score among students from nuclear family structures is attributed to having a more modern family setup.

Although there was no notable difference between the educational level of the students' mothers and their sexual myths scores, those whose mothers were illiterate exhibited the highest sexual myths score, suggesting that the maternal education level has an impact on the presence of sexual myths in their children.

According to the results of the Household Labor Force Survey, the labor force participation rate for individuals aged 15 years and over was reported as 51.4% in 2021, with rates of 32.8% for women and 70.3% for men[25], which is consistent with our study. Considering that the participation of both men and women in the labor force in Turkey improves the socio-economic status of families, it can be inferred that individuals whose parents are employed have lower sexual myth scores compared with those whose parents are unemployed. Furthermore, medical faculty students had higher SMS scores than those in the midwifery department. These findings suggest that the level of belief in sexual myths among students studying health-related disciplines may vary across different departments.

Although there was no statistically significant difference between the class levels of the students and their sexual myths scores, it was observed that fourth-year students had lower sexual myths scores compared with lower-class students. This could be attributed to the lack of completion of courses related to sexual and reproductive health until the fourth year, which may contribute to a decrease in sexual myth scores.

Limitations of the research

As the research was conducted with students at a university located in the capital of Turkey and this university accepts students from many different provinces of the country, it is thought to be a sample close to national representation. However, as the study was conducted at a single university, its generalizability to the whole country is limited.

CONCLUSION AND RECOMMENDATIONS

Despite studying in a health-related department and taking relevant courses, the moderate level of sexual myths among the participants indicates that, contrary to popular belief, there are still knowledge gaps and misconceptions regarding sexuality among students. Considering these findings, it is recommended to provide comprehensive reproductive health and sexual health education, particularly targeting university students enrolled in health-related departments, and expand the content of these courses to address common misconceptions about sexuality.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

ETHICAL APPROVAL

The study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments and the Good Clinical Practice Guidelines. Before starting the study, ethics committee approval numbered 2022035 (2022/44) was obtained from the Ethics Committee of Lokman Hekim University. Informed consent was obtained from all individual participants included in the study.

AUTHORS' CONTRIBUTIONS

EİK: Conceptualization, Data curation, Formal Analysis, Writing – original draft. SD: Conceptualization, Data curation, Formal Analysis. GKB: Conceptualization, Data curation, Formal Analysis. DŞK: Conceptualization, Data curation, Formal Analysis. ZG: Conceptualization.

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ORIGINAL ARTICLE

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Assessment of cognitive function in elderly patients with heart failure

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SUMMARY

OBJECTIVE: To compare the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) tests for the identification of cognitive deficit (CD) in elderly patients with heart failure (HF).

METHODS: This was a cross-sectional study with an observational design involving 43 elderly patients with HF of both sexes, treated by the Unified Health System, who were able to understand and follow the study instructions. A sociodemographic and clinical questionnaire and the MMSE and MoCA neurocognitive tests were applied.

RESULTS: The mean age of the patients was 67 years; 67.44% were male; 53.49% were white; 58.14% had 1–4 years of schooling; 58.14% had an income of half to one minimum wage; 55.81% were married; 53.49% had a family history of HF; 90.7% denied smoking; 83.72% denied alcohol intake; 65.12% did not practice physical activity; 83.72% were hypertensive; 30.23% were diabetic; 57.89% had LVEF ≥ 50%; 39.53% have NYHA II; and 88.37% did not have a pacemaker. In the identification of CD, the MMSE test detected it in 25.58% of the patients, while the MoCA test identified it in 23.26% (p=0.043).

CONCLUSION: It was concluded that the MMSE test performed better than the MoCA test in the identification of CD in elderly patients with HF.

KEYWORDS: Cognition. Neuropsychological tests. Heart failure.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from structural or functional problems affecting ventricular filling or blood ejection. This condition compromises the heart's ability to supply sufficient oxygen to tissues to meet their metabolic needs[1,2].

Although likely underestimated, the prevalence of HF is estimated to be between 1 and 2% of the general adult population. It affects 6.5 million Brazilians and 5.7 million Americans. According to estimates, the prevalence of HF will increase by 46% between 2012 and 2030, resulting in over 8 million people with HF in Brazil, mainly due to population aging[1].

Studies have demonstrated common triggers between cardiovascular diseases and dementia, such as inflammation, oxidative stress, oxygen deprivation, and adrenergic signaling[3,4]. Maintaining normal brain function requires a constant supply of metabolites, which depends on proper heart function. As a systemic disease, HF can damage other organs, including the brain[5].

Neuropsychological tests are frequently used to detect brain dysfunction, such as cognitive deficit (CD), and evaluate performance in different cognitive areas, including learning and memory, language, visuospatial abilities, executive function, and psychomotor function. CD is defined as the decline or loss of at least one of these five domains[6].

Currently, there are no well-defined guidelines for cognitive screening, and standardized cognitive screening tests can determine the prevalence of CD in older adults with HF. Early detection of cognitive changes allows for rapid intervention through multidisciplinary follow-up, preventing the progression of functional impairment in the HF population.

Therefore, this study aims to compare the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) tests for identifying CD in older adults with HF.

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METHODS

This is a cross-sectional study with an observational design, conducted with 43 elderly patients with HF, seen at the Cardiology Outpatient Clinic of the University Hospital of the Federal University of Maranhão (HUUFMA), in the city of São Luís, MA. The research was carried out between February and December 2022 and was previously approved by the HUUFMA Ethics and Research Committee (Opinion No.: 3.902.939/CAAE: 24168819.2.0000.5086).

Patients with HF of both sexes who were 60 years of age or older, NYHA functional classes I to IV, able to comprehend and adhere to the study's instructions, and who consented to participate by signing the Informed Consent Form (TCLE) were included. The European Society of Cardiology's (2021) guidelines were taken into consideration for diagnosing heart failure (HF).

Patients with chronic atrial fibrillation; acute decompensation of HF, with a clear history of central nervous system injury, such as trauma, tumor, infection, carbon monoxide poisoning, and demyelinating disorders; alcohol abuse (as measured by the CAGE questionnaire); use of drugs or psychoactive substances (as measured by the ASSIST instrument) that can demonstrably cause changes in the nervous system and cognition; and disorders related to hearing, reading, language expression, or writing were excluded.

The following sociodemographic data were collected: age, sex, race, income, education, marital status, and clinical data such as family history of HF, ejection fraction (EF), functional classification (NYHA), and the presence of comorbidities such as hypertension and diabetes, history of smoking, alcohol consumption, and physical activity practice.

A neuropsychological assessment was also performed by a psychologist to identify CD. The MMSE test was initially applied; it has strong reliability and internal consistency, and its use is validated and recommended in Brazil, which enables a rapid assessment of cognitive functions by examining both verbal and non-verbal forms of responses.

The MMSE score ranges from 0 to 30, with higher scores indicating better cognitive performance. The test results in this study were adjusted according to the individual's education level, as described by Brucki et al[7], applying the following cut-off criteria: 20 points for illiterate patients; 25 points for those with 1–4 years of study; 26.5 points for 5–8 years; 28 points for 9–11 years; and 29 points for more than 11 years.

In addition, the MoCA test, validated for the Portuguese language, was used. A point is added to the maximum total possible score of 30 points if the individual has less than 12 years of education. In this study, the following cut-off scores were considered for the detection of CD: illiterate, score ≤ 11; 1–4 years of schooling, score ≤ 17; 5–8 years of schooling, score ≤ 19; 9–11 years of schooling, score ≤ 19; and ≥ 12 years of schooling, score ≤ 21[8].

Microsoft Office Excel (version 365) was used to tabulate the data, and R Studio (R Core Team, 2021®) was used for statistical analysis. The normality of the continuous variables was initially examined using the Shapiro-Wilk test. The description of the continuous data was given by medians and interquartile ranges (IIQ), while the categorical variables were described in simple frequencies (n) and percentages (%). The relationship between categorical variables was established using Fisher's exact test. Subsequently, the Spearman Correlation test was performed to evaluate the existence of proportionality between the continuous variables that were being studied. Statistical significance was set at $p<0.05$.

RESULTS

The sociodemographic and clinical data of 43 elderly patients with HF were analyzed. The mean age was 67 years, 67.44% were male, the white race was predominant (53.49%); 58.14% had 1–4 years of education; 58.14% had an income of half to one minimum wage; 55.81% were married; 53.49% had a family history of HF; 90.7% were non-smokers; 83.72% did not drink alcoholic beverages; 65.12% did not practice physical activity; 83.72% were hypertensive; and 30.23% were diabetic. Regarding clinical data, 57.89% had EF ≥ 50%; 39.53% NYHA II, and 88.37% did not have a pacemaker (Table 1).

In a comparative analysis of the applied tests, considering the cut-off points for the screening of CD (based on educational level), it was observed that MoCA identified CD in 23.26% of the sample and MMSE identified CD in 25.58% of the sample.

Regarding the distinction between patients with and without CD, there was a statistically significant difference between the two tests (Table 2).

There was a strong correlation between the neurocognitive test scores in identifying CD in the analyzed patients ($p<0.001$), as described in Table 3.

DISCUSSION

In line with the current study's findings, an analysis of 545 medical records of patients with heart failure (HF) receiving treatment from the Unified Health System (SUS) showed that 55.6% were male, 76.7% had hypertension, and 37.2% had diabetes[9]. According to the National Health Survey (2019), low

Table 1. Sociodemographic characteristics and clinical data of elderly patients with heart failure in São Luís, MA, Brazil, 2022.

Variable	n=431	Variable	n=431
Age	67.00 (63.50, 73.50)	Smoker	
Gender		Yes	4 (9.30%)
Female	14 (32.56%)	No	39 (90.70%)
Male	29 (67.44%)	Drinks alcohol	
Ethnicity/color		Yes	7 (16.28%)
White	23 (53.49%)	No	36 (83.72%)
Black	8 (18.60%)	Engages in physical activity	
Brown	12 (27.91%)	Yes	15 (34.88%)
Educational level		No	28 (65.12%)
Incomplete elementary school	25 (58.14%)	Hypertension	
Elementary school graduate	5 (11.63%)	Yes	36 (83.72%)
High school graduate	10 (23.26%)	No	7 (16.28%)
Incomplete bachelor's degree	1 (2.33%)	Diabetes	
Bachelor's degree	2 (4.65%)	Yes	13 (30.23%)
Income		No	30 (69.77%)
Less than ½ minimum wage	3 (6.98%)	Pacemaker	
½ to 1 minimum wage	25 (58.14%)	Yes	5 (11.63%)
1 to 2 minimum wages	12 (27.91%)	No	38 (88.37%)
2 to 5 minimum wages	3 (6.98%)	LVEF (%)	
Marital status		<40%	11 (28.95%)
Single	8 (18.60%)	40 to 49%	5 (13.16%)
Divorced	5 (11.63%)	≥50%	22 (57.89%)
Married	24 (55.81%)	NYHA	
Widowed	6 (13.95%)	I	10 (23.26%)
HF family history		II	17 (39.53%)
Yes	23 (53.49%)	III	13 (30.23%)
No	20 (46.51%)	IV	3 (6.98%)

Median (IQR); n (%); HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

Table 2. Comparison between Mini-Mental State Examination and Montreal Cognitive Assessment tests in the identification of cognitive deficit in elderly patients with heart failure in São Luís, MA, Brazil, 2022.

	MMSE (n=43)	MoCA (n=43)	p
Cognitive deficit	11 (25.58%)	10 (23.26%)	0.043
No cognitive deficit	32 (74.42%)	33 (76.74%)	

MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

Table 3. Correlation between the scores of the applied tests in elderly patients with heart failure in São Luís, MA, Brazil, 2022.

	Coefficient	p
Score MMSE vs. score MoCA	0.786	<0.001

MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

education and income between half and one minimum wage are consistent with the sociodemographic profile of SUS care[10].

It was observed that 57.89% of the sample had EF ≥ 50%, classifying the patients as heart failure with preserved ejection fraction (HFpEF). Additionally, mild symptoms (NYHA II) were assigned to 17 patients (39.53%).

The diagnosis of systemic arterial hypertension (SAH) was found in 83.72% of the sample, confirming the significance of this condition for the development of HF, in addition to family history also being relevant for this. SAH is one of the primary causes of HF in Brazil[11]. Hypertension acts in the pathophysiology of cognitive impairment through neurodegeneration[12]. Thus, there is an association between SAH, HF, and cognitive decline.

Table 2 indicates that there was a statistically significant difference between the tests that were used, which has been observed in other studies including patients with SAH, cerebrovascular disease[13], and HF[14]. In the comparison between the tests applied in patients with HF, the MMSE obtained a higher prevalence of cognitive decline (25.58%) compared to the MoCA (23.26%), with a statistically significant difference.

In a study that evaluated both tests in 106 patients diagnosed with HF and with a mean age of 68 years, it was observed that the MMSE detected cognitive decline in 68% while the MoCA test in 65% of the sample[15]. Although the prevalence of cognitive deterioration identified in the present study is lower than that predicted in the literature, these results support the findings of the present study, which similarly focused primarily on patients with HF.

A systematic review[16] showed that in the vast majority of articles analyzed, the MoCA was superior to the MMSE in detecting individuals with mild cognitive impairment (MCI), but both were similar in detecting Alzheimer's disease. In a different study, 93 hospitalized patients with HF and a mean age of 70 years were studied. It was observed that the MoCA identified MCI in 41% more cases than the MMSE, indicating that the changes in the visuospatial dimension of the MoCA were clinically more significant than those found in a similar task in the MMSE[14].

In a cross-sectional analysis of the Chinese population>55 years of age, the MoCA performed better than the MMSE, particularly in the identification of MCI, with 36.2% versus 28.6% of the sample[17]. However, in this sample, only 31.8 and 1.9% reported a history of hypertension and acute myocardial infarction, respectively, which are among the leading causes of HF in the world[11]. In the present study, 83.72% of the individuals had a history of hypertension, which may perhaps justify the discordant findings between the two studies.

Another factor for the MMSE's better performance in detecting cognitive decline may be linked to the low educational level of the sample in the present study (50.14%). In turn, the MoCA has a greater sensitivity in identifying cognitive decline in patients with higher educational levels[18], thus justifying the results obtained.

This study had some limitations, such as the lack of sample size calculation, with the sample being obtained by convenience according to the cases seen at the outpatient clinic. Another factor is the predominance of low educational level among the patients evaluated, which could have affected the diagnosis of MCI because education is a variable that significantly affects both tests.

CONCLUSION

The MMSE test performed better in detecting cognitive decline (CD) in elderly patients with heart failure (HF) compared to the MoCA test, possibly due to the low educational level of the sample analyzed. The application of neurocognitive screening tests is essential for the early identification of CD in patients with HF, aiming to provide appropriate treatment for patients.

AUTHOR CONTRIBUTIONS

LMS: Data curation, Project administration. **CPBMS:** Data curation. **NESG:** Data curation. **LPM:** Data curation. **GSP:** Data curation. **EJFF:** Data curation. **JAFN:** Formal Analysis, Supervision.

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ORIGINAL ARTICLE

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An investigation of the umbilical artery N-terminal proBrain natriuretic peptide levels of fetuses due to fetal distress in term pregnancies

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SUMMARY

OBJECTIVE: This study aimed to investigate umbilical artery N-terminal proBrain natriuretic peptide (NT-proBNP) in fetuses delivered by cesarean section due to fetal distress in term pregnancies.

METHODS: This prospective case-control study was conducted at the Antalya Training and Research Hospital Obstetric Department, Turkiye. A total of 140 pregnant women, 70 underwent elective cesarean sections between weeks 37 and 40 of gestation (Group 1, the control group) and 70 underwent cesarean sections due to fetal distress (Group 2, the study group), were included. The participants' sociodemographic and obstetric data and fetal umbilical blood NT-proBNP levels were recorded in a database.

RESULTS: Age, body mass index, gestational age, prenatal diagnostic tests, fetal anatomical scanning, and baby gender ratios were comparable between the groups (p>0.05), while statistically significant differences were observed in terms of gravidity (3.0 vs. 1.0, p≤0.001) and parity numbers (2 vs. 0, p≤0.001), baby height (50.36±0.88 vs. 49.80±0.86, p≤0.001) and weight (3422.43±409.16 vs. 3239.86±293.74, p=0.003), 1-min Apgar (9.0±0.1 vs. 8.5±1.3, p≤0.001) and 5-min Apgar (10.0±0.1 vs. 9.8±0.4, p=0.026) scores, umbilical artery pH (7.32±0.05 vs. 7.25±0.07, p≤0.001), umbilical artery base deficit (-2.48±1.23 vs. -4.36±1.09. p≤0.001), and NT-proBNP levels [8.77 (7.72–9.39) vs. 12.35 (9.69–12.92), p<0.001].

CONCLUSION: This study showed that NT-proBNP can be used as an important marker in the diagnosis of fetal distress. Prospective studies with more participants are now needed to confirm the accuracy of our results.

KEYWORDS: Fetal distress. Hypoxia. NT-proBNP. Pregnancy.

INTRODUCTION

Fetal distress is a syndrome involving respiratory and circulatory failure caused by intrauterine fetal hypoxia during birth and is closely associated with changes in fetal heart rate patterns. Fetal distress can cause hypoxic-ischemic encephalopathy and eventually lead to cerebral palsy and even perinatal death. Early detection and diagnosis of fetal distress can help prevent damage to the fetus's vital organs before birth[1-3].

The natriuretic peptide family mainly consists of brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and atrial natriuretic peptide (ANP) secreted from atrial myocytes. Although BNP was first isolated from pig brain tissue in 1988, later studies showed that it was largely synthesized and secreted from cardiac ventricular myocytes. It is mainly synthesized and secreted due to increased myocyte tension as a result of myocytes in the left ventricular wall being exposed to excessive pressure or increasing ventricular volume[4].

BNP plays an especially important role in cardio-renal functions. It reduces sodium absorption in the proximal tubules and distal nephrons in the kidney and causes vasodilation by inhibiting renin, which causes vasoconstriction, thus resulting in diuresis and natriuresis. It also reduces the release of antidiuretic hormone and the synthesis and release of aldosterone, increases the glomerular filtration rate and renal blood flow, and reduces the release of endothelin by inhibiting the cardiac sympathetic system. BNP lowers cardiac preload and afterload to reduce stress on myocytes, leading to ventricular dysfunction in patients with acute coronary syndrome[5]. It has also been suggested that BNP is secreted to compensate for cardiac effects as a result of hypoxia. Pulmonary vasoconstriction, pulmonary hypertension, and overload on the right side of the heart occur

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in cases of fetal hypoxia. BNP and NT-proBNP are released from ventricular myocytes due to cardiac effects as a result[6].

The aim of this study was to evaluate the umbilical artery NT-proBNP levels of fetuses delivered by cesarean section due to fetal distress in term pregnancies.

METHODS

This prospective case-control study was conducted between 1 April and 1 December 2023, with the permission of the Health Sciences University Antalya Training and Research Hospital Ethics Committee, Türkiye (22-12-2022 and 23-3). A total of 70 pregnant controls who underwent elective cesarean sections (Group 1) and 70 women who underwent cesarean sections due to fetal distress between 37 and 41 weeks of gestation were included in the study. The two groups' sociodemographic and obstetric characteristics and routine laboratory parameters were recorded in a database. Healthy pregnant women aged between 18 and 35 years at 37–41 weeks of gestation with no chronic diseases capable of adversely affecting fetal development (such as hypertension and systemic lupus erythematosus) were included. Fetal growth restriction, and congenital anomalies, and malformations detected in the fetus were excluded from the study.

Fetal distress assessment

A fetal distress assessment was performed for the contraction stress test (CST). For the CST, a dilute oxytocin solution is infused until three contractions occur within 10 min. A positive (abnormal) test was accepted for late decelerations following ≥50 percent of contractions. The test was commented on as positive even if the contraction frequency was less than three in 10 min. The births of pregnant women with positive CST were performed by cesarean section because a positive (abnormal) CST indicates transient fetal hypoxemia during uterine contractions and may be an indication for delivery, depending on the clinical scenario.

Serum N-terminal proBrain natriuretic peptide measurement

Fetal blood samples were obtained immediately after the fetal umbilical cord was clamped during the cesarean section; approximately 2 cc of sera were separated from the fetal cord blood. The samples were allowed to clot completely at room temperature and were centrifuged within 30 min at 3,000 rpm for 20 min. The samples were frozen at -80°C within 2 h and kept frozen until analysis.

A human NT-proBNP Elisa kit (Catalog No.: E1239Hu) was used to measure serum NT-proBNP levels. Sensitivity was studied using the enzyme-linked immunosorbent assay (ELISA) method with a standard curve range of 0.1–40 ng/mL and a sensitivity of 0.054 ng/mL. Plasma NT-proBNP levels were expressed as μg/mL.

Statistical analysis

IBM Statistics Version 22 software was used for statistical evaluation. The normality of the distribution was evaluated using the Shapiro-Wilk test, with $p>0.05$ being regarded as a normal distribution. Normally distributed data were evaluated using the Student's t-test, and non-normally distributed data were evaluated using the Mann-Whitney U test. Cut-off values for NT-proBNP levels were determined using ROC analysis. The 95% confidence interval (CI) was calculated for the area under the curve (AUC). The sensitivity, the specificity, and the positive and negative predictive values of this variable were calculated in terms of its ability to predict fetal distress. Statistical significance was set at $p<0.05$.

RESULTS

A total of 140 pregnant women, 70 underwent elective cesarean sections and 70 underwent cesarean sections due to fetal distress between 37 and 41 weeks of gestation, were prospectively enrolled consecutively in the study between 1 April and 1 December 2023.

The participants' sociodemographic and obstetric characteristics and perinatal outcomes are presented in Table 1. Significant differences were observed in terms of gravidity [3.0 (2.0–4.0) vs. 1.0 (1.0–2.0), $p<0.001$], parity numbers [2.0 (1.0–2.0) vs. 0 (0–1.0), $p<0.001$], fetal length (50.36±0.88 vs. 49.80±0.86, $p<0.001$), birthweight (3422.43±409.16 vs. 3239.86±293.74, $p=0.003$), and 1-min Apgar (9.0±0.1 vs. 8.5±1.3, $p<0.001$) and 5-min Apgar (10.0±0.1 vs. 9.8±0.4, $p=0.026$) scores.

Maternal and fetal laboratory values are presented in Table 2. Serum Htc (34.17±3.33 in Group 1 vs. 35.67±4.20 in Group 2, $p=0.021$), WBC (9.84±2.13 vs. 11.31±2.77, $p=0.002$), and CRP [5.9 (3.5–9.3) vs. 9.2 (3.3–6.4), $p=0.001$] values differed significantly. Additionally, fetal umbilical artery pH (7.32±0.05 vs. 7.25±0.07, $p<0.001$), umbilical artery base deficiency (-2.48±1.23 vs. -4.36±1.09, $p<0.001$), umbilical artery pO_2 (27.83±6.56 vs. 25.42±6.29, $p=0.029$), and umbilical artery NT-proBNP [8.77 (7.72–9.39) vs. 12.35 (9.69–12.92), $p<0.001$] levels differed significantly between the groups, while umbilical artery $SatO_2$ and umbilical artery pCO_2 were comparable between them.

Table 3 shows the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for umbilical

Table 1. The groups' sociodemographic and obstetric characteristics and perinatal results.

			Control group (n=70)	Study group (n=70)	p
Age (years)			29.47±6.36	27.47±6.21	0.335
BMI (kg/m^2)			30.73±4.09	31.02±3.12	0.645
Gravidity			3.0 (2.0–4.0)	1.0 (1.0–2.0)	<0.001*
Parity			2.0 (1.0–2.0)	0 (0–1.0)	<0.001*
Number of cesarean deliveries			1.0 (0–1.0)	–	
Gestational age (weeks)			39.1±1.1	39.2±1.3	0.512
Indication (n, %)	CPD		6 (8.6%)	0 (0%)	<0.001*
	Before cesarean delivery		21 (30.0%)	0 (0%)	
	PROM		0 (0%)	29 (41.4%)	
	Macrosomia		6 (8.6%)	0 (0%)	
	Recurrent cesarean delivery		34 (48.6%)	0 (0%)	
	Term pregnancy		0 (0%)	27 (38.6%)	
	Presentation abnormality		3 (4.3%)	0 (0%)	
	Surmaturity		0 (0%)	14 (20.0%)	
Double screening test (n, %)	Normal		36 (51.4%)	27 (38.6%)	0.126
Triple screening test (n, %)	Normal		29 (41.4%)	25 (35.7%)	0.487
Fetal anatomical screening (n, %)	Normal		41 (58.6%)	34 (48.6%)	0.236
OGTT (n, %)	Normal		31 (44.3%)	25 (35.71%)	0.301
Fetal height (cm)			50.36±0.88	49.80±0.86	<0.001*
Birth weight (g)			3422.43±409.16	3239.86±293.74	0.003*
Sex (n, %)		Female	37 (52.9%)	36 (51.4%)	0.866
		Male	33 (47.1%)	34 (48.6%)	
Apgar score		1-min	9.0±0.1	8.5±1.3	<0.001*
		5-min	10.0±0.1	9.8±0.4	0.026*
NICU admission (n, %)			0 (0%)	4 (5.7%)	0.120
NICU duration (days)			–	0 (0–0)	–

BMI: body mass index; CPD: cephalo-pelvic disproportion; PROM: premature rupture of membranes; OGTT: oral glucose tolerance test; NICU: neonatal intensive care unit. *Statistically significant.

artery NT-proBNP (AUC: 0.894; cut-off value: 8.54; CI: 0.800–0.927; sensitivity: 86%; specificity: 57%; PPV: 67%; NPV: 83%).

DISCUSSION

This study showed that umbilical artery pH and pO_2 levels decreased, base deficit increased, and fetal height, weight, and 1- and 5-min Apgar scores were lower in the fetal distress group. In addition, umbilical artery NT-proBNP levels were higher in the fetal distress group.

A previous study from Turkiye involving 130 pregnant women investigated the effect of the level of prenatal bonding between the mother and the fetus on prenatal outcomes. The authors reported that 49.2% of the participants had gravida 1 and 34.6% had gravida 2, while 62.3% had parity 0 and 30.8% had parity 1. The participants' mean age was 30.37±4.75[7]. In the present study, the average age of the patients in the fetal distress group was 27.47±6.21, which is consistent with the literature. The median gravidity value was 1, and the median parity value was 0.

Jadhav et al. examined Doppler parameters in 32 pregnant women with fetal distress and 100 women who delivered by elective cesarean section. They found that the gravidity number of pregnant women who underwent an elective cesarean section was found to be higher (3.4±0.8 vs. 1.2±0.4) than that

Table 2. The groups' laboratory values.

		Control (n=70)	Study (n=70)	p
MATERNAL	Hb (10^3/mm^3)	11.3±1.2	11.5±1.5	0.321
	Htc (10^3/mm^3)	34.17±3.33	35.67±4.20	0.021*
	WBC (10^3/mm^3)	9.84±2.13	11.31±2.77	0.002*
	PLT (10^3/mm^3)	228.64±59.60	251.23±75.31	0.051
	Glucose (mg/dL)	80.57±13.64	79.91±11.26	0.75
	Creatinine (mg/dL)	0.65±0.09	0.64±0.09	0.58
	ALT (U/L)	14.0 (10.0–17.0)	12.0 (9.0–16.0)	0.206
	AST (U/L)	15.0 (12.0–18.25)	16.5 (13.0–21.0)	0.142
	CRP (mg/L)	5.9 (3.5–9.3)	9.2 (3.3–6.4)	0.001*
	Leucocyte in urine	0 (0–2.75)	0 (0–4.0)	0.118
	Leucocyte esterase in urine	0 (0–0)	0 (0–0)	0.118
	Bacteria in urine	0 (0–0)	0 (0–0)	0.629
	Protein in urine	0 (0–0)	0 (0–0)	0.247
FETAL	Umbilical artery pH	7.32±0.05	7.25±0.07	<0.001*
	Umbilical artery base deficiency	-2.48±1.23	-4.36±1.09	<0.001*
	Umbilical artery $SatO_2$	58.09±11.34	58.10	0.995
	Umbilical artery pCO_2	41.87±6.81	42.95±8.93	0.423
	Umbilical artery pO_2	27.83±6.56	25.42±6.29	0.029*
	Umbilical artery NT-proBNP (µg/mL)	8.77 (7.72–9.39)	12.35 (9.69–12.92)	<0.001*

Hb: hemoglobin; Hct: hematocrit; WBC: white blood cell; PLT: platelet; ALT: alanine amino-transferase; AST: aspartate amino-transferase; CRP: C-reactive protein; $SatO_2$: oxygen saturation; pCO_2: partial carbon dioxide; pO_2: partial oxygen; NT-proBNP: N-terminal proBrain natriuretic peptide. *Statistically significant.

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive values for umbilical artery N-terminal proBrain natriuretic peptide.

	AUC	Cut-off value	95%CI	Sensitivity	Specificity	PPD	NPD	p
Umbilical artery NT-proBNP	0.894	8.54	0.800–0.927	86%	57%	67%	83%	**<0.001***

AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; NT-proBNP: N-terminal proBrain natriuretic peptide. *Statistically significant.

in the fetal distress group[8]. In another study involving multiparous and nulliparous women (nulliparous: 456 and multiparous: 152), the fetal distress rate was significantly higher in the nulliparas[9]. In the present study, gravidity and parity were both significantly lower in the fetal distress group.

Premature membrane rupture, which occurs spontaneously in 3% of women after the 37th week of pregnancy, can result in 85% neonatal morbidity and mortality. This condition was observed in 41.4% of the case group in the present study, the prevalence was 13.7% in Addisu et al.'s[10] study.

Post-term pregnancy is associated with negative perinatal and maternal outcomes, and fetal morbidity and mortality increase in line with the gestation period[11]. A retrospective study from Iran of 8888 births between 2020 and 2022 reported a prevalence of 4.1%. For macrosomic babies, the odds ratio (OR) for premature birth was 2.24 (95%CI: 1.34–3.0), the OR for meconium amniotic fluid was 2.32 (95%CI: 1.59–3.14), and the OR for fetal distress was 2.38 (95%CI: 1.54–2.79)[12]. In the present study, premature pregnancies occurred in 20% of the fetal distress group, and we concluded that prolonging pregnancy exacerbates fetal distress, a finding consistent with the previous literature.

A study of the relationship between NICU requirements and fetal distress reported that fetal distress affecting birth weight and NICU requirements were higher in low birth weight babies[13]. In the present study, the height and weight of the babies in the fetal distress group were significantly lower than those of the control group babies, with 5.7% of the fetal distress group babies requiring NICU admission whereas none of the control group babies did.

Fetal acid-base balance affects the oxygenation of fetal organs, especially in the central nervous system and cardiovascular system, as well as Apgar scores[14]. The main buffers used to neutralize hydrogen ion production by the fetus are plasma bicarbonate and Hb. Although inorganic phosphates and erythrocyte bicarbonate also represent potential buffers, they play a less important role in fetal acid-base homeostasis[15]. In high-risk situations such as fetal distress, fetal acid-base balance is disrupted and meconium is observed in the amniotic fluid, resulting in changes in the fetal heart rate pattern[16]. A study of 216 pregnant women observed a decreased umbilical artery pH in the fetal distress group compared to the control group. In addition, a positive correlation was found between the level of acidosis in fetal umbilical artery pH and fetal hypoxia[17]. Bligard et al. reported that the risk of neonatal morbidity was twice as high in cases of fetal acidemia and that the risk of fetal mortality increased in line with the deepening of acidosis[18]. Consistent with the previous literature, significantly increased acidosis and higher base deficit were observed in the fetal distress group compared to the control group in our study, while no significant difference was observed in terms of partial carbon dioxide or saturation values.

BNP inhibits the cardiac sympathetic system in the circulatory system and reduces the release of endothelin. It also reduces the release of antidiuretic hormone and the synthesis and release of aldosterone in the urinary system, resulting in diuresis and natriuresis[19]. A study examining vasoactive and natriuretic mediators in umbilical cord blood reported BNP values between 4 and 17.4 pg/mL, with an average of 5 pg/mL[20]. Itoh et al. observed that umbilical artery BNP levels increased in newborns with fetal distress[21]. Vijlbrief et al. reported that BNP, whose median value was 69 pmol/L in umbilical blood samples from 164 newborns, was associated with fetal distress[22]. In the present study, the median umbilical artery NT-proBNP value of the fetuses in the fetal distress group was 12.35 µg/mL, higher than that of the control group.

Yadav et al. examined NT-proBNP levels in the intrauterine cord blood. The authors went on to suggest that NT-proBNP secretion increased as a result of myocardial insufficiency due to anemia. They also showed that NT-proBNP values were higher in patients with hydrops than in those without and were positively correlated with the degree of anemia[23]. In the present study, NT-proBNP levels increased significantly in the group that developed fetal distress as a result of fetal hypoxia.

Bayman et al. investigated the effect of gestational diabetes on BNP levels in the fetal umbilical artery. Although those authors determined no significant difference between the groups in terms of umbilical cord BNP levels, cord blood BNP values were higher in girls than in boys, and in the gestational diabetes (GDM) group using insulin compared to the non-insulin GDM group[24]. No significant difference was observed in BNP levels between male and female babies in the present study.

The fact that this study was conducted at a tertiary reference center represents an important limitation. However, a particular strength of the research is that the results from the study region can be adapted to all of Türkiye.

In conclusion, hypoxia and acidosis caused by stress increased the umbilical artery NT-proBNP values in newborns. Increased NT-proBNP levels resulting from changes caused by fetal distress may represent a harbinger of fetal morbidity and mortality. Prospective studies with larger numbers of participants are now needed to confirm the results of this study.

AUTHORS CONTRIBUTIONS

DE: Project administration, Writing – review & editing. **MBB:** Project administration. **DO:** Data curation. **MK:** Data curation. **HYE:** Data curation. **ZOI:** Data curation, Writing – review & editing.

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ORIGINAL ARTICLE

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Anti-thyroid peroxidase antibody in stroke localization: exordium doorway of preliminary findings in thyroidology?

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SUMMARY

OBJECTIVE: Stroke is a chronic health problem that affects all areas of life. The presence of thyroid autoantibodies can augment the severity of stroke. The aim of this work is to investigate whether there is a relationship between the site of stroke involvement and the anti-thyroid peroxidase antibody (anti-TPO) or not. This is the first study in the English-language literature.

METHODS: A total of 39 patients with a diagnosis of acute ischemic stroke were included, and the cases under 18 years of age with an infection and the ones with autoimmune diseases other than Hashimoto's thyroiditis were excluded from the study design. The patients' age, gender, smoking status, comorbid conditions, and stroke localization in brain imaging were recorded. The region involving the anterior circulation area originating from the internal carotid artery was evaluated as anterior, and the region possessing the vertebrobasilar circulation area from the vertebral arteries was considered posterior involvement. Thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C-reactive protein (CRP), sedimentation, and anti-TPO were retrospectively analyzed.

RESULTS: As a consequence, gender distribution, smoking, comorbid conditions, TSH, T3, T4, triglyceride, HDL, LDL, CRP, and sedimentation did not differ significantly, while the age of the posterior-located stroke was lower than that of the cases with the anterior. The anti-TPO value was significantly lower in posterior-located strokes than in the anterior system.

CONCLUSION: In summary, the anti-TPO value was recognized as higher in the anterior stroke localization. Thyroiditis and accompanying anti-TPO autoantibody positivity are conditions that should not be ignored by thyroidologists and thyroid-health providers.

KEYWORDS: Stroke. Thyroid gland. Peroxidase. Thyroidologists. Pathology.

INTRODUCTION

Hashimoto's thyroiditis (HThy) is an autoimmune thyroid disease and the most common cause of hypothyroidism in developed countries. Both cellular and humoral responses play a role in pathogenesis. Initially, activation of thyroid-specific CD4+ T cells stimulates the generation of CD8+ cytotoxic T cells and autoantibodies. Cytotoxic T cells are mainly responsible for parenchymal destruction, and sensitized B cells secrete antibodies that block the action of TSH, contributing to the development of hypothyroidism. As a result of the presentation of thyroid antigens released by tissue destruction to the immune system, antithyroglobulin (anti-Tg) and antithyroid peroxidase antibodies (anti-TPO) are released into the circulation, which are helpful in diagnosis. HThy is associated with many systemic diseases as well as local effects, which can be essential and affect the person's vital functions. HThy is blamed for many significant cardiovascular[1] and cerebrovascular diseases[2].

Stroke has a vital place in cerebrovascular diseases and is a chronic health problem that affects all areas of life. It is the world's most common cause of death after heart disease and cancer, and the third most common cause of death. A stroke is defined as a sudden and rapidly developing loss of motor control, sensation deficit, balance disorder, speech, and cognition from dysfunction to coma for more than 24 h[3]. Autoimmunity, particularly anti-TPO levels in the thyroid, has been raised as associated with the development of intracranial stenosis even in euthyroid patients[4]. The presence of thyroid autoantibodies without hypothyroidism has been reported as a condition that

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augments the severity of stroke[5]. The relationship between one of these antibodies, anti-TPO, and stroke localization has not been clearly demonstrated.

Evaluations regarding anterior and posterior strokes and clinical, etiological, radiological, and outcome factors are scarce. Approximately 80% of cerebral blood flow is obtained from the anterior circulation, and 20% is from the posterior. Arterial anatomy and location of occlusion show significant differences in anterior and posterior strokes[6]. Data on stroke mechanisms in posterior and anterior strokes are conflicting. There are studies supporting the fact that embolism is more common in the posterior and lacunae in the anterior[7,8]. To the best of our knowledge, the present study is the first work in the English-language literature to evaluate the liaison between anti-TPO levels and the site of stroke involvement.

In this study, in which we investigated the relationship of anti-TPO with strokes in the anterior and posterior circulation regions of the brain, we found that anti-TPO levels were higher in strokes in the anterior circulation systems.

METHODS

Study design and participants

A total of 39 patients with a diagnosis of acute ischemic stroke were included in this study. The inclusion criteria were possessed a diagnosis of acute ischemic stroke, being under 18 years of age, and having an infection. The exclusion criteria were having autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis and having positive autoantibodies other than thyroid autoantibodies, which may be a marker of autoimmunity. All participants provided written informed consent, and the study was performed in accordance with the Declaration of Helsinki.

The patients' age, gender, smoking status, comorbid conditions, and stroke localization in brain imaging were recorded. In the laboratory, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), anti-TPO, and other laboratory parameters that constitute risk factors for stroke, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C-reactive protein (CRP), and sedimentation levels were measured. Participants' thyroid function test results were consistent with euthyroidism. Diffusion magnetic resonance imaging (MRI) was used as the brain imaging method. Anterior involvement, which originates from the internal carotid artery, and posterior involvement, which is involved from the vertebrobasilar circulation, were evaluated with an MRI, which was performed at the time of diagnosis.

Sample size and statistical analyses

G*Power (V3.1) software (Informer Technologies, Inc., Los Angeles, CA, USA) was used to calculate the required sample size. To the best of our knowledge, there is no study comparing the anterior and posterior regions in the English-language literature. We set the effect size to 0.95. Based on a power of 80% and a 5% level of significance, the total sample size required was calculated as 38. In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. An independent sample t-test and a Mann-Whitney U test were used to analyze the quantitative independent data. Afterward, the chi-square test was utilized in the analysis of qualitative independent data, and the Fischer test was performed when the chi-square test conditions were not met. The SPSS 28.0 program was used in the analysis. The receiver operating characteristic (ROC) curve was created by selecting options for the anti-TPO threshold value depending on different sensitivity-specificity characters. The choice of optimum cut-off sensitivity and specificity was made considering the case where the Youden index is the largest.

RESULTS

Gender distribution, smoking, comorbid conditions, and laboratory values such as TSH, T3, T4, triglyceride, HDL, LDL, CRP, and sedimentation did not differ significantly in the group with stroke localization in the anterior and posterior systems. The age of the posterior-located stroke patients was lower than that of the cases with the anterior system. The anti-TPO value was significantly lower in the group with stroke localization in the posterior system than in the group with stroke localization in the anterior system (Table 1).

A significant [area under the curve: 0.724 (0.518–0.930)] effectiveness of the anti-TPO value was observed in the differentiation of patients with stroke localization from the anterior and posterior systems. A significant [area under the curve: 0.729 (0.540–0.919)] efficacy of the anti-TPO 10 cut-off value was observed in the differentiation of patients with stroke localization from the anterior and posterior systems (Figure 1). At the anti-TPO 10 cut-off value, the sensitivity was 70.0%, the positive prediction was 50.0%, the specificity was 75.9%, and the negative prediction was 88.0% in separating patients with stroke localization from the anterior and posterior systems (Table 2).

DISCUSSION

Hashimoto's thyroiditis is considered an autoimmune thyroid disease characterized by high antibody titers, which frequently

affects females and is most often diagnosed between the ages of 30 and 50. HThy may be accompanied by many clinical findings, both locally and systemically. However, studies have shown that various systemic problems are more common in the presence of thyroid autoantibodies in patients without hypothyroidism. There are various studies in the literature that have shed light on the recent relationship between increased stroke cases and thyroid autoantibody positivity. There is a relationship between young stroke cases and thyroid autoantibody-positive euthyroid patients[9]. It has been shown that anti-TPO plays a role in arterial remodeling in patients with intracranial stenosis, which is the most common cause of ischemic stroke worldwide[4]. This study exhibits that anti-TPO levels are associated with stroke with anterior circulation involvement, independent of thyroid functions.

Thyroid hormones are modulators that critically affect different aspects of tissue development. The brain is a vital target

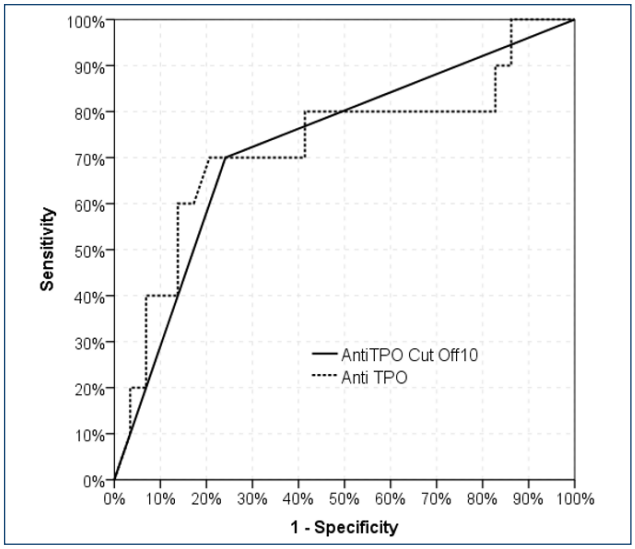

Figure 1. The ROC curves of the anti-TPO w/wo 10 cut off value to differentiate the patients with stroke in the anterior and posterior systems.

Table 1. Demographic, clinical, and laboratory characteristics according to the stroke involvement site.

		Stroke localization								p	
		Anterior (n=29)				Posterior (n=10)					
		Mean±SD/n-%			Median	Mean±SD/n-%			Median		
Age		77.3	±	10.4	80.0	68.5	±	13.6	69.5	0.039	t
Gender	Female	15		51.7%		7		70.0%		0.315	X^2
	Male	14		48.3%		3		30.0%			
Smoking	No	18		62.1%		7		70.0%		0.884	X^2
	Ex-smoker	3		10.3%		0		0.0%			
	Yes	8		27.6%		3		30.0%			
Diabetes	(-)	18		62.1%		8		80.0%		0.300	X^2
	(+)	11		37.9%		2		20.0%			
Hypertension	(-)	4		13.8%		4		40.0%		0.077	X^2
	(+)	25		86.2%		6		60.0%			
Cardiovascular disease	(-)	16		55.2%		5		50.0%		0.777	X^2
	(+)	13		44.8%		5		50.0%			
TSH		1.9	±	1.6	1.3	2.4	±	2.1	1.9	0.520	m
T3		2.6	±	0.5	2.6	2.3	±	0.4	2.4	0.209	t
T4		1.2	±	0.2	1.2	1.1	±	0.2	1.1	0.082	t
Anti-TPO		21.3	±	28.7	12.4	11.3	±	7.9	9.0	0.037	m
Triglyceride		127.7	±	55.9	124.0	162.6	±	63.9	137.0	0.109	t
HDL (mg/dL)		41.7	±	9.1	43.0	43.1	±	12.2	45.5	0.702	t
LDL (mg/dL)		104.1	±	32.8	105.0	111.3	±	43.1	120.0	0.584	t
CRP (mg/L)		23.1	±	30.0	12.7	52.4	±	128.5	4.6	0.139	m
Sedimentation		36.8	±	17.5	35.0	28.0	±	23.8	19.5	0.062	m

[t]Independent sample t-test; [m]Mann-Whitney U test; [X^2]Ki-kare test (Fischer's exact test).

Table 2. The receiver operating characteristic analysis in terms of anti-thyroid peroxidase antibody cut-off 10.

		Area under the curve		% 95 Confidence Interval			p
Anti-TPO		0.724		0.518	-	0.930	0.037
Anti-TPO cut-off 10		0.729		0.540	-	0.919	0.032
		Anterior	Posterior				%
Anti-TPO	<10	22	3	Sensitivity			70.0%
	>10	7	7	Positive prediction rate			50.0%
				Specificity			75.9%
				Negative prediction rate			88.0%

tissue for thyroid hormones, and deficiency or excess in thyroid hormone levels disrupts neuronal organization during embryonic and adult life, and cognitive functionality may be lost. Research results explaining the relationship between acute cerebral and cardiac diseases and thyroid hormones have been increasing recently. Ischemic stroke is a significant neurological disease and a major cause of disability and death. Neurological findings vary according to the size and location of the infarction. Temporary or permanent occlusion of cerebral vessels causes significant functional losses in patients after neuronal damage[10-12].

Atherosclerosis is always accompanied by an autoimmune response, which has a secondary autoimmune component, and a self-antigen-specific adaptive immune response plays a role in the disease. The improvement of intracranial stenosis associated with Graves' disease after high-dose methylprednisolone and plasmapheresis treatment and the stabilization of Moya Moya disease with hyperthyroidism after plasmapheresis have been demonstrated in case reports[13,14]. Elevation of anti-TPO, a substantial thyroid autoantibody in thyroidology[15-19], was found in patients with euthyroid young intracranial stenosis in a study[9]. Inappropriate autoimmune responses trigger vascular damage, contributing to endothelial dysfunction and atherosclerosis[20]. Xiang et al.[21] advocated that endothelium-dependent arterial dilatation is impaired in patients with euthyroid autoimmune thyroiditis. Piga et al.[22] stated that brain perfusion was reduced in patients with autoimmune thyroiditis. Compared to healthy donors, it has been shown that higher rates of interferon-γ (IFN-γ) are produced from T cells of patients with high anti-TPO titers by Laurat and colleagues[23]. It has been emphasized in studies that the presence of aberrant T cells in atherosclerosis lesions and inappropriate IFN-γ release from these T cells play a momentous role in the development of atherosclerosis[24], which results point to a link between thyroid autoantibodies and atherosclerosis. Tanaka et al.[25] revealed that thyroid antibodies were associated with stenotic lesions in the terminal portion of the internal carotid artery. In this respect, in our study showing that anti-TPO positivity is at high titers in patients with stroke with anterior system involvement, we think that interventions to reduce autoimmunity against the thyroid gland may also prevent the recurrence of a new stroke that may develop. However, these are preliminary findings, and comprehensive studies are required in the future.

Limitations

Our study has some limitations. The small numeric values of patients, the fact that the patient diagnosed with stroke had brain imaging at the time of diagnosis, and the lack of serial measurements of anti-TPO values with previous imaging methods can be considered limitations. Non-HDL cholesterol components, which are an important cardiovascular risk factor, were not included in the laboratory parameters, and the relationship between anti-TPO values and clinical findings was not evaluated, which is an additional limitation. Furthermore, there may be anatomical variations between people that were not taken into account in the study.

CONCLUSION

In summary, the prevention of stroke cases, which significantly affects public health, is an issue that should be considered. In this respect, studies supporting the relationship between autoinflammation and atherosclerosis, which is the leading cause of stroke, are essential. The findings of this study point out that the anti-TPO value was significantly higher in the anterior stroke localization. Finally, thyroiditis and accompanying anti-TPO autoantibody positivity are conditions that should not be ignored by thyroidologists and thyroid-health providers.

AUTHORS' CONTRIBUTIONS

NCY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration,

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

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ORIGINAL ARTICLE

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Serologic screening for viral infections among blood donors: a study in a blood bank in southern Brazil

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SUMMARY

BACKGROUND: Routine screening for viral infections at blood donation is important to avoid transfusion-transmitted infections. It also offers an opportunity to detect an asymptomatic infection.

OBJECTIVE: To study changes in serology positivity for viral infections (B and C hepatitis, HTLV-1/2, and HIV) at blood donation in a blood bank from Southern Brazil, comparing two periods of 5 years: the period from 2013 to 2017 with the period from 2018 to 2022. In addition, data on the donor fidelity rate during the studied period were sought.

METHODS: Retrospective study using data from 2013 to 2022 from a single blood center electronic database from Curitiba, Southern Brazil.

RESULTS: A significant drop in positive serology for all studied viruses was observed: highest in HIV (OR=0.39; 95% CI=0.27–0.57) and lowest in total anti HBc (0.56; 95 CI=0.50–0.63). Anti HBc serology became more commonly seen in women in the period of 2018–2022 when compared to men. No changes in the distribution of positive serology according to donors' ages were observed. Loyalty rates had a median of 70%, with the lowest being 60% in 2013, while the highest was 73% in 2018 and 2022.

CONCLUSION: A significant reduction in discarded blood bags due to viral serology was observed when the period of 2013–2017 was compared to 2018–2022 on this blood bank; the highest reduction was observed in HIV serology and the lowest in HBc serology, which became more common in women in the second period. High rates of donor fidelity were observed during the period studied.

KEYWORDS: Blood donors. Viral diseases. Viral hepatitis. HIV.

INTRODUCTION

While blood transfusion may be a lifesaving or health-improving medical intervention, it also carries some risks and complications[1]. Transfusion-transmitted viral infections such as hepatitis C and B, infection by human immunodeficiency virus (HIV), and human T cell lymphotropic virus (HTLV) 1/2 are some of them[1]. To ensure a safe blood transfusion, screening for viral infections is routinely included among the protective measures used at blood banks.

Hepatitis B and C are major causes of chronic hepatic diseases, liver cirrhosis, and hepatocarcinoma[2], as well as several extrahepatic manifestations such as mixed cryoglobulinemia, lymphoproliferative disorders, renal disease, insulin resistance, type 2 diabetes, and rheumatic manifestations[3,4]. From 1999 to 2020, approximately 689,933 new cases of viral hepatitis were registered in Brazil, 254,389 (36.9%) cases of hepatitis B, and 262,815 (38.1%) of hepatitis C[2]. In this same time period, 78,642 deaths from viral hepatitis were recorded (21.3% from hepatitis B and 76.2% from hepatitis C)[1]. Fortunately, hepatitis B vaccination and effective treatment for hepatitis C have reduced the burden of these two infections in the general population[5]. In Brazil, hepatitis B vaccination was initially introduced in the National Immunization Calendar in the 1990s and was intended for all children in their first year of life; in 2016, the coverage was expanded to include all individuals, irrespective of age[6]. Although there is no effective vaccination for hepatitis C, treatment with direct-acting antiviral agents has resulted in high rates of sustained virologic response[5]. interrupting the sequence of transmission. Considering this, it is possible to hypothesize that, among blood donors, the number of individuals who are positive for hepatitis B and C has dropped recently, reducing the number of blood bags discarded because of these infections.

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HTLV-1 is considered the most oncogenic human retrovirus pathogen[7]; it is associated with the occurrence of at least two severe diseases: adult T cell leukemia-lymphoma[8] and HTLV-1-associated myelopathy, a fatal disease also known as tropical spastic paraparesis[9]. This infection has also been associated with uveitis, autoimmune thyroiditis, myositis, arthritis, and Sjogren's syndrome[10]. Differently from other viral blood transmitted infections, HTLV-1 results in the transference of infected lymphocytes rather than cell-free viral particles[11]. Its structure is very similar to that of HIV, but it differs in that it does not induce T cell death but rather cell proliferation and transformation[12]. The frequency of HTLV infections in Brazil ranges from 0.01 to 1.35% in the general population, depending on the geographical area and the presence of behavioral risk factors[13]. It is more frequent in women, with lower levels of education[14]. In Brazil, blood products have been obligatorily screened for HTLV infections since 1993[14].

Regarding HIV, from 2007 to July 2021, 381,793 infections were registered in Brazil: 69.8% in men and 30.2% in women[14]. According to the Ministry of Health, there was a decrease of 35.7% in the detection rate from 2012 to 2020, but underreported rates during the COVID-19 pandemic may be responsible for this reduction, especially in 2020[14].

The purpose of this study was to investigate the prevalence of seropositivity for viral infections – HIV 1/2, HTLV1/2; hepatitis B and C – in blood donors from a southern Brazilian blood bank, comparing rates of positive serology from 2013 to 2017 with 2018 to 2022, with the objective of accounting for the demographic changes that may have occurred during this time period. In addition, data on the donor loyalty rate during the studied period were sought.

METHODS

Ethical issues

This study was approved by the local Research Ethics Committee under protocol number 5.902.331, effective February 2023.

Design study and data collection

A retrospective study was conducted using data from 2013 to 2022 from a single blood center electronic database in Curitiba, southern Brazil.

The study took into consideration the number of blood donations per year, donor loyalty rates in the period studied, the number of annual donations by sex, and the total number of blood donors rejected annually due to positive viral hepatitis, HTLV-1, and HIV serologies from January 2013 to December 2022. The study period was divided into two groups, the first 5 years (2013–2017) were compared to the last five years (2018–2022).

The National Health Surveillance Agency (ANVISA) standards were followed at this blood bank. Validated commercial kits that detect antibodies or antigens by immunoenzymatic methods (Chemiluminescence) using automated procedures (Alinity, Abbott, Lake Forest, USA) were used to detect hepatitis B (anti-HBc and HBsAg), hepatitis C (anti-HCV), HIV (anti-HIV-I, anti-HIV-II, and HIV antigen testing p24), and HTLV (anti-HTLV-1 and anti-HTLV-2).

According to the recommendation of ANVISA, when the initial sample taken at the time of donation was positive, it was considered a rejected donation by positive serology, regardless of subsequent confirmatory testing[15].

Statistical analysis

Data was expressed in absolute numbers, and frequencies were expressed in percentages. Comparison analysis was performed using the χ^2 test using the software Graph Pad Prism version 6.0 (GraphPad Software Inc., La Jolla, CA, USA). p-values less than 0.01 were considered significant.

RESULTS

Approximately 264,922 blood donations were registered between 2013 and 2022, with 46.0% from women and 53.9% from men. During this time period, 216 (0.082%) blood bags were rejected due to positive serology for hepatitis C; 106 (0.040%) due to positive HBsAg; 1485 (0.561%) due to positive total anti-HBc; 71 (0.027%) due to positive HTLV; and 136 (0.051%) due to positive HIV.

Donor loyalty rates in the period had a median of 70%, with the lowest in 2013 (64%) and the highest in 2018 and 2022 (73% in both).

Figure 1 shows the results of the first 5-year time period (2013–2017) compared to the last 5-year time period (2018–2022). A significant reduction in positive serology for all studied viruses was found, with HIV showing the greatest reduction and total anti-HBc serology the lowest.

The comparison of positive serology by sex for these two time periods is shown in Table 1. In both time periods, women had a slightly higher positive rate in total anti-HBc than men; in the years 2018–2022, the proportion of positivity increased in women and decreased in men significantly. The proportion of changes in positive HIV serology was similar in both sexes.

The distribution of rejection bags based on positive serology and age is shown in Table 2.

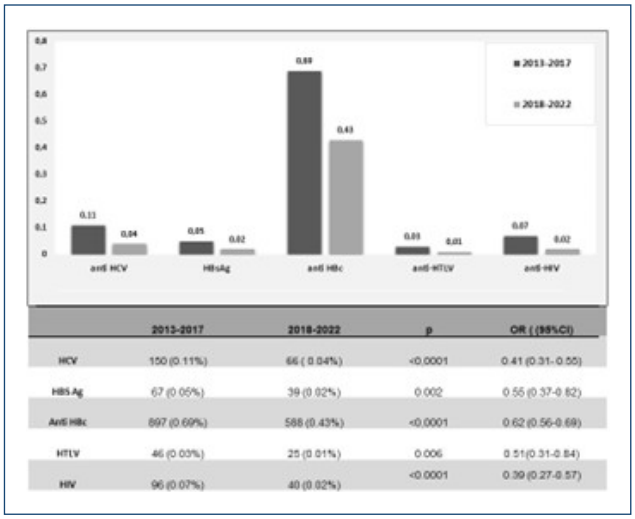

Figure 1. Comparison of positive viral serology between 2013–2017 and 2018–2022.

DISCUSSION

Screening for viral infections during blood donation not only reduces the risk of transmission but also offers an opportunity to detect the carrier of an asymptomatic disease and establish proper treatment. The prevalence of blood bags rejected by these infections may provide some perspective on how these infections affect the local region. Although blood donors are usually healthier than the general population and most positive serological tests detected at blood donation are in asymptomatic or unknown carriers, and in a lower proportion than the overall population, the change in serological test positivity over time may show a trend in the prevalence of infections in a given geographical region. In this study, there was a significant reduction in the prevalence of all studied viral infections from the first five studied years (2013–2018) compared to the second five studied years (2019–2022). The most commonly positive serology was for total anti-HBc, which also had the lowest serology reduction between the two studied periods.

The first viral antigen identified in the blood after an individual has an acute-phase infection by the hepatitis B virus is

Table 1. Comparison of discharged bags according to viral serology by sex during the periods of 2013–2017 and 2018–2022.

		Women	Men	p	OR (95%CI)
HCV	2013–2017	40.0%	60.0%	0.65	–
	2018–2022	43.3%	56.6%		
HBs Ag	2013–2017	43.2%	56.7%	0.77	–
	2018–2022	46.1%	53.8%		
Total anti-HBc	2013–2017	51.0%	48.9%	0.004	OR=1.36 (1.10–1.67)
	2018–2022	58.6%	41.3%		
HTLV	2013–2017	48.6%	51.3%	0.72	
	2018–2022	50.8%	49.1%		
HIV	2013–2017	52.7%	47.2%	0.35	
	2018–2022	48.8%	51.1%		

Table 2. Comparison of discharged bags due to viral serology according to donors' age during the periods of 2013–2017 and 2018–2022.

		<20 years	20–39 years	40–59 years	≥60 years	p
HCV	2013–2017	3.8%	53.0%	41.5%	1.5%	0.42
	2018–2022	1.1%	61.6%	34.8%	2.3%	
HBs Ag	2013–2017	4.4%	55.2%	32.8%	7.4%	0.14
	2018–2022	0	56.4%	43.5%	0	
Anti-HBc	2013–2017	2.2%	50.1%	45.3%	2.2%	<0.0001
	2018–2022	0.8%	37.2%	59.1%	2.7%	
HTLV	2013–2017	25.3%	31.3%	27.3%	16.0%	0.95
	2018–2022	24.1%	34.4%	26.7%	14.6%	
HIV	2013–2017	27.1%	28.5%	26.6%	17.7%	0.62
	2018–2022	23.8%	32.0%	28.5%	15.6%	

hepatitis B surface antigen (HBsAg), which remains positive even in the chronic phase, but becomes undetectable after the virus is cleared. Therefore, HBsAg is the infection marker used to detect the virus[16]. The core particle (HBc) encloses the HBV genome; the anti-HBc IgM is produced when the host clears the HBsAg by producing HBsAg antibodies. Isolated total anti-HBc (with negative HBsAg and anti-HBs) is the only marker of HBV infection when the host has undetectable levels of HBsAg, but has not yet developed anti-HBs. Blood donors are infectious at this stage; therefore, it is necessary to measure total anti-HBc during screening[16-18]. Chronic HBV infection is associated with IgG anti-HBc antibodies. Anti-HBc antibodies are also useful in detecting occult HBV infection, which occurs when there is low-level HBV DNA in the serum, hepatic tissue, or immune cells of a patient with serological markers of the previous infection (anti-HBc or anti-HBs positive) and the absence of serum HBsAg. Therefore, a positive anti-HBc antibody is a key marker of an occult HBV infection[17-20]. A significant difference between the positivity of HBsAg and anti-HBc was found in this study, emphasizing the importance of undertaking both serologic tests.

In most blood banks, including the one where this study was conducted, screening is done with HBsAg and anti-HBc total (IgM+IgG), and the latter test is useful to identify previous and current HBV infection[15]. Curiously, the proportion of women detected by anti-HBc but not by HBsAg increased during the second studied time period (2018–2022). Fasola et al.[16] found no sex differences in anti-HBc positive blood donors in a Nigerian Blood Bank, but this prevalence was higher in individuals over the age of 36. In our study, almost all detected infections occurred in donors aged 20–59 years during the two studied periods. In a study carried out at the same blood bank in the period ranging from January 2003 to December 2012, of the total number of donations, the serological testing with the highest positivity was anti-HBc (2.7% of discards), HIV (0.9%), hepatitis C (0.8%), HBsAg (0.3%), and HTLV (0.2%)[21]. Data from the Brazilian Ministry of Health showed that between 2011 and 2019, hepatitis B detection rates in Brazil decreased by 20.7%, from 8.5 to 6.7 cases per 100,000 inhabitants. In 2021, the detection rate dropped to 3.4 cases per 100,000 inhabitants, the lowest recorded in the historical series[2].

Among the studied serological tests, HIV positivity showed the greatest decline. Interestingly, the proportion of HIV seropositive donors was similar in both sexes, despite the fact that the infection is more frequent among men in the general population[2]. Concerning HIV testing, it has been observed that, in Brazil, some individuals seek the blood bank in order to have the HIV test done, due to unfavorable perceptions of free public Volunteer Testing Centers[22]. This may have affected the results, but despite this possibility, HIV testing has shown the greatest reduction among the tested viral serologies.

When the two study periods were compared, HTLV positivity also decreased, but the sex and age distribution profiles remained unchanged.

In our study, we observed a high rate of fidelity among blood donors (above 70%). Blood donor fidelity is crucial to reducing positivity rates in serological tests[23]. Regular donors undergo frequent and rigorous screening, increasing the likelihood of identifying and ruling out possible infections. Additionally, continued education about risk behaviors and health care reinforces the responsibility of loyal donors[23]. In this way, fidelity not only ensures a constant supply of safe blood, but also contributes to the integrity of the donation system.

This study has some limitations inherent to its design. The study design, using a database, did not allow access to donor clinical information. All positive tests for the first test were confirmed, but unfortunately, we do not have access to confirmatory test data.

In conclusion, a significant reduction in discarded blood bags due to viral serology was observed between 2013–2017 and 2018–2022 on this blood bank; the highest reduction was observed in HIV serology and the lowest in HBc serology, which became more common in women during the two observed periods. High rates of donor fidelity were observed during the period studied.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Committee of Ethics in Research from Institution under protocol number 5.902.331.

CONSENT TO PARTICIPATE

All participants signed an informed consent.

CONSENT FOR PUBLICATION

Yes.

TRANSPARENCY DECLARATION

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

AUTHOR CONTRIBUTIONS

GSB: Conceptualization, Data curation. **MF:** Conceptualization, Data curation. **TLS:** Conceptualization, Formal Analysis, Writing – original draft. **CAPI:** Conceptualization. **KBF:** Conceptualization, Data curation. **PTRA:** Conceptualization, Data curation. **MOA:** Conceptualization. **RN:** Conceptualization, Formal Analysis, Writing – original draft.

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ORIGINAL ARTICLE

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Endocan may predict the presence of coronary slow flow and coronary artery disease

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SUMMARY

OBJECTIVE: Coronary artery disease (CAD) is frequent, but coronary slow flow (CSF) is a less common cardiovascular disease with a significant risk of mortality and morbidity. Endocan is a proinflammatory glycopeptide that has been investigated in cardiovascular diseases as well as some inflammatory diseases in recent years. We planned to compare the levels of endocan in both CAD and CSF in a similar population and examine the relationship of endocan with additional clinical variables.

MATERIALS AND METHODS: In the trial, we included 169 consecutive subjects having a coronary angiography indication. According to the results of coronary angiography, 58 people were included in the CAD group, 52 were in the CSF group, and 59 people were in the control group. The control group includes those who did not have any lesions in their epicardial coronary arteries. Thrombolysis in myocardial infarction (TIMI)-frame counts (TFC) were calculated for all patients.

RESULTS: Notably, 2.6% of the population in our study had CSF. Both the CAD (555±223 pg/mL) and CSF (559±234 pg/mL) groups had higher endocan levels than the control group (331±252 pg/mL) (p<0.001). There were similar endocan levels between the CAD and CSF groups. Endocan levels were shown to be favorably associated with mean TFC (r=0.267; p0.001). Serum endocan levels (particularly those above 450 pg/mL) and the presence of hyperlipidemia were the most important predictors of both CAD and CSF.

CONCLUSION: Endocan levels are higher in CAD and CSF patients than in those with normal coronary arteries.

KEYWORDS: Coronary angiography. Coronary artery disease. Coronary vessels.

INTRODUCTION

Coronary slow flow (CSF) is characterized by slower-than-normal blood flow into the distal coronary arteries. It is a well-known but poorly understood form of coronary artery disease; therefore, it is sometimes referred to as the CSF phenomenon[1-3]. CSF, which can be detected during coronary angiography (CAG), is defined as delayed filling of the distal portions of the coronary arteries without significant stenosis of the epicardial arteries. Endocan, which is an endothelial cell-specific protein, is a proteoglycan released from endothelial cells and can be measured in serum. Endocan acts as an adhesion molecule in inflammation-related processes. Therefore, it is considered a key molecule in endothelial dysfunction[4-7]. Endocan may be a biomarker for both lifestyle changes for therapeutic purposes and for follow-up to assess the success of treatments. Some studies show an elevation in endocan levels in CAD and CSF[8-10]. However, there is no study in the literature that compares endocan levels in CAD and CHF in the same cross-sectional study setting.

Considering atherosclerosis and endothelial dysfunction, we hypothesized that endocan may be a potential biomarker associated with CAD and CSF. Therefore, we sought the relationship between serum endocan levels and CAD as well as CSF.

METHODS

We prospectively enrolled patients (n=1,997) who presented to our institution for a routine follow-up visit to our outpatient clinic with tests suggestive of ischemia and stable angina pectoris and underwent coronary angiography consecutively.

The exclusion criteria were as follows: those with age below 30 years and above 75 years, acute coronary event, moderate or severe valvular dysfunction, acute coronary syndrome, rhythm other than normal sinus rhythm (except for infrequent atrial and ventricular premature beats), and left or right bundle branch block. The exclusion criteria were stent implantation for known CAD and history of coronary bypass surgery, systolic heart failure (left ventricular ejection fraction<50%), chronic or active infection, chronic kidney (glomerular filtration rate [GFR] <60 mL/min) and liver or thyroid dysfunction,

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and history of malignancy. The body mass index (BMI) was calculated as follows: body weight (kg)/square of height (m^2).

Coronary angiography

Coronary angiography was performed on a Siemens (Artiz Zee, Munich, Germany) device as shown below: coronary arteries were visualized with a 6F or 7F Judkins catheter. Images of the LAD were obtained in at least two positions, left oblique and cranial. The acquisition rate for the planned images was set to 25 image frames/second and the minimum number of images was 80. For each suspected lesion, images were taken in different projections for verification. For this purpose, 6–8 mm of opaque material was manually administered. A total of 50–100 mL of nonionic radio-opaque material was used for each patient.

At least two cardiologists evaluated the coronary anatomy and flow velocity on the archival images. Coronary blood flow velocity and the number of images per second were quantitatively determined as described by Gibson et al., and the reliability of measurements made with this technique has been determined from thrombolysis in myocardial infarction (TIMI) studies[11]. The TIMI frame count values of the arrival of the opaque substance from the ostium to the distal mustache for the LAD artery, from the ostium to the site of separation of the distal posterior branch or distal obtuse margin branch for the circumflex, and from the ostium to the site of separation of the posterolateral branch for the RCA were obtained by finding the picture count values. Normal TIMI frame count (TFC) intervals were determined as 36.28±2.6, 22.28±4.1, and 20.48±3.0 for the LAD, circumflex, and RCA, respectively. These values were found as follows in these studies: normal flow velocities in normal epicardial arteries greater than two standard deviations (presence of CSF means in case of higher TFC than the mean TFC+ 2 x standard deviation) were considered to indicate the presence of CSF. The LAD artery is 1.7 times longer than the circumflex and RCA; therefore, a correction is made for the LAD value. This correction is divided by 1.7 to obtain the TFC of the LAD artery. Mean TFC is the arithmetic mean value of the values obtained from all three arteries. Patients were included in the CAD group if any of the epicardial coronary arteries had a 50% or more reduction in lumen diameter or a 70% or more reduction in area on coronary angiography.

Blood samples and analysis of endocan levels

Fasting venous blood samples were obtained immediately after the procedure from the patients whose consent was obtained after angiography and who were included in the study.

The samples were immediately centrifuged at 3,000 *g* and stored at -80°C until analysis. Serum endocan levels were measured by enzyme-linked immunosorbent assay (ELISA). Elabscience Human ESM1-Endothelial Cell Specific Molecule 1 (Endocan) ELISA Kit (Cat# E-EL-H1557, Elabscience, Texas, USA) was used for the test. The detection range of the kit was 15.63–1,000 pg/mL. The coefficient of variation in reproducibility was less than 10%. ELISA assays were performed after the reactive agent was prepared by dilution technique.

This cross-sectional study was initiated after obtaining permission from a local ethics committee (30.04.2020 and 2020.77.04.01).

Statistical analysis

All statistical analyses of the data were performed with IBM® SPSS® Statistics for Mac, Version 20 software (IBM Corp., Armonk, NY).

Continuous variables were presented as either mean±standard deviation or median (min–max). Categorical variables were reported as percentages. Variables were tested for normality of distribution using the Kolmogorov-Smirnov test. The three patient groups were compared by ANOVA for normally distributed variables and the Kruskal-Wallis test for abnormally distributed variables. In case of significant deviations in ANOVA, post hoc analysis was performed using the Tukey test, depending on the homogeneity of variances. Similarly, following the Kruskal-Wallis test, the Dunn test was used in the nonparametric pairwise multiple comparison procedure. Differences between categorical variables obtained as a result of the study were revealed through the "chi-square" test. Spearman or Pearson correlation coefficients were calculated to assess continuous and noncontinuous relationships between biomarkers and other variables. Univariate and multivariate logistic regression analyses were used to determine significant factors affecting CSF. ROC analysis was used for the predictive value of the dependent variable endocan. The statistical significance level for the study was set as $p<0.05$.

RESULTS

Patients were similar in terms of demographic characteristics except hyperlipidemia. The CSF and CAD groups had higher rates of hyperlipidemia and higher rates of beta-blocker, aspirin, and statin drug use than the NCA group ($p<0.05$). LDL-cholesterol and endocan levels were similar in the CSF and CAD groups, but the values of LDL-cholesterol and endocan levels in these two groups were higher than those in the NCA group ($p<0.05$). The mean number of TFC of the LAD artery,

circumflex artery, and RCA was higher in the CSF group compared to the other two groups (p<0.05) (Table 1).

Serum endocan levels were positively but weakly correlated with total cholesterol (r=0.193; p=0.012) and LDL-cholesterol (r=0.167; 0.035). Endocan and mean TIMI-FC were positively correlated (r=0.267; p<0.001). Mean TIMI-FC was positively and weakly correlated with uric acid and creatinine. There was no difference in endocan levels between the CSF and CAD groups; therefore, we considered the presence of the CSF or CAD group as a single dependent variable and then performed a logistic regression analysis. The presence of hyperlipidemia (OR: 2.701 [2.011–5.678]; p=0.039) and endocan levels (OR=1.984 [1.319–2.578]; p<0.001) was found to be significant variables for the presence of CSF and CAD. In the logistic regression analysis between the CAD and control groups, the variables predicting the presence of CAD were again hyperlipidemia (OR=4.643 [2.861–7.877]; p<0.001) and endocan levels (OR=2.235 [1.434–2.784]; p<0.001) (Table 2). On ROC analysis, endocan levels above 450 pg/mL predicted the presence of CAD and/or CSF with 75% sensitivity and 60% specificity (AUC=0.779 [0.690–0.850], p<0.001).

Table 1. Demographic, clinical characteristics and laboratory values.

Variables	CSF (n=52)	CAD (n=58)	Control (n=59)	p-value
Age, years	52.9 ± 9.1	53.3 ± 8.5	51.1 ± 8.9	0.156
Gender, male n (%)	39 (75%)	42 (%72.4)	43 (72.9%)	0.949
BMI, kg/m^2	30.3 ± 4.0	29.3 ± 4.3	28.9 ± 3.8	0.192
Smoking, n (%)	24 (46%)	18 (31%)	28 (47%)	0.139
Diabetes, n (%)	15 (28%)	20 (34%)	12 (20%)	0.228
Hypertension, n (%)	27 (51%)	37 (63%)	32 (54%)	0.403
Hyperlipidemia, n (%)	25 (48%)	20 (34%)	5 (8%)	<0.001
Beta blocker, n (%)	30 (57)	23 (39)	20 (33)	0.033
ASA, n (%)	44 (84)	38 (65)	24 (40)	<0.001
Statin, n (%)	28 (53)	24 (41)	5 (8)	<0.001
CCB, n (%)	11 (21)	11 (19)	8 (13)	0.546
ACEI/ARB, n (%)	22 (42)	31 (53)	27 (45)	0.483
Glucose, mg/dl	122 ± 42	127 ± 54	108 ± 26	0.062
Total cholesterol, mg/dl	195 ± 50	189 ± 48	178 ± 36	0.066
Triglycerides, mg/dl	188 ± 171	186 ± 109	185 ± 138	0.855
HDL cholesterol	43 ± 9	41 ± 11	44 ± 12	0.458
LDL cholesterol	117 ± 36	110 ± 40	96 ± 32	0.016
Uric acid, mg/dl	5.7 ± 1.1	5.1 ± 1.3	5.3 ± 1.3	0063
GFR, ml/dk	92.2 ± 14	94 ± 14	98.6 ± 13	0.062
Creatinine, mg/dl	0,8 ± 0,1	0.8 ± 0.1	0.8 ± 0.1	0.338
Hemoglobin, mg/dl	14.7 ± 1.8	14.4 ± 2.1	14.2 ± 1.7	0.103
Endocane, pg/ml	559 ± 234	555 ± 223	331± 252	<0.001
CRP, mg/dl	3.1 (0–10)	3.2 (0–10)	1.7 (0–9)	0.256
SBP mmHg	129 ± 17	124 ± 16	125 ± 13	0.299
DBP, mmHg	78 ± 11	75 ± 9	77 ± 9	0.145
LAD TIMI-FC	32.5 ± 6.8	19.8 ± 0.9	19.8 ± 0.8	<0.001
CX TIMI-FC	22.3 ± 8.6	18.1 ± 0.8	17.8 ± 0.8	<0.001
RCA TIMI-FC	27.2 ± 9.9	17.4 ± 0.75	17 ± 0.8	<0.001
Mean TIMI- TF	27.3 ± 4.2	18.4 ± 0.6	18.2 ± 0.6	<0.001

CSF: coronary slow flow; CAD: coronary artery disease; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ASA: acetyl salicylic acid; BMI, body mass index; CCB, calcium channel blocker; CRP: C-reactive protein; DBP: diastolic blood pressure; HDL: high-density lipoprotein; GFR: glomerular filtration rate; LAD: left anterior descending; LDL: low-density lipoprotein; RCA: right coronary artery; SBP: systolic blood pressure; TIMI-FC: TIMI frame count.

Table 2. Univariate and multivariate logistic regression analysis.

Dependent variable: Presence of CSF			
	Beta ± standard deviation	Odds ratio and 95% confidence Interval	p-value
Univariate			
Age	0.23±0.22	0.978 (0.916–1.356)	0.348
Diastolic blood pressure	0.25±0.23	1.674 (0.946–1.564)	0.349
Glucose	0.001±0.07	0.912 (0.767–1.347)	0.102
Hyperlipidemia	0.11±0.08	3.564 (2.061–6.877)	0.025
Beta blocker	0.45±0.68	1.578 (0.608–3.207)	0.749
ASA	0.36±0.67	3.789 (1.298–6.567)	0.018
Statin	0.77±0.53	6.712 (2.386–11.342)	<0.001
GFR	0.04±0.02	1.457 (0.798–1.347)	0.206
Uric asid	0.143±0.64	1.236 (0.856–1.956)	0.459
Endocan	0.001±0.001	1.890 (1.546–2.678)	<0.001
Multivariate			
Hyperlipidemia	0.11±0.08	4.643 (2.861–7.877)	0.025
Endocan	0.001±0.002	1.235 (1.434–2.784)	<0.001

GFR: glomerular filtration rate.

DISCUSSION

The most important findings of our study were as follows: (1) 2.6% of the population we screened during our study had CSF; (2) both the CSF and CAD groups had higher endocan levels than the control group; (3) there were similar endocan levels between the CSF and CAD groups; (4) endocan levels were positively correlated with the mean TIMI-FC; and (5) serum endocan levels (especially values ≥450 pg/mL) and the presence of hyperlipidemia were the main predictors of the presence of both CSF and CAD.

In a previous meta-analysis of 15 studies[5], high endocan levels were also associated with cardiovascular diseases. The results of our study were consistent with the meta-analysis published in the literature. As the age, gender, diabetes, smoking, and hypertension rates of the control group and the other study groups were similar in the study population, only hyperlipidemia was found to be a predictive clinical feature for the presence of CSF and/or CAD. However, other cardiovascular risk factors other than hyperlipidemia were not found to be the main predictors of CSF and CAD.

In our study, CRP and endocan were not correlated. Although they are inflammatory markers, we think that the lack of correlation between endocan and CRP is related to their use of different inflammatory pathways[12-16]. In our study, CRP values were similar in all three groups. The reason why CRP values were not different between the CSF and CAD groups is as follows. First, we excluded acute or chronic infection in our study. Second, other cardiovascular risk factors, except for hyperlipidemia in the control group, were similar in the CSF and CAD groups. In this study, endocan levels predicted cardiovascular disease much better than CRP.

A few small population case/control studies show that endocan levels are correlated with increased blood pressure in hypertensive patients[17,18]. When confounding factors such as the prevalence of micro atheroma accompanying hypertension are taken into account, our findings seem potentially accurate.

Studies show that uric acid is elevated in patients with CSF. Increased uric acid levels show proinflammatory properties and vascular endothelial damage occurs more rapidly at levels higher than normal in uric acid levels[19]. In our findings, the mean TIMI-FC and uric acid values were weakly correlated and were compatible with the literature. In addition to uric acid, we found a correlation between creatinine values and mean TIMI-FC.

Our study has some limitations. In the control group, cardiovascular risk factors were similar except for hyperlipidemia. This strengthened our study. The reason for this may be that we are a tertiary center and the patients included in coronary angiography are selected from those who are symptomatic or present with some findings indicating ischemia, as well as those with additional cardiovascular risk factors. Therefore, the association between endocan and other cardiovascular risk factors may have been statistically blunted. If we had also analyzed the levels of some cytokines such as IL-1 or IL-6, which are involved in the NF-κB pathway, we could have better evaluated the correlations of endocan with inflammatory cytokines involved in atherosclerosis.

CONCLUSION

Increased endocan levels (≥450 pg/mL), especially in asymptomatic patients with cardiovascular risk factors, may be a good biomarker for further investigations. Additional studies are needed to clarify its value. Endocan levels are not only elevated in CSF and CAD but also associated with CSF and CAD. Therefore, it appears to be a potent proinflammatory proteoglycan in atherosclerosis.

AUTHORS' CONTRIBUTIONS

MME: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources.
AA: Conceptualization, Formal Analysis, Funding acquisition,

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

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ORIGINAL ARTICLE

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Can the SYNTAX score predict mortality in patients with cardiac arrest?

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SUMMARY

OBJECTIVE: Sudden cardiac death or arrest describes an unexpected cardiac cause-related death or arrest that occurs rapidly out of the hospital or in the emergency room. This study aimed to reveal the relationship between coronary angiographic findings and cardiac death secondary to acute ST-elevation myocardial infarction.

MATERIALS AND METHODS: Patients presenting with acute ST-elevation myocardial infarction complicated with cardiac arrest were included in the study. The severity of coronary artery disease, coronary chronic total occlusion, coronary collateral circulation, and blood flow in the infarct-related artery were recorded. Patients were divided into two groups, namely, deaths secondary to cardiac arrest and survivors of cardiac arrest.

RESULTS: A total of 161 cardiac deaths and 42 survivors of cardiac arrest were included. The most frequent (46.3%) location of the culprit lesion was on the proximal left anterior descending artery. The left-dominant coronary circulation was 59.1%. There was a difference in the SYNTAX score (16.3±3.8 vs. 13.6±1.9; p=0.03) and the presence of chronic total occlusion (19.2 vs. 0%; p=0.02) between survivors and cardiac deaths. A high SYNTAX score (OR: 0.38, 95%CI: 0.27–0.53, p<0.01) was determined as an independent predictor of death secondary to cardiac arrest.

CONCLUSION: The chronic total occlusion presence and SYNTAX score may predict death after cardiac arrest secondary to ST-elevation myocardial infarction.

KEYWORDS: Sudden cardiac death. Survivors. Sudden cardiac arrest. Myocardial infarction.

INTRODUCTION

Sudden cardiac death/sudden cardiac arrest refers to an unexpected death or arrest from a cardiovascular cause that occurs rapidly out of the hospital or in the emergency room[1]. The presumption based on epidemiologic studies is that the most common cardiac pathology underlying all sudden cardiac deaths is attributable to coronary heart disease[2]. Ventricular tachycardia and ventricular fibrillation are the most frequent in the first hours of an infarction[3]. Ventricular tachycardia or ventricular fibrillation accounts for the majority of episodes. However, bradyarrhythmia is responsible for some cases of sudden cardiac death/sudden cardiac arrest[4]. The largest experience with acute ST-elevation myocardial infarction (MI) comes from the GUSTO-1 trial of 40,895 patients who were treated with thrombolytic therapy[5]. The overall incidence of ventricular tachycardia or ventricular fibrillation was 10.2%. Approximately 80–85% of these arrhythmias occurred in the first 48 h. These data do not include patients with SCD who do not survive until hospitalization. It has been estimated that more than 50% of deaths due to acute myocardial infarcts occur out of the hospital, and most episodes occur within 1 h of symptom onset[6].

The aim of this study was to identify the coronary anatomy of patients with acute ST-elevation MIs complicated by sudden cardiac death or sudden cardiac arrest. More specifically, we studied the differences between sudden cardiac death and survivors of sudden cardiac arrest.

METHODS

Patients presented with acute anterior and inferior myocardial infarction between January 2013 and March 2024 were examined. Patients with out-of-hospital cardiac arrest or in-hospital cardiac arrest were included in the study. Coronary angiography and primary angioplasty were performed as treatment immediately after the patient arrived at the hospital. Right and left coronary angiograms were obtained in multiple projections. None of the patients received fibrinolytics. Two experienced cardiologists who were blinded to angiographic data interpreted all coronary angiographies recorded upon admission. The principal angiographic and clinical data were entered into a database. The reduction in luminal diameter was visually estimated to be due to graded coronary stenoses.

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The lesion was considered the culprit if it was a fresh occlusion at angiography. Epicardial blood flow in the infarct-related artery was graded according to the thrombolysis in myocardial infarction (TIMI) group definitions[7]. The occlusion was classified as acute if angiography showed a thrombus at the location of the occlusion or if a guide wire was able to pass through the occlusion easily. If there was no acute occlusion, the lesion with the most severe reduction was assigned as the culprit if lesion localization corresponded with the location of ST segment elevations.

The coronary arteries were divided into proximal, mid, and distal segments. The severity of coronary artery disease was scored using the SYNTAX score I[8]. Coronary chronic total occlusion was defined as an occluded coronary artery with TIMI 0 flow for at least 3 months. The Rentrop-Cohen method was used to categorize coronary collateral circulation[9].

Patients with known heart failure and coronary artery disease (coronary angioplasty and previous MI), left bundle branch block, Brugada syndrome, QT prolongation, congenital short QT syndrome, Wolff-Parkinson-White syndrome, familial polymorphic VT, and sudden unexplained death were not included in the study.

Statistical analysis

Descriptive statistics for baseline parameters of continuous variables with a normal distribution were presented as mean±standard deviation. Qualitative variables were presented as numbers and percentages. The significance of differences in the means of continuous variables was evaluated using the Student's t-test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Univariate logistic regression analysis was used to determine the independent predictor of mortality after cardiac arrest. The sensitivity and specificity of the SYNTAX score 1 to predict death were analyzed by receiver operating characteristics (ROC) analysis. A p-value below 0.05 was considered statistically significant. All tests were performed using the SPSS 22.0 (SPSS Inc., Chicago, IL) software version.

RESULTS

A total of 302 sudden cardiac arrests were examined. After exclusion criteria, 203 arrests associated with ST-elevation MI were included in the study. A total of 161 deaths occurred within 1 h after the angiogram. Notably, 42 patients were included in the survivors group. Demographic data on deaths and survivors are summarized in Table 1. The time from symptom onset to collapse in patients with ventricular fibrillation and out-of-hospital cardiac arrest secondary to acute coronary syndrome is unknown. The median time between collapse and angiogram was 22.5±11.2 min after in-hospital cardiac arrest. Anterior localization was statistically more frequent in all cardiac arrests secondary to acute coronary events (68.5 vs. 31.5%; p=0.05).

Angiographic data are summarized in Table 2. The infarct-related artery in all cardiac arrests was LAD, RCA, or CX in 63.1, 29.6, and 7.4%, respectively. The most frequent (46.3%) location

Table 1. Baseline characteristics of the study patients.

Variables	Deaths secondary to cardiac arrest (n=161)	Survivors of cardiac arrest (n=42)	All cardiac arrests (n=203)	p-value
Age	71.5±11	73.5±8	71.9±10.5	0.27
Male	78 (48.4)	12 (28.6)	90 (44.3)	**0.021**
Smoking	90 (55.9)	20 (47.6)	110 (54.2)	0.603
Hypertension	29 (18)	7 (16.6)	36 (17.7)	0.940
Alcohol intake	87 (54.0)	19 (45.2)	106 (52.2)	0.459
Obesity	103 (64)	23 (56.1)	126 (62)	0.295
LVEF (%)	34.9±10.3	38.2±7.7	35.6±9.9	0.086
ST-segment elevation				
Anterior	109 (67.7)	30 (71.4)	139 (68.5)	0.643
Non-anterior	52 (32.3)	12 (28.6)	64 (31.5)	0.643
Complaints at first arrival				
Chest pain	17 (10.6)	33 (78.6)	50 (24.6)	**<0.01**
Cardiac arrest*	144 (89.4)	9 (21.4)	153 (75.4)	**<0.01**

LVEF: left ventricular ejection fraction. *Patients with ventricular fibrillation out-of-hospital cardiac arrest secondary to acute coronary syndrome. Bold indicates significant values (p<0.05).

of the culprit lesion was in the proximal LAD, followed by the proximal RCA (25.1%). Considering coronary dominance in all cardiac arrest cases, 59.1% left-dominant, 21.2% right-dominant, and 19.7% co-dominants were detected. Flow in the infarct artery was absent or severely decreased in 74.9% of all cardiac arrests. Rentrop grade 2–3 collaterals to the infarct-related coronary artery were present in 21.2% of the patients. There were no differences between the two groups concerning the location of the culprit along the coronary arteries, the presence or absence of collaterals to the infarct artery, and coronary dominancy. Left ventricular ejection fraction (LVEF) was 34.9±10.3% in deaths and 38.2±7.7% in survivors (p=0.086).

Between survivors and deaths, there was a difference in the SYNTAX score and the presence of chronic total occlusion. Of all cardiac arrests, 31 (15.2%) had chronic occlusions in a non-infarct related coronary artery. All of the patients with chronic occlusion died within 1 h after coronary angiography, secondary to acute coronary events. On the contrary, in the survivor group, chronic total occlusion was not found (19.2 vs. 0%; p=0.02). It was found that the SYNTAX score was higher in the death group (16.3±3.8 vs. 13.6±1.9; p=0.03). The receiver operating characteristic (ROC) curve was used to test the accuracy of the SYNTAX score in the prediction of deaths secondary to acute coronary events. The optimal SYNTAX score cut-off value of 13.5 provided the highest sensitivity (84.5%) and specificity (71.4%) for predicting death. The area under the curve for the SYNTAX score was 0.898

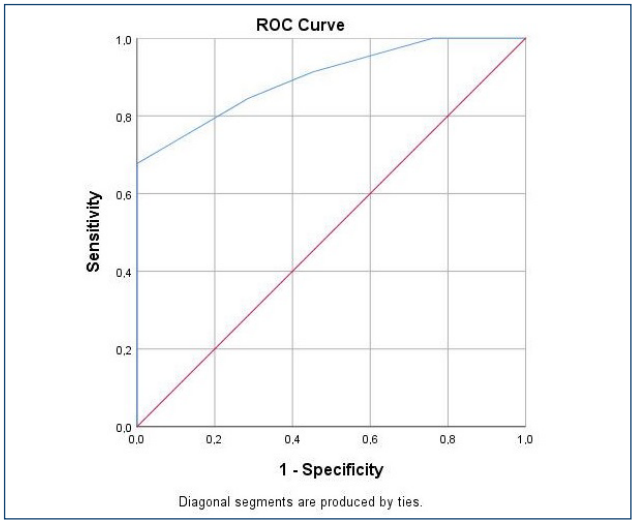

Figure 1. Determination of SYNTAX score cut-off value for predicting death.

Table 2. Coronary angiography results of the patients.

Variables	Deaths secondary to cardiac arrest (n=161)	Survivors of cardiac arrest (n=42)	All cardiac arrests (n=203)	p-value
Location of culprit lesion on LAD	103 (64)	25 (59.5)	128 (63.1)	0.877
Location of culprit lesion on RCA	46 (28.6)	14 (33.3)	60 (29.6)	0.877
Location of culprit lesion on CX	12 (7.5)	3 (7.1)	15 (7.4)	0.877
Coronary dominancy				
Left	94 (58.4)	26 (61.9)	120 (59.1)	0.475
Right	37 (23)	6 (14.3)	43 (21.2)	
Codominancy	30 (18.6)	10 (23.8)	40 (19.7)	
Chronic total occlusion other than IRA	31 (19.2)	0	31 (15.2)	**0.033**
LAD	24 (14.9)	0	24 (11.8)	
RCA	7 (4.3)	0	7 (3.4)	
CX	6 (3.7)	0	6 (2.9)	
SYNTAX score	16.7±3.5	12.1±1.7	15.8±3.7	**0.031**
TIMI-flow grade				
0–1	125 (77.6)	27 (64.3)	152 (74.9)	**0.084**
2–3	36 (22.4)	15 (35.7)	51 (25.1)	
Collaterals to IRA*				
0–1	129 (80.1)	31 (73.8)	160 (78.8)	0.372
2–3	32 (19.9)	11 (26.2)	43 (21.2)	

CX: circumflex artery; LAD: left anterior descending artery; IRA: infarct-related artery; RCA: right coronary artery; SYNTAX: SYNergy between PCI with TAXUS and Cardiac Surgery; TIMI: thrombolysis in myocardial infarction. *Six patients had two chronic occlusions.
Bold indicates significant values (p<0.05).

(p<0.01) (Figure 1). A high SYNTAX score (OR: 0.38, 95%CI: 0.27–0.53, p<0.01) was determined as an independent predictor of mortality after cardiac arrest.

The mortality rate in patients with out-of-hospital VF was 89.4%. The mortality rate was found to be 10.6% in patients who presented with a complaint of chest pain (in-hospital cardiac arrest).

DISCUSSION

According to our study results, the presence of chronic total occlusion and a higher SYNTAX score may be predictive of mortality after cardiac arrest secondary to ST-elevation MI. Additionally, the mortality rate in out-of-hospital VF was found to be higher than in-hospital cardiac arrest. Our finding is the increased risk of mortality with acute occlusion in the proximal LAD when compared with acute occlusion of the RCA or CX. The size of the infarct is correlated with early VF in large studies of patients hospitalized for AMI. Proximal LAD occlusion, which is associated with a large amount of myocardium, has a larger region at risk of necrosis[10]. However, it defies previous theories that acute RCA occlusions, which typically supply the conduction system, are more likely to result in potentially fatal arrhythmias[11]. Previous studies found associations between early VF and IRAs inconsistent, but some either included few or no patients with out-of-hospital VF or had no angiographic data. Other studies did not specifically address out-of-hospital VF secondary to ST-elevation MI and possibly included a heterogeneous group of patients with cardiac arrest[12]. In addition, a hypothesis, generated by previous studies, is that vagal tone in patients with acute occlusion of RCA protects against early VF during AMI. The cause of the vagotonia appears to be stimulation of cardiac vagal afferent receptors common in the inferoposterior of the left ventricle[13].

One of our study findings is the presence of an association between mortality and the extent of coronary artery disease. The SYNTAX score was significantly higher in deaths secondary to acute coronary events. Our results conflict with autopsy data from patients who experienced an out-of-hospital cardiac arrest, where the degree of CAD was not substantially different from that of patients who had stable angina or a prior infarction[14]. This discrepancy could be explained by the different autopsy methods used to characterize the degree of CAD. According to Kyriakidis et al., there is a correlation between the Gensini score, which measures the extent of CAD, and in-hospital primary VF[15].

Coronary dominance is defined based on the vascular supply of the posterior interventricular septum. When the interventricular septum is supplied by the posterior descending branch of the left circumflex artery, it is a left-dominant circulation. Left-dominant circulation is reported to be present in 2–10.1% of the general population[16]. However, we found the left dominance rate to be 59.1%. Several studies have attempted to determine the effect of coronary dominance on mortality as an outcome in patients with acute coronary syndrome. Observational data suggest that left-dominant circulation may be a risk factor for adverse outcomes[17]. Considering that our study population was sudden cardiac death or sudden cardiac arrest survivors, unlike the general population, and the left dominance was detected as more common, it can be thought that our study results support the previous studies.

In our study, mortality was found to be 89.4% in patients with cardiac arrest at the first admission to the hospital. Factors such as the time to reach the patient, the time to arrive at the hospital, and resuscitation experience determine mortality. Mortality among patients who collapse in an unmonitored setting correlates with the duration of the arrest[18].

Limitations

The study was somewhat limited by the small number of patients. Victims in whom resuscitation was unsuccessful may have had a different coronary anatomy from those who were successfully revived. Lack of knowledge about preexisting LVEF is one of the study limitations. These data are only accessible through prospective study designs, which are highly difficult to perform. Some risk factors that may be different between the two groups (sleep apnea syndrome, regular physical activity, depression, anxiety, psychological stress, and caffeine intake) were not recorded.

CONCLUSION

According to our data obtained by acute angiography, LAD proximal lesions were the most common location in sudden cardiac arrest and sudden cardiac death secondary to ST-elevation MI. The presence of a chronic occlusion in a non-infarct-related artery or a higher SYNTAX score is possibly an additional independent determinant of mortality after a cardiac arrest.

AUTHORS' CONTRIBUTIONS

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

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REVIEW ARTICLE

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The effectiveness of kinesiology taping on balance, gait, and gross motor function in the lower limbs of children with cerebral palsy: a systematic review

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INTRODUCTION

Cerebral palsy (CP) encompasses a range of motor impairment disorders and is the most common cause of physical disabilities among children in high-income countries, with an incidence of 2.11 per 1000 births[1,2]. Lower extremity dysfunctions in children with CP affect crucial activities for mobility and daily functioning, including postural control, functional mobility, sit-to-stand transfers, and gait abnormalities[3].

Rehabilitation for children with CP is aimed at enhancing gross motor function (GMF), postural control, functional mobility, and independence[4,5]. Physiotherapy interventions, including neurodevelopmental therapy, manual stretching, splints, adaptive furniture, and orthosis, are commonly used, but their effectiveness remains inconclusive[6-8]. Children with CP often have reduced sensory stimuli reception and sensory-motor integration deficits, indicating a need for rehabilitative techniques that stimulate sensory pathways and promote muscle activation, like kinesiology taping (KT)[9-11].

Previous research primarily focused on the impact of KT on the upper limb rather than the lower extremity[6-8]. Clinical trials have shown the effects of KT on lower extremity functional outcomes, including improvements in sit-to-stand (STS) and timed up-and-go (TUG) tests, better performance in the lateral step-up test, and enhancements in functional independence, GMF, and balance[9,11-13]. However, inconsistencies exist in the literature, with some studies not reporting significant improvements after KT application[3,14]. The aim of this review is to determine the effects of KT application on lower limb functional outcomes in children with CP.

METHODS

The study was conducted according to the criteria in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[15]. The study was registered in the PROSPERO database with the registration number CRD42023464972.

Search strategy

The databases searched included PubMed, Web of Science, PEDro, and Cochrane, as well as a manual search in Google Scholar. Keywords including "Kinesio-tape OR K-tape OR taping," "Cerebral palsy," "Lower limb OR Lower extremity," "Function," and "Gait" were used by two authors independently. Studies published in English between January 2000 and September 2023 were searched, and citations were imported into Endnote for deduplication.

Eligibility criteria

Only clinical trials that assessed the effects of KT on lower limb functional outcomes in children clinically diagnosed with CP were included in this review. Studies were excluded if subjects had undergone any orthopedic surgery or received a botulinum toxin injection in the 6 months preceding the evaluation date.

Methodological quality

The Cochrane Risk of Bias (ROB) tool was used to assess studies according to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, intention to treat, and description of exclusion and losses[16].

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Data extraction

Two authors independently screened all titles, abstracts, and full texts for eligibility. The disagreement over inclusion was resolved through a consensus meeting with a third reviewer. The relevant data from the included studies were extracted and presented in Table 1.

RESULTS

A total of 119 papers were retrieved from databases such as PubMed (n=11), Web of Science (n=85), PEDro (n=7), and Cochrane (n=4), and 12 studies were identified by hand searching. After removing duplicates, 83 studies were screened based on their titles and abstracts. Subsequently, 16 articles were examined thoroughly, and 7 of them were excluded owing to reasons depicted in Figure 1. Finally, nine studies were included in this review. The studies were published between 2011 and 2022. Six of the trials were randomized clinical trials[5,11,13,14,17,18]; two controlled trials[3,19]; and one placebo-controlled repeated measure[10]. The review involved a total of 206 participants, with ages between 2 and 18 years, the majority of whom suffered from spastic CP. Table 1 provides the details of the study characteristics.

Quality of studies

The risk of bias among studies was assessed with the Cochrane ROB tool. Two out of the nine studies scored high in terms of random sequence allocation[3,19]. Allocation concealment was clearly observed in four studies[10,11,13,18]. Blinding of assessors was only possible in two studies[10,13], while no single study was

Table 1. Description of the characteristics of sample demographics, interventions, outcome measures, and results of the included studies.

Author	N (EG/ CG)	Severity of CP	Age (years)	Treatment	Purpose/location of tape	Duration	Outcome measures	Results
Costa Brazil	4	GMFCS I and II	9–11	EG: KT CG: untreated	-Muscular activation -Ankles, hip, and sacral region	1 day	STS PBS TUG	Significant decrease in TUG, but not in STS and PBS (p>0.05).
Şimşek et al. Turkey	30 15/15	GMFCS III and IV	6.87	EG: KT+PT CG: PT	-Postural alignment -Paraspinal musculature	12 weeks	GMFM Wee-FIM	No significant improvements in GMFM and Wee-FIM (p>0.05) when compared to CG post-intervention.
Santos et al. Brazil	11	GMFCS I and II	6–12	EG: KT CG: Placebo	-Postural alignment -Rectus femoris muscle	1 day	STS	Decreased duration to perform STS in elevated sitting when compared to without taping (p=0.046) and placebo (p=0.044).
Kaya Kara et al. Turkey	30 15/15	GMFCS I and II	9.7	EG: KT + PT CG: PT	-Functional correction -Hip abductors and knee extensors	12 weeks	Wee-FIM BOTMP STS	Significant improvements in STS, BOTMP, Wee-FIM in the EG (p<0.05) when compared to CG.
Partoazar et al. Italy	38 19/19	Not specified	10.79	EG: KT CG: Sham	-Function and balance -Paravertebrals	2 days	BBS TUG	Significant increase in BBS and TUG in EG (p<0.001), no significant changes in CG.
Özmen et al. Turkey	19	GMFCS I and II	11.62	EG: KT	-Muscle activation -Gastrocnemius and tibialis	2 days	TUG PBS	Significant improvement in TUG and PBS after KT application (p<0.05).
Ghalwash et al. Egypt	14 7/7	GMFCS III	6.19	EG:KT+PT CG: Knee cage+PT	-Postural alignment and control -Posterior–anterior knee.	12 weeks	GMFM	There was no significant difference between the two groups post-treatment (p>0.05).
Tabatabaee et al., 2019 a Iran	30 15/15	GMFCS I–III	6.93	EG:KT+OT+PT CG: OT+PT	-To improve muscular activity -Ankle and tibialis muscle	14 days	BBS FFR	Day 2: no significant improvement in both EG and CG, Day 14: significant differences in BBS only in the EG (p<0.001).
Tabatabaee et al., 2019 b Iran	30 15/15	GMFCS I–III	6.93	EG: KT+PT CG: sham + PT	-Improve function -Anterior–posterior lower limb	14 days	TUG	Significant changes in functional mobility only in the EG (p<0.05).

BBS: Berg Balance Scale; BOTMP: The Bruininks-Oseretsky Test of Motor Proficiency-version; CG: control group; EG: experimental group; FFR: forward functional reach test; GMFCS: gross motor function classification system; GMFM: gross motor function measurement; KT: kinesiology taping; OT: occupational therapy; PBS: Pediatric Balance Scale; STS: sit-to-sStand; PT: physiotherapy; Wee-FIM: The Functional Independence Measure for Children; TUG: timed-up-and-go.

able to blind participants. The details of the individual ROB of the studies are demonstrated in Table 2.

Outcome measures

Three studies examined the GMF of the lower limb using the D and E components of the GMFM, which assesses standing, walking, running, and jumping[13,14,18]. GMFM comprises 88 items scored on a four-point scale across five domains. Two of these studies investigated the long-term effects of KT over 12 weeks[14,18], while one focused on short-term effects over 1 week[13]. One study reported improvement in both KT and control groups, but the difference was statistically insignificant for both GMFM D and E components[18]. Another study found no significant difference between the KT and control groups ($p>0.05$)[14]. Kaya Kara et al. observed short-term effects and also found no significant improvement between KT and control groups ($p>0.05$)[13]. The Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) is another tool used to evaluate GMF, demonstrating high reliability[20]. One study utilizing BOTMP reported a significant difference in GMF between KT and control groups[13]. Thus, only one study among those that evaluated GMF in children with cerebral palsy found improvement between the experimental and control groups.

Four studies evaluated performance using the TUG test, which measures functional mobility, balance, gait, and fall risk[21]. Costa et al. found a significant difference in TUG times between the KT group and the control ($p=0.048$)[3], with the KT group showing faster completion times. Partoazar et al. observed no immediate effects of KT on functional mobility ($p=0.32$)[11]. Özmen et al. reported significant changes in TUG readings 48 h post-KT treatment but not immediately after application ($p>0.05$)[19]. Tabatabaee, Cheraghifard, et al. found no significant difference between the first and second TUG assessments in the KT group but observed improvement between the first and third assessments ($p=0.001$)[5].

The Functional Independence Measure for Children (Wee-FIM) assesses functional performance in self-care, mobility, and cognition[22]. One study initially found higher Wee-FIM scores in the control group compared to the KT group, but after 12 weeks, the KT group showed significant improvement

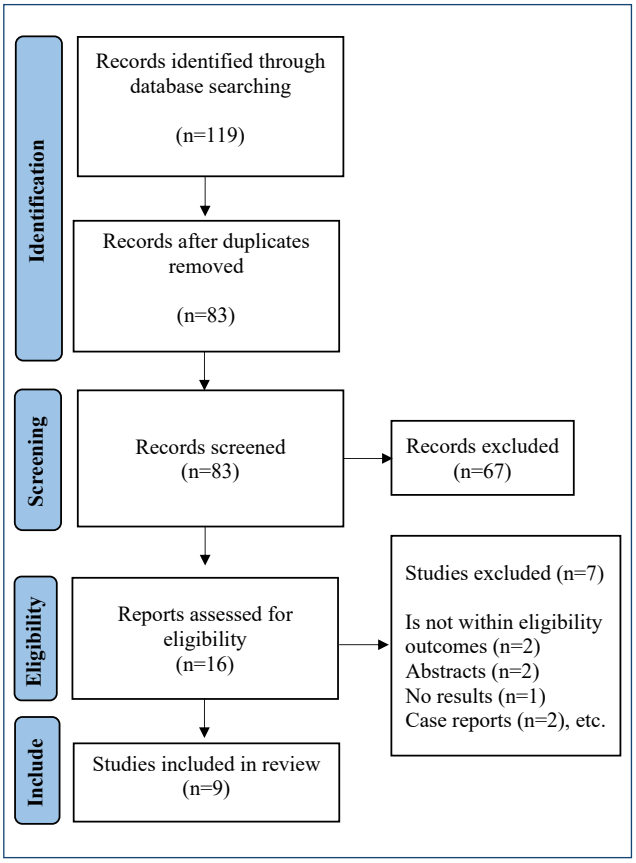

Figure 1. The PRISMA flowchart of the study selection procedure.

Table 2. The Cochrane Risk of Bias (ROB) assessment scores of included studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Intention to treat analysis	Description of exclusion and loses
Costa et al.[3]	High	High	High	High	Low	Low
Şimşek et al.[14]	Low	High	High	High	Unclear	Low
Santos et al.[10]	Low	Low	High	Low	Low	Low
Kaya Kara et al.[13]	Low	Low	High	Low	High	Low
Partoazar et al.[11]	Low	Low	High	High	Low	Low
Özmen et al.[19]	High	High	High	High	Low	Low
Ghalwash et al.[18]	Low	Low	High	High	Low	Low
Tabatabaee et al.[5]	Low	Unclear	High	High	Low	Low
Tabatabaee et al.[17]	Low	Unclear	High	High	Low	Low

in Wee-FIM scores, with a substantial difference between the KT and control groups[13]. Şimşek et al. observed significant post-intervention improvement in Wee-FIM scores in the KT group compared to their initial assessment, while no significant change was noted in the control group ($p<0.05$)[14].

The Pediatric Balance Scale (PBS) evaluates functional skills like rising from a seated position and reaching beyond one's base of support[23]. Costa et al. found an increase in mean PBS-dynamic scores in the KT group compared to the control but no significant change in mean PBS-static scores ($p=0.102$)[3]. Two studies also examined balance using the Berg Balance Scale (BBS), with Partoazar et al. reporting a significant immediate rise in BBS scores post-KT application and removal[17], while Tabatabaee, Shamsoddini, et al. found no short-term difference in BBS scores between KT and control groups but observed a significant long-term improvement in the KT group[17]. These findings suggest inconsistency in the effectiveness of KT in improving balance outcomes among children with cerebral palsy.

DISCUSSION

The aim of the review was to determine the therapeutic effects of KT on the lower limb functional outcomes of children with CP. The review showed that KT does not enhance GMF in children with CP. Nonetheless, functional mobility could be significantly improved with KT when coupled with conventional PT. Application of KT targeting specific muscles of the trunk and lower limb may also improve balance outcomes.

The review found that KT did not enhance GMF, especially in severe cases. Although some studies showed improvements in specific measures like GMFM D and E and BOTMP scores when KT was used alongside conventional PT, overall, there were no significant differences compared to groups without KT or control groups[13,14,18]. Other reviews also support this, with only limited evidence suggesting improvements in GMF with KT application[6-8,24]. The short duration of the KT application may contribute to the lack of significant improvement in GMF, as the rehabilitation of children with CP typically progresses slowly. Overall, the data suggest that KT may enhance functional mobility in children with CP, particularly with consecutive applications over time. Partoazar et al. observed significant decreases in TUG duration over time in the KT group but not in the control group[11]. Another study found no significant difference in TUG scores between the KT group and a sham group after 2 days but noted a significant difference after 2 weeks of intervention[17]. Another study reported no immediate effects of KT on TUG, but significant improvements were seen after 2 days[19]. However, Costa et al. found significant improvement in TUG immediately after KT application[3]. Three of the four studies reported significant improvements in balance among children with CP who received KT[5,11,19], while KT was therapeutically ineffective among children with CP in one study[3]. Balance is important to provide children with CP with the ability to achieve physical movement, perform basic activities of daily living, and participate safely in the environment.

Overall, there was an improvement in functional independence[13,14], but only one study found a significant improvement in the group receiving KT compared to the group without KT[13]. With regards to leg strength and endurance, one study reported a decrease in the duration of STS immediately after KT application[10], while another showed substantial improvement in STS after 12 weeks of KT application compared to physiotherapy only[13]. However, in a study that measured only the immediate effects of KT, there were peak values in STS without significant differences between baseline and final values, possibly due to the short duration of KT application[3].

The studies reviewed aimed to improve muscle activation and activity in children with CP using KT. Despite similar goals, each study employed different KT methods, including specific taping techniques like Helen Hayes marker placement, Y banding, and I-banding. KT was utilized for various purposes, such as postural alignment, balance improvement, and reducing spasticity. Overall, the studies demonstrated consistency in therapeutic goals but utilized diverse approaches to KT application[3,5,10,13,19]. The studies used in this review may be at higher risk of bias due to the impracticality of blinding patients and researchers. Moreover, the small sample sizes limit the generalizability of the findings. The outcomes measured in these studies offer limited insight into the social integration and participation of children with CP after applying this modality. Future research should focus on developing feasible methods for blind participants and researchers to reduce bias and improve outcome measurement accuracy.

CONCLUSION

The review shows that the KT application does not enhance gross motor gains when compared to conventional PT. However, functional mobility could be improved with KT application when coupled with conventional PT. Due to the slowness of functional recovery among children with CP, it is recommended to apply KT consecutively for at least 12 weeks.

AUTHORS' CONTRIBUTIONS

SKA: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – editing & review. **DA:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – editing & review. **RM:** Conceptualization, Data curation, Formal Analysis, Supervision, Writing –editing & review. **AAO:** Data curation, Formal Analysis, Methodology.

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REVIEW ARTICLE

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Outcomes of COVID-19 infection in patients with chronic lymphocytic leukemia: a systematic review and meta-analysis

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INTRODUCTION

Since the beginning of the COVID-19 pandemic, complications of this disease among vulnerable populations have been a primary concern. Cancer patients are among the most vulnerable groups of patients owing to the compromised immune system and weakened overall health status[1].

As a clonal malignancy of B lymphocytes, in which the abnormal monoclonal B lymphocytes are accumulated in the peripheral blood, bone marrow, and lymphoid tissues, chronic lymphocytic leukemia (CLL) results in compromised immune system by quantitative and qualitative deficiencies in lymphocyte populations vital for effective immune response and surveillance[2]. Additionally, cells exhibit aberrant expression of surface markers and altered cytokine signaling, resulting in impaired antigen presentation, defective cytotoxicity, and compromised humoral immunity[3]. Consequently, CLL patients show heightened susceptibility to bacterial, viral, and fungal infections, with increased morbidity and mortality attributable to infectious complications[4].

Given the vulnerability of CLL patients and their susceptibility to COVID-19-related adverse events, this study aims to evaluate the impact of COVID-19 on the general conditions, prognosis, and clinical outcomes of patients with CLL.

METHODS

This review was conducted in compliance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), following an evidence-based research question, defined to address the impact of COVID-19 infection on clinical outcomes of CLL patients[5]. The study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021244712).

Search strategy

Medline (via PubMed), Scopus, Web of Science, and Cochrane Library were systematically searched using the free keywords and MeSH terms related to COVID-19, SARS-CoV-2, and Chronic Lymphocytic Leukemia, with no limitation in language and date of publication till the end of February 2024. To have a complete pool of related studies, the reference lists of studies were also assessed.

Inclusion criteria and study selection

Two independent researchers screened the results by title, abstract, and full-text articles. All types of clinical studies were included if adult patients with CLL, small lymphocytic leukemia, or monoclonal B-cell lymphocytosis, and a confirmed diagnosis

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of COVID-19 were present. Studies with insufficient sample size, animal studies, reviews, consensus papers, and practical guidelines were excluded.

Quality assessment and statistical analyses

Based on the type of the study, the remaining records were critically appraised by two independent researchers using the proper JBI Critical Appraisal Tools. CMA v2.0 was used to pool the data. A high degree of heterogeneity was defined as p value<0.05 or I^2>50%, where a random-effect model would be used for pooling.

RESULTS

From the 1,044 search results, 387 duplicate records were removed. After screening the records, 24 were selected based on compatibility with the inclusion criteria (Figure 1). Of the 24 studies, 4 were flagged as high in risk of bias, but no study was removed from the pool.

Patient characteristics

A total of 24 articles, reporting the results of 25 studies, with 7,091 patient records were included[6-29]. Most studies reported a median age of 68–72 years at the time of COVID-19 diagnosis (Table 1). Of the included patients, 64.6% were male, 39.82% were treatment-naïve, and 37.96% were under treatment at the time of COVID-19 diagnosis, most common with Bruton's tyrosine kinase inhibitor (59.34%).

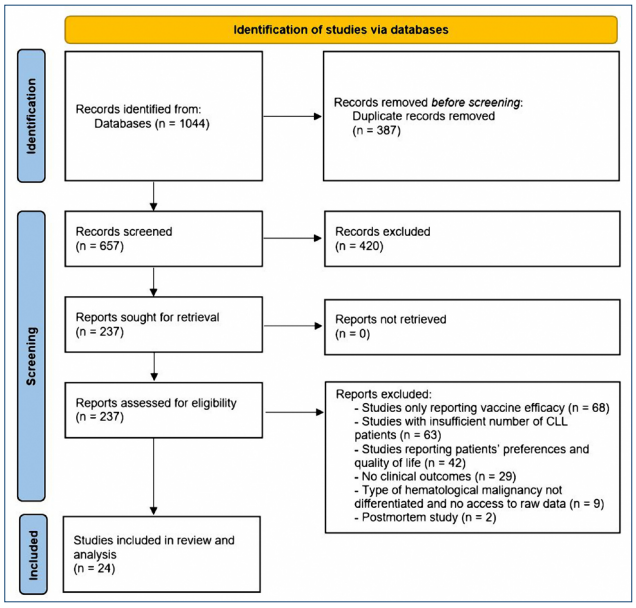

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of the study.

Hospitalization and mortality

Data regarding COVID-19-related mortality with a follow-up time of at least 1 month were pooled. Twenty-two independent studies with 5,167 patients had available data for COVID-19-related mortality in CLL patients. The pooled mortality risk was estimated as 23.53% (95%CI: 18.12–28.94%), with a considerable heterogeneity (I^2=96.04%, p value<0.01). The pooled risk of hospitalization was estimated as 69.13% (95%C I: 61.14–77.11%), also with a high heterogeneity (I^2=96.64%, p value<0.01) (Figure 2). A 28.27% (95%CI: 23.55–33.52%) risk of admission to intensive care unit was estimated among hospitalized patients. The included studies reported decreased hospitalization rates through the pandemic; however, sufficient data were unavailable to perform a pooled analysis. An overall mortality of 33.3% (95%CI: 29.72–37.16%) was estimated among the hospitalized patients. No statistically significant difference was detected in the pooled risk of hospitalization between male and female patients within the available data (OR=1.19, 95%CI: 0.50–2.84, p value: 0.68).

Underlying conditions and medical history

The pooled risks of hospitalization and death in patients with a history of hypertension were 90.09% (95%CI: 82.56–94.58%) and 28.18% (95%CI: 14.09–48.43%), and in patients with a history of diabetes mellitus were 81.17% (95%CI: 71.69–88%) and 30.4% (95%CI: 20.45–42.73%), respectively. The pooled risks of hospitalization and death in patients with a history of coronary artery disease and/or cardiac failure were 78.43% (95%CI: 54.3–91.75%) and 32.03% (95%CI: 19.93–47.13%), respectively. The risks of hospitalization and mortality were not reported in a sufficient number of studies to report a pooled ratio for patients with a history of arrhythmia, asthma, chronic obstructive pulmonary disease, and chronic kidney disease. CLL patients with active smoking were at an 81.18% (95%CI: 66.64–90.31%) risk of hospitalization and 38.58% (95%CI: 13.38–71.86%) mortality risk. Overall, 46.1% of the patients had a Cumulative Illness Rating Scale (CIRS) score over 6. Patients with CIRS>6 had an 87.73% (95%CI: 76.23–94.1%) risk of hospitalization and 34.75% (95%CI: 22.3–49.7%) risk of mortality.

A poor Eastern Cooperative Oncology Group (ECOG) performance status scale was significantly reported with an increased risk of COVID-19-related mortality. Also, age over 65 years at the time of COVID-19 diagnosis was significantly associated with higher hospitalization and mortality rates; however, these variables had insufficient data for pooling.

Table 1. Characteristics of the included studies.

Authors	Year	Country	Number of CLL patients			Age (median)	Hospitalized	ICU admission	Deaths
			Total	Male	Female				
Aleshina et al.[6]	2023	Russia	45	N	N	N	45	18	14
Antic et al.[7]	2022	International	793	551	242	69 (IQR: 61–77)	593	162	N
Autore et al.[8]	2023	Italy	104	72	32	69 (IQR: 67–72)	N	N	10
Blixt et al.[9]	2022	Sweden	60	39	21	71 (range: 43–97)	46	11	14
Bronstein et al.[10]	2023	Israel	128	91	37	72 (IQR: 64–78)	34	N	6
Chatzikonstantinou et al.[11]	2021	International	941	628	313	69 (IQR: 61–77)	695	177	257
Cuneo et al.[12]	2021	Italy	494	N	N	324 patients >65 years	307	N	122
Glenthøj et al.[13]	2021	Denmark	31	19	12	(mean ± SD: 67.0 ± 16.7)	25	6	6
Kochneva et al.[14]	2022	Russia	136	84	52	66 (range: 42–90)	119	30	34
Mato et al.[15]	2020	International	198	125	73	70.5 (range: 38–98)	178	68	66
Mato et al.[16]	2023	USA	50	N	N	67 (range: 43–86)	28	N	14
Merli et al.[17]	2023	Italy	256	155	101	70 (IQR: 38–94)	176	50	77
Muntañola et al.[18]	2020	Spain	165	112	53	73 (range: 37–94)	152	47	45
Niemann et al.[19]	2022	Denmark	793	487	306	72 (IQR: 64–78)	105	13	37
Niemann et al.[20]	2022	International	67	N	N	69 (range: 43–90)	47	N	20
Puła et al.[21]	2022	Poland	188	119	69	68 (range: 37–87)	111	25	50
Roeker et al.[22]	2020	USA	30	22	8	65 (range: 41–82)	19	N	4
Roeker et al.[23]	2020	International	281	188	93	72 (range: 37–94)	281	56	85
Roeker et al.[23]	2020	International	130	83	47	68 (range: 41–98)	130	63	44
Scarfò et al.[24]	2020	International	190	126	64	72 (range: 48–94)	169	39	56
Šimkovič et al.[25]	2023	Czech Republic	341	237	104	69 (range: 39–92)	206	72	95
Stahl et al.[26]	2021	USA	25	N	N	N	N	N	2
Tekinalp et al.[27]	2022	Turkey	50	23	27	73 (range: 31–93)	50	36	13
Trajkova et al.[28]	2022	Republic of Macedonia	55	44	11	65	N	N	26
Visentin et al.[29]	2023	International	1,540	998	542	69 (IQR: 62–77)	1,007	240	368

CLL: chronic lymphocytic leukemia; ICU: intensive care unit; IQR: interquartile range; N: not reported.

Clinical presentation, symptoms, and complications

Fever, cough, dyspnea, and fatigue were the most common presentations in CLL patients with COVID-19 infection, with a prevalence of 74.30%, 60.14%, 48.05%, and 37.97%, respectively. Myalgia, diarrhea, and nausea/vomiting were the less common symptoms, with a prevalence of 15.52%, 13.46%, and 8.01%, respectively. From 1,142 available patient records, a pooled risk of disseminated intravascular coagulation /thrombosis of 11% (95%CI: 7.13–16.59%) was estimated for CLL patients as the main complication of COVID-19 infection.

Unlike other symptoms, fever at the time of COVID-19 diagnosis is suggested to be associated with hospitalization in the included studies (reported HR=2.07, 95%CI: 1.03–4.19, p value<0.05); however, available data were not sufficient for a pooled analysis. Anemia, thrombocytopenia, and elevated lactate dehydrogenase level at the initial assessment were statistically associated with adverse clinical outcomes and COVID-19-related mortality. One study (Visentin et al.) reported the WHO-defined post-COVID condition in CLL COVID-19 survivors, with a prevalence of 15.8%.

DISCUSSION

Due to the global impact of the COVID-19 pandemic, cancer patients who contact the virus have experienced adverse

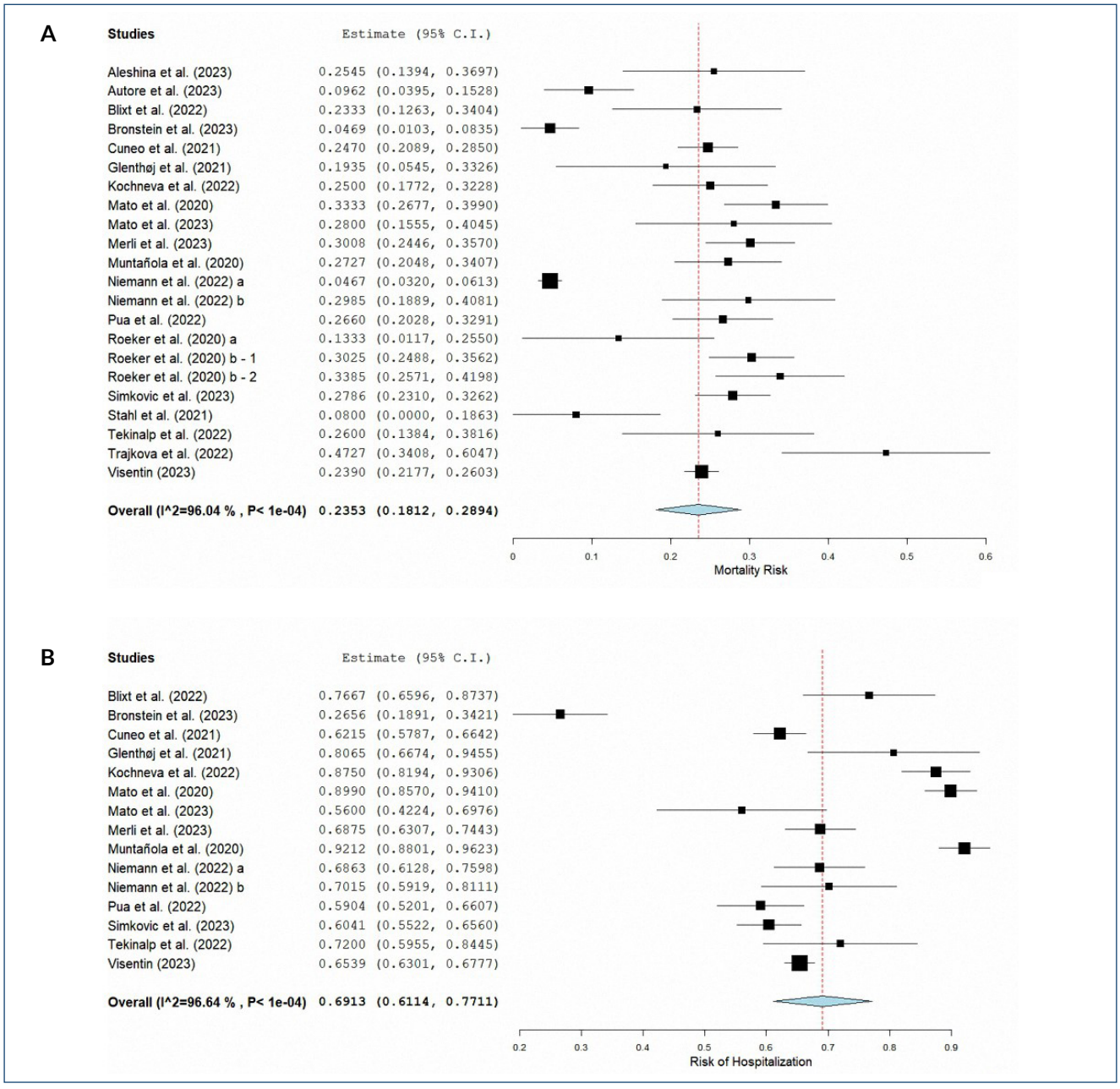

Figure 2. Pooled analysis for risk of mortality (a) and hospitalization (b) in chronic lymphocytic leukemia patients with COVID-19 infection.

outcomes. Recent data indicate a general susceptibility of individuals with hematological malignancies to SARS-CoV-2 infection, and, at the top of all, CLL, making them more prone to severe forms of COVID-19[30].

The mortality rate in CLL patients varies based on different factors, including age, stage of the disease, overall health, the presence of underlying comorbidities, and the effectiveness of supportive treatments. In the context of COVID-19, CLL patients may face an increased risk of mortality due to the immunocompromised state associated with the disease and the systemic treatment. Previous studies have reported a case fatality rate of 32–47%[31,32]. CLL patients with symptomatic COVID-19 and requiring inpatient admission showed high mortality rates.

Advanced age is consistently associated with increased mortality in COVID-19 patients, and a similar trend has been observed among CLL patients as well. Aging is associated with a weakened immune system, limited physiological reserve, and organ failures. Underlying health conditions or comorbidities, such as cardiovascular disease, diabetes, or respiratory conditions, may lead to a higher rate

of mortality in CLL patients with COVID-19. The severity of both CLL and COVID-19 plays a crucial role in this matter. Patients with advanced CLL may have compromised immune systems, making them more vulnerable to severe manifestations of COVID-19[33].

Humoral and cellular immunity dysfunctions contribute to the heightened susceptibility. Antineoplastic CLL therapies, such as specific immunosuppressive or chemotherapeutic agents, may affect the patient's ability to mount an effective immune response against infections, possibly due to different impacts on immune system components. For instance, some studies suggest that CLL patients under ibrutinib are less likely to require hospitalization, suggesting diverse effects of anti-leukemic treatments[34].

The COVID-19 pandemic has significantly affected the means, standards, and quality of care as the medical care has undergone major changes in adaptations during the pandemic in both oncology and nononcology care settings[35,36]. Further general and cancer-oriented studies are required to clarify these transforms and draw updated clinical conclusions for future practice[37]. Current review suggests that CLL patients, specifically symptomatic patients, suffer from higher mortality and morbidity due to COVID-19 regardless of their disease phase or treatment status. These results highlight the importance of understanding and addressing the specific challenges that CLL patients may encounter in the context of COVID-19 and future pandemics.

CONCLUSION

CLL patients are at higher risk of COVID-19-related adverse outcomes, including hospitalization, need for intensive care, and mortality. Further population-based studies should be conducted to determine the role of underlying conditions, the status of antineoplastic treatment, and potential antiviral therapies on the clinical course of COVID-19 and post-COVID condition.

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AUTHORS' CONTRIBUTIONS

MAA: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **YVG:** Data curation, Investigation, Methodology, Writing – review & editing. **FJ:** Data curation, Investigation, Writing – original draft. **AGB:** Methodology, Writing – review & editing. **SH:** Data curation, Investigation, Writing – original draft. **SS:** Data curation, Formal Analysis, Writing – review & editing. **ARM:** Visualization, Writing – review & editing. **MSH:** Conceptualization, Formal Analysis, Methodology, Supervision, Visualization, Writing – original draft.

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COMMENTARY

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Prevalence of sleep disorders and daytime sleepiness depends on many influencing factors that should be taken into account

Josef Finsterer[1*]

Dear Editor,

We read with interest Souza et al.'s article on a cross-sectional study of sleep quality and daytime sleepiness in 179 students at a private university between August 2021 and March 2022 using the Pittsburgh Sleeping Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) in the form of an electronic questionnaire[1]. According to the PSQI, 65% of students had poor sleep quality, with no difference between gender, BMI, and graduation category[1]. Students with a BMI >25 kg/m^2 had longer sleep latency and shorter sleep duration than students with a lower BMI[1]. According to ESS, 44% of students had daytime sleepiness[1]. The study is impressive, but some points require discussion.

The first point is the use of an electronic questionnaire. Electronic questionnaires have the disadvantage that the correctness of the answers cannot be easily checked, and it is difficult to judge whether the addressee is actually the person who answered and whether the respondent was mentally capable of understanding the questions correctly and giving appropriate answers.

The second point is that various causes of sleep loss and daytime sleepiness were not taken into account. Sleep disorders can also be due to unusually high consumption of adrenergic stimulants (coffee, tea, cacao, cola, Red Bull, nicotine), acute or chronic stress, abuse of illegal drugs, alcohol addiction, unpleasant sleeping places (bright, noisy, increased humidity, not well tempered), unusually frequent use of electronic devices (laptop, tablet, cell phone), abuse of TV watching or computer work before going to bed, chronic cardiac disease, chronic muscle disease, endocrine disease, metabolic disease, and psychiatric disorder. Furthermore, it would have been mandatory to report the current medication of all included patients. We should also know how many of the students included were using illegal drugs, either stimulants (e.g., speed) or sedatives (e.g., cannabis).

A third point is that the study was obviously carried out during the pandemic. Therefore, it is imperative to rule out complications of SARS-CoV-3 infection[2] or SARS-CoV-2 vaccination[3], including post-COVID-19 syndrome or long post-COVID-19 vaccination syndrome. We should know how many suffered from the SARS-CoV-2 infection and how many suffered from severe side effects after the SARS-CoV-2 vaccination.

A fourth point is that the number of females was significantly higher than that of men. This inequality can lead to bias.

A fifth point is that sleep quality can also depend on a person's social status and income. We should know whether the cohort could be divided into high- and low-income students and whether sleep quality and daytime sleepiness differed between high- and low-income students. It should also be reported whether academic performance differs between people with and without sleep disorders or daytime sleepiness.

In summary, the excellent study has limitations that make the results difficult to interpret. Removing these limitations could strengthen and support the study's message. Sleep quality and daytime sleepiness depend on numerous influencing factors that must be included in the analysis in order to make conclusive statements.

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