ISSN 0104-4230 ISSN 1806-9282 (On-line)

Ramb'S 2021 Journal Citation Reports-Impact Factor: **1,712**

Journal of The Brazilian Medical Association

Volume 69, Number 4 April, 2023







Journal of The Brazilian Medical Association

Volume 69, Number 4, April, 2023







ISSN 0104-4230 ISSN 1806-9282 (On-line)

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The RAMB, Journal of The Brazilian Medical Association, is an official publication of the Associacao Medica Brasileira (AMB – Brazilian Medical Association), indexed in Medline, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B1 Capes databases, and licensed by Creative CommonsR.

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How may ChatGPT impact medical teaching?

Gerson Hiroshi Yoshinari Júnior^{1*} ⁽⁰⁾, Luciano Magalhães Vitorino¹ ⁽⁰⁾

On November 22, 2022, ChatGPT, a chatbot created by OpenAI, a branch of Microsoft nowadays, was released to the public. Besides the lack of mediatic attention, that date is already marked in history. ChatGPT is an AI-powered computer program that can understand and generate human-like language¹. It has been trained on vast amounts of text to analyze language patterns, allowing it to provide accurate responses to a wide range of questions. So, why the buzz²?

DropBox took 7 months to reach 1 million users, Spotify took 5 months, and Instagram took 2.5 months. ChatGPT reached the mark of 1 million users in only 5 days after release. The tool is so powerful that its application possibilities seem to be limitless. ChatGPT has already been proven to be an excellent doctor, in a sense. It was able to pass the US Medical Licensing Examination (USMLE), at least the multiple choice questions³. But how can we use it for the benefit of medical education?

When we asked ChatGPT that same question, here are some answers: Medical Q&A, virtual patient simulations, language translation, personalized learning, continuing medical education, and remote learning.

When we asked about the dangers of using ChatGPT in medical education, some answers were as follows: inaccurate information, overreliance on technology, privacy concerns, bias, lack of Personalization, Limited Interactivity, etc.

We agree with the presented potential benefits, partially. First, the ChatGPT database (until this letter is written) is upper-limited to 2021. So the "up-to-date information" is compromised. The GPT-3 model (used by ChatGPT) is not meant to be re-trained with specific datasets (as presented by the developers in the paper "Language Models are Few-Shot Learners," 2020), so the "training in large medical databases and clinical guidelines" is also compromised. While talking about the dangers, the authors also agree with ChatGPT. The risk of inaccurate information may be one of the most important, but it is also one of the most evident and easily correctable.

Nevertheless, some other issues must be taken into consideration:

- To obtain the six items on the list of benefits, we had to regenerate the response three times. Only inaccurate information and privacy concerns were present in all three responses. That is a problem in learning: we must have consistency in the information. Otherwise, it will be very difficult to transform it into knowledge.
- 2. Ethical behavior is key in medical practice and must be developed throughout the formation. Although ChatGPT has mechanisms to prevent "morally unacceptable answers," the specificity of medical ethics has not been fully assessed. The developers addressed the issue in the cited paper. This text was written with the aid of ChaGPT, and another AI performed grammar and orthographic revision.

One thing is for sure, ChatGPT is the first of many to come, and we will have to learn to work with it, not against it.

AUTHORS' CONTRIBUTIONS

GHYJ: Conceptualization, Supervision, Validation, Writing – review & editing. **LMV:** Conceptualization, Validation, Writing – review & editing.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none. Received on March 07, 2023. Accepted on March 16, 2023.



The use of esketamine in the treatment of patients with severe depression and suicidal ideation: systematic review and meta-analysis

Idevaldo Floriano¹, Antônio Silvinato^{1,2*}, Wanderley Marques Bernardo^{2,3}

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct, and to 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 clinical condition of each patient. Guideline conclusion: March 2023. Societies: Brazilian Medical Association.

INTRODUCTION

Depression is a very common and disabling mental illness and can be assessed by applying several questionnaires, the most common being the Montgomery-Asberg rating scale¹, scoring on a scale of 0–60, where 7–19 denotes mild depression, 20–34 moderate depression, and greater than 34 severe depression. Major or severe depression is commonly associated with suicidal ideation, resulting in a suicide attempt or suicide.

Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a nonselective, noncompetitive antagonist of the N-methyl-Daspartate receptor and the ionotropic glutamate receptor. It promotes increased stimulation of the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and neurotrophic signaling, which restore brain synaptic function. However, the mechanism by which esketamine exerts its antidepressant effect is unknown. Unlike other antidepressant treatments, the primary antidepressant action of esketamine does not directly involve monoamine, GABA, or opioid receptors².

The aim of this systematic review was to evaluate the use of esketamine compared to placebo in patients with severe depression and suicidal ideation.

CLINICAL DOUBT

What is the efficacy and safety of using esketamine in the treatment of patients with severe depression and suicidal ideation?

METHODOLOGY

Eligibility criteria were as follows:

- 1. Patients with major depression and suicidal ideation.
- 2. Esketamine treatment plus standard care (antidepressants) compared to placebo plus standard care.
- 3. Outcomes improvement in the state of depression, evaluated in appropriate scores.
- 4. Included randomized controlled trials (RCTs) and observational studies.
- 5. No restrictions on publication date and language.
- 6. Full text available for access.
- 7. Follow-up time: minimum 25 days.

The search for evidence will be carried out in the Medline/ PubMed and Central Cochrane virtual scientific information base, using the following search strategy: (Depressive Disorder OR Depressive Disorder, Major OR Depressive Disorder, Treatment-Resistant) AND Esketamine AND Random*. The search in these databases was carried out until the month of

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on March 01, 2023. Accepted on March 28, 2023.

September 2022. A systematic review was carried out according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)³.

The risk of bias for randomized clinical trials will be assessed using the items of the RoB 2 tool⁴, plus other fundamental elements and expressed as low risk, and in some concerns, as high risk of bias. The risk of bias assessment will be carried out by two independent reviewers (AS and IF), and in case of disagreement, a third reviewer (WB) may deliberate on the assessment. The certainty of the evidence will be extrapolated from the risk of bias obtained from the study(ies) (if no meta-analysis) using the GRADE terminology⁵ in very low, low, moderate, and high, and through the GRADEpro software⁶ (if meta-analysis) into very low, low, moderate, and high.

The measures used to express benefit or harm varied according to the outcomes and were expressed through continuous variables (mean and standard deviation) or categorical variables (absolute number of events). For continuous measurements, the result will be the difference in means (DM) and its standard deviation (SD); for categorical measures, it will be the risk difference (RD) and number needed to treat (NNT) or harm (NNH). The confidence level used is 95%.

When there are common outcomes between the included studies, the results will be expressed through meta-analysis, using the RevMan 5.4 software⁷, with the global RD with 95% confidence intervals (CI) being the final measure used to support the synthesis of the evidence, which will answer the clinical question. Estimation of the size of the combined effects was performed by a fixed or random effect model after evaluating the heterogeneity results. Heterogeneity was calculated using the I² value.

RESULTS

In the search for evidence, 90 new studies were retrieved; 23 were selected based on title and abstract, of which 3^{8-10} were selected to support this evaluation, whose characteristics are described in Table 1 (ANNEXES). The list of those excluded and the reasons are available in the references and Figure 1.

The population included was 524 patients, aged between 18 and 64 years, diagnosed with major depression and suicidal ideation, without associated psychopathy and evaluated using the Montgomery-Asberg Depression Rating Scale with a score \geq 22, and confirmed by the Mini International Neuropysichiatric Interview (MINI) (Table 1, ANNEXES).

The exclusion criteria were as follows: bipolar psychiatric disorder, drug addiction, intellectual disability, antisocial personality disorder, borderline personality, and psychotic disorder. A total of 261 patients received esketamine (84 mg, nasal route, 3 puffs in total, alternating nostrils, with an interval of 5 min, twice a week) associated with treatment with antidepressants, individualized for each patient (*standard-of-care*), and 263 received placebo plus *standard-of-care*.

The primary outcome considered was the reduction of depressive symptoms assessed by the Montgomery-Asberg Depression Rating Scale (MADRS), and the secondary ones were remission of depression (MADRS ≤ 12), response $\leq 50\%$ in the reduction of the MADRS score, and serious adverse events.

Regarding the risk of bias, there was no analysis by intention to treat, >20% losses occurred in 3 studies⁸⁻¹⁰, and the overall risk of bias can be considered a moderate-to-severe risk. The evaluation was done through the RoB 2 tool (Figure 2).

- Results of the comparison between the use of esketamine and placebo in participants with major depression and suicidal ideation.
 - 1.1. Mean reduction in MADRS including three studies⁸⁻¹⁰ with a total of 522 participants.
 - 1.1.1. One day after the first dose, esketamine may reduce depression rating scale scores over placebo, standardized mean difference (SMD) -3.18, 95%CI -1.58 to -4.78; I²=0%; p=0.0001 (Figure 3). High evidence certainty (Table 2, ANNEXES).
 - 1.1.2. At the 25-day follow-up, in pre-dose analysis, there was a mean reduction of 2.94 points, SMD -2.94, 95%CI -0.89 to -4.99; I²=0%; p=0.005, in the esketamine group compared to placebo group (Figure 4). Certainty of moderate evidence.
 - 1.1.3. In a pre-dose analysis and 90-day follow-up, there was a mean reduction of 1.75 points in the esketamine group compared to placebo, SMD -1.75, 95%CI -1.28 to -2.22; I2=89%; p=0.00001 (Figure 5). Very low certainty of evidence.
 - 1.1. Remission rate (≤ 12 points on the MADRS).
 - 1.1.1. Three studies⁸⁻¹⁰, with a total of 522 patients and 24-h follow-up after the first dose, showed a 5% increase in the remission rate with the use of esketamine compared to placebo, RD=-5%, 95%CI -0.1 to -9; I²=0%; p=0.05, being necessary to treat 20 patients for a benefit (NNT=20) (Figure 6). High evidence certainty.
 - 1.1.2. In a pre-dose analysis, with a follow-up of up to 8 days, two studies⁹⁻¹⁰ with a total



Figure 1. Evidence retrieval and selection diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal. pmed1000097



Figure 2. Risk of bias.

of 456 participants showed no difference in the remission rate between groups, RD=5%, 95%CI -3 to 13; p=0.2; I²=0%; NNT=not significant (NS) (Figure 7). High evidence certainty.

1.1.3. Evaluating the pre-dose 25-day follow-up, three studies⁸⁻¹⁰ (522 participants) showed a 12% increase in the remission rate with the use of esketamine compared to placebo, RD=12%, 95%CI 4 to 20; I²=0%; p=0.004; being necessary to treat 8

| | Experimental Control | | | | | | Mean Difference | Mean Difference | |
|--|----------------------|----------|-------|-----------|------|-------|-----------------|--------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% Cl | IV, Fixed, 95% Cl |
| Canuso 2018 | 10.2 | 9.74 | 35 | 8.3 | 7.12 | 31 | 15.3% | 1.90 [-2.19, 5.99] | |
| Fu 2020 | 13.5 | 10.89 | 114 | 10.9 | 9.69 | 112 | 35.4% | 2.60 [-0.09, 5.29] | |
| lonescu 2020 | 12.2 | 9.87 | 115 | 8.2 | 7.62 | 115 | 49.2% | 4.00 [1.72, 6.28] | a 🖉 🖉 🖉 |
| Total (95% Cl) | . 1 OE df | - 2 /0 - | 264 | 12 - 0.07 | | 258 | 100.0 % | 3.18 [1.58, 4.78] | |
| Heterogeneity: Chi² = 1.05, df = 2 (P = 0.59); l² = 0% Test for overall effect: Z = 3.90 (P < 0.0001) | | | | | | | | | -10 -5 0 5 10 Favours [Control] Favours [Experimental] |

Figure 3. Meta-analysis of the mean reduction in Montgomery-Asberg Rating Scale 1 day after the first dose.

| | Esketamine Placebo | | | | | | Mean Difference | Mean Difference | |
|---|--------------------|-------|-------|------|-----------|-------|-----------------|--------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% Cl | IV, Fixed, 95% CI |
| Canuso et al. 2018 | 19.3 | 9.61 | 35 | 16 | 10.54 | 31 | 17.6% | 3.30 [-1.59, 8.19] | · · · · · · · · · · · · · · · · · · · |
| Fu et al. 2020 | 24.8 | 13.63 | 114 | 23 | 12.41 | 112 | 36.4% | 1.80 [-1.60, 5.20] | |
| lonescu et al. 2020 | 26.2 | 11.09 | 115 | 22.5 | 12.23 | 115 | 46.1% | 3.70 [0.68, 6.72] | |
| Total (95% CI) | | | 264 | | | 258 | 100.0% | 2.94 [0.89, 4.99] | ◆ |
| Heterogeneity: Chi² = 0.70, df = 2 (P = 0.71); l² = 0% Test for overall effect: Z = 2.81 (P = 0.005) | | | | | | | | | -10 -5 0 5 10 Favours (Placebo) Favours (Esketamine) |

Figure 4. Meta-analysis of mean reduction in Montgomery-Asberg Rating Scale, 25-day follow-up and pre-dose analysis.

| | Esketamine Placebo | | | | | | Mean Difference | Mean Difference | |
|---|--------------------|-----------|---------|------|--|-------|-----------------|--------------------|--------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% Cl | IV, Random, 95% Cl |
| Canuso et al. 2018 | 20.3 | 8.02 | 35 | 18 | 9.92 | 31 | 1.1% | 2.30 [-2.09, 6.69] | |
| Fu et al. 2020 | 26 | 0.69 | 114 | 24 | 0.79 | 112 | 48.3% | 2.00 [1.81, 2.19] | • |
| lonescu et al. 2020 | 28 | 0.49 | 115 | 26.5 | 0.49 | 115 | 50.6% | 1.50 [1.37, 1.63] | • |
| Total (95% CI) | | | 264 | | | 258 | 100.0% | 1.75 [1.28, 2.22] | ◆ |
| Heterogeneity: Tau ² = 0.11; Chi ² = 18.04, df = 2 (P = 0.0001); I ² = 89% | | | | | | | | | |
| Test for overall effect: | Z=7.24 | (P < (| 0.00001 | | Favours (Placebo) Favours (Esketamine) | | | | |

Figure 5. Meta-analysis of mean reduction in Montgomery-Asberg Rating Scale, 90-day follow-up and pre-dose analysis.

| | Esketamine Placebo | | | Risk Difference | Risk Difference | | |
|-----------------------------------|--------------------|----------|-------------|------------------------|-----------------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | I M-H, Fixed, 95% CI |
| Canuso et al. 2018 | 4 | 35 | 2 | 31 | 12.6% | 0.05 [-0.09, 0.19] |] |
| Fu et al. 2020 | 12 | 114 | 9 | 112 | 43.3% | 0.02 [-0.05, 0.10] |] |
| lonescu et al. 2020 | 12 | 115 | 4 | 115 | 44.1% | 0.07 [0.00, 0.13] |] |
| Total (95% CI) | | 264 | | 258 | 100.0% | 0.05 [0.00, 0.09] | |
| Total events | 28 | | 15 | | | | |
| Heterogeneity: Chi ² = | 0.78, df= | 2 (P = 0 |).68); l² = | 0% | | | |
| Test for overall effect: | Z = 2.00 (| P = 0.05 | 5) | | | | Favours [Placebo] Favours [Esketamine] |

Figure 6. Meta-analysis of the remission rate (reduction \leq 12 points on the Montgomery-Asberg Rating Scale), 24 h after the first dose.

| | Esketamine Placebo | | | | | Risk Difference | | Risk Difference | | |
|--|--------------------|-------------------------|--------|-------|--------|------------------------|--|-------------------------------------|-----|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | | M-H, Fixed, 95% Cl | | |
| Fu et al. 2020 | 30 | 114 | 23 | 112 | 49.6% | 0.06 [-0.05, 0.17] | | | | |
| lonescu et al. 2020 | 28 | 115 | 23 | 115 | 50.4% | 0.04 [-0.06, 0.15] | | | - | |
| Total (95% CI) | | 229 | | 227 | 100.0% | 0.05 [-0.03, 0.13] | | | | |
| Total events | 58 | | 46 | | | | | | | |
| Heterogeneity: Chi ² = | 1 (P = 0 |).86); I ^z = | 0% | | | + | | <u> </u> | | |
| Test for overall effect: Z = 1.29 (P = 0.20) | | | | | | | | Favours [Placebo] Favours [Esketami | ne] | |

Figure 7. Meta-analysis of the 8-day remission rate and pre-dose analysis.

patients for a benefit (NNT=8) (Figure 8). Certainty of moderate evidence.

- Response rate with ≥50% reduction in initial MADRS points, esketamine versus placebo.
 - 1.2.1. Two studies⁸⁻¹⁰ (296 participants), 24 h post-dose follow-up, showed an increase of 18% in the response rate, in patients who used esketamine compared to placebo, RD=18%, 95%CI 9 to 26; I²=0%, p=0.00001; NNT=6 (Figure 9). High evidence certainty.
 - 1.2.2. There was no difference between the groups when we evaluated in the follow-up for 8 days, in one study¹⁰ (230 participants), RD=3%, 95%CI -9 to 16; p=0.59; NNT=NS (Figure 10). High evidence certainty.
 - 1.2.3. In 25-day follow-up and pre-dose analysis, two studies⁸⁻¹⁰ (296 participants) showed no difference between groups, RD=7,95%CI-12 to 26, I²=57%, p=0.13, NNT=NS (Figure 11). Certainty of moderate evidence.
- 1.3. Serious adverse events.
 - 1.3.1. Three studies⁸⁻¹⁰, with a total of 522 patients in a 25-day follow-up and pre-dose analysis, showed no difference when comparing esketamine versus placebo, RD=2%, 95%CI -2 to 5, I²=43%, p=0.30, NNH=NS (Figure 12). Very low certainty of evidence.

EVIDENCE SUMMARY

The use of esketamine in patients with major depression and suicidal ideation was compared to placebo.

- It reduces depression rating scale scores (MADRS), standardized mean difference of 3.18 points, and 24 h after the first dose. High evidence certainty.
- It reduces depression rating scale scores (MADRS), standardized mean difference of 2.94 points, and pre-dose analysis in the 25-day follow-up. Certainty of moderate evidence.
- It reduces depression rating scale scores (MADRS), standardized mean difference of 1.75 points, and predose analysis in the 90-day follow-up. Low certainty of evidence.
- It increases the remission rate by 5% (MADRS ≤12 points), NNT=20, in 24 h after the first dose of treatment. High evidence certainty.
- There is no difference in remission rate at 8-day follow-up and pre-dose analysis. High evidence certainty.
- Increases remission rate by 12% (MADRS ≤12 points), NNT=8, at 25 days and pre-dose analysis. Certainty of moderate evidence.
- 18% increase in response rate (≥50% point reduction from baseline MADRS), NNT=6, within 24 h after first dose. High evidence certainty.
- There is no difference in response rate at 8-day follow-up and pre-dose analysis. High evidence certainty.
- There is no difference in response rate at 25-day follow-up and pre-dose analysis. High evidence certainty.
- There is no difference in the number of serious adverse events within 25 days. Very low certainty of evidence.

DISCUSSION

Countless deaths in the world are due to suicide, and people with severe depression are vulnerable to suicidal ideation. According to the World Health Organization (WHO)¹¹, approximately

| | Esketamine Placebo | | | | Risk Difference | Risk Difference | | |
|-----------------------------------|--------------------|----------|-------------|-------|-----------------|--------------------|--------------------------------------|-----------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl | |
| Canuso et al. 2018 | 21 | 35 | 13 | 31 | 12.6% | 0.18 [-0.06, 0.42] | | _ |
| Fu et al. 2020 | 46 | 114 | 38 | 112 | 43.3% | 0.06 [-0.06, 0.19] | | |
| lonescu et al. 2020 | 49 | 115 | 31 | 115 | 44.1% | 0.16 [0.04, 0.28] | — — — | |
| Total (95% CI) | | 264 | | 258 | 100.0% | 0.12 [0.04, 0.20] | • | |
| Total events | 116 | | 82 | | | | | |
| Heterogeneity: Chi ² = | 1.35, df = | 2 (P = 0 |).51); I² = | 0% | | | | 0.5 |
| Test for overall effect: | Z = 2.86 (| P = 0.00 |)4) | | | | Favours [Placebo] Favours [Esketamin | 0.5 e] |

Figure 8. Meta-analysis of depression remission results with esketamine, 25 days and pre-dose analysis.

| | Esketamine Placebo | | | | Risk Difference | | Risk Difference | | |
|--|--------------------|----------|--------|-------|-----------------|--------------------|-----------------|--|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | | M-H, Fixed, 95% Cl | |
| Canuso et al. 2018 | 9 | 35 | 4 | 31 | 22.2% | 0.13 [-0.06, 0.31] | | | |
| lonescu et al. 2020 | 30 | 115 | 8 | 115 | 77.8% | 0.19 [0.10, 0.28] | | | |
| Total (95% CI) | | 150 | | 146 | 100.0% | 0.18 [0.09, 0.26] | | • | |
| Total events | 39 | | 12 | | | | | | |
| Heterogeneity: Chi ² = 0.35, df = 1 (P = 0.55); l ² = 0% | | | | | | | -0.5 | | - |
| Test for overall effect: | Z = 4.17 (| P < 0.00 |)01) | | | | -0.5 | Favours [Placebo] Favours [Esketamine] | |

Figure 9. Meta-analysis of response rate at 24 h post-dose follow-up.

| | Esketamine Placebo | | | | Risk Difference | Risk Difference | |
|--|--------------------|-------|--------|-------|-----------------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| lonescu et al. 2020 | 48 | 115 | 44 | 115 | 100.0% | 0.03 [-0.09, 0.16] | |
| Total (95% CI) | | 115 | | 115 | 100.0% | 0.03 [-0.09, 0.16] | - |
| Total events | 48 | | 44 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | | | | Favours [Placebo] Favours [Esketamine] |

Figure 10. Meta-analysis of response rate reduction, 8-day pre-dose follow-up.

| | Esketar | nine | Place | bo | | Risk Difference | | Risk Difference |
|--|---------|-------|--------|-------|--------|------------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | | M-H, Random, 95% Cl |
| Canuso et al. 2018 | 26 | 35 | 17 | 31 | 39.0% | 0.19 [-0.03, 0.42] | | |
| lonescu et al. 2020 | 60 | 115 | 61 | 115 | 61.0% | -0.01 [-0.14, 0.12] | | |
| Total (95% CI) | | 150 | | 146 | 100.0% | 0.07 [-0.12, 0.26] | | |
| Total events | 86 | | 78 | | | | | |
| Heterogeneity: Tau ² = 0.01; Chi ² = 2.33, df = 1 (P = 0.13); l ² = 57% | | | | | | б | 15 | |
| Test for overall effect: Z = 0.71 (P = 0.48) | | | | | | | -0.0 | Favours [Placebo] Favours [Esketamine] |

Figure 11. Meta-analysis of response rate reduction, 25-day follow-up and pre-dose analysis.

| | Esketamine Placebo | | | | Risk Difference | Risk Difference | |
|---|--------------------------|----------------------|-------------------|-------|-----------------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| Canuso et al. 2018 | 4 | 35 | 0 | 31 | 12.6% | 0.11 [-0.00, 0.23] | |
| Fu et al. 2020 | 4 | 114 | 2 | 112 | 43.3% | 0.02 [-0.02, 0.06] | - |
| lonescu et al. 2020 | 5 | 115 | 6 | 115 | 44.1% | -0.01 [-0.06, 0.05] | |
| Total (95% CI) | | 264 | | 258 | 100.0% | 0.02 [-0.02, 0.05] | • |
| Total events | 13 | | 8 | | | | |
| Heterogeneity: Chi ² = Test for overall effect: | 3.54, df = Z = 1.04 (| 2 (P = 0 P = 0.30 |).17); I² =)) | 43% | | | -0.5 -0.25 0 0.25 0.5 Favours [Placebo] Favours [Esketamine] |

Figure 12. Meta-analysis of adverse events, 25-day follow-up and pre-dose analysis.

700,000 people commit suicide worldwide, influenced by numerous psychological, social, and cultural factors.

In this systematic review with meta-analysis, we aggregated only studies that used esketamine in patients with depression and suicidal ideation in the search for evidence of efficacy and safety.

In the primary outcome, which measured the reduction in the score on the Montgomery-Asberg Depression Rate Score, used to grade levels of depression, we obtained a standardized mean reduction of 3.18 points with the use of esketamine and individualized antidepressants in comparison with placebo and individualized antidepressants. It should be noted that all patients included had a MADRS score of \geq 22.

For another evaluated endpoint, which was the remission rate (MADRS \leq 12 points), esketamine, compared to placebo, showed a benefit with a reduction of 5% (NNT=20) in 1 day after the first dose and 12% (NNT=8) at the 25-day follow-up and pre-dose analysis.

Regarding death by suicide: there was no death in both groups (esketamine/placebo) in a follow-up of up to 90 days.

Esketamine has been shown to be a fast-acting treatment for patients with severe depression and suicidal ideation; however, responses to treatment are often transient, and the antidepressant action of esketamine lacks robust clinical durability; studies with long follow-up are lacking. Little is known about which patient characteristics are associated with more rapid esketamine responses and/or more durability.

Esketamine is shown to be safe without increasing serious adverse events.

CONCLUSION

The use of esketamine and *standard-of-care* compared to placebo in patients with major depression (MADRS >22 points) and suicidal ideation reduces scores by an average of 3.18 and 2.94 points, respectively, in the follow-ups of 24 h post-dose and 25 days pre-dose.

There is an increase in response rate (≥50% reduction in baseline MADRS points) by 18% at 24 h follow-up after the first dose, and there is no difference at 25-day follow-up and pre-dose analysis.

Therefore, it is concluded that patients with major depression and suicidal ideation benefit from the use of esketamine 84 mg, nasal spray 1 puff 3 times, with an interval of 5 min, twice a week for 4 weeks, associated with antidepressants, in follow-up for up to 25 days.

AUTHORS' CONTRIBUTIONS

IF: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. WMB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Resources, Software, Supervision, Validation, Visualization, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ANNEXES

| Studies | Population | Intervention | Comparison | Outcome | Follow-up |
|-----------------------------------|---|--|---------------------------------|--|---|
| Canuso CM 2018 | The study selected 68 participants (19–64 years old) who had a diagnosis of severe depressive disorder (DMD) with active suicidal ideation, without psychotic characteristics according to DSM- IV-TR criteria and confirmed by applying the Mini International Neuropsychiatric Interview (MINI). Participants scored ≥22 on the Montgomery-Åsberg Depression Rating Scale (MADRS). Several psychiatric comorbidities were excluded: current diagnosis of bipolar disorder, moderate-to- severe substance use disorder, intellectual disability, antisocial personality disorder, current diagnosis of borderline personality disorder, or past psychotic disorder. | Esketamine 84 mg, nasal spray 1 puff, 3 times, 5 min apart, twice a week, for 4 weeks, associated with antidepressants. | Placebo and antidepressants. | Primary: mean reduction in MADRS scale score. Secondary: remission of depression (MADRS ≤12), response ≤50% in MADRS score reduction, and adverse events. | 80 days with segmentation in the first 25 days. |
| Fu DJ, 2020 (ASPIRE I) | Phase 3, multicenter, double- blind study (ASPIRE I), conducted between June 2017 and December 2018, 226 adult participants (18–64 years old) with a diagnosis of major depressive illness (DMD) and suicidal ideation, without psychotic features according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM- 5), confirmed by MINI. Eligibility criteria required patients to respond affirmatively to mini- questions B3 ("Have thoughts of suicide [killing yourself]?") and B10 ("Do you intend to take action or have thoughts of killing yourself in the past 24 hours?") within 24 h of randomization, be in clinical need of acute psychiatric hospitalization due to imminent risk of suicide, and >28 pre-dose MADRS points on day 1. | Esketamine 84 mg, nasal spray 1 puff, 3 times, 5 min apart, twice a week, for 4 weeks, associated with antidepressants. | Placebo and antidepressants. | Primary: mean reduction in MADRS scale score. Secondary: remission of depression (MADRS ≤12), response ≤50% in MADRS score reduction and adverse events, and change in CGI-SS-r score 24 h after the first dose. | 90 days with segmentation in the first 25 days. |
| lonescu DF 2021 (ASPIRE II) | Study conducted with 230 randomized patients (115 per arm), multicenter, double-blind (ASPIRE II) between June 2017 and April 2019. Eligible patients were between 18 and 64 years old, complied with the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) criteria for MDD (without psychosis) based on diagnostic assessment using MINI questionnaire and MADRS score >28. | Esketamine 84 mg, nasal spray 1 puff, 3 times, 5 min apart, twice a week, for 4 weeks, associated with antidepressants. | Placebo and antidepressants. | Primary: mean reduction in MADRS scale score. Secondary: remission of depression (MADRS ≤12), response ≤50% in MADRS score reduction and adverse events, and change in CGI-SS-r score 24 h after the first dose. | 90 days with segmentation in the first 25 days. |

MDD: major depressive disorder.

| able 2. (| Quality of evider | nce (GRADE). | | | | | | | | | |
|-------------------|----------------------|----------------------|---------------------------------|------------------|--------------------------------|-------------------------|--|-------------------|------------------------|---|--------------------------|
| | | Ŭ | ertainty assessn | nent | | | No. of p | atients | | Effect | |
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Esketamine | Placebo | Relative (95%Cl) | Absolute (95%Cl) | Certainty |
| Average | MADRS reducti. | on, up to 24 h afte | er the first dose (i | follow-up: mear | 1 days) ו 1 | | | | | | |
| 3 | Randomized trials | Not serious | Not serious | Not serious | Notserious | None | 264 | 258 | ı | MD 3.18 points at MADRS higher (1.58 higher to 4.77 higher) | ⊕⊕⊕⊕ High |
| MADRS | average reductio | on in 25 days, pre- | dose | | | | | | | | |
| С | Randomized trials | Serious ^a | Not serious | Not serious | Notserious | None | 264 | 258 | ı | MD 2.94 points at MADRS higher (0.9 higher to 4.98 higher) | @@@ O Moderate |
| MADRS | average reductio | on, pre-dose, up to | o 90 days | | | | | | | | |
| c | Randomized trials | Serious ^a | Very serious ^b | Not serious | Notserious | None | 264 | 258 | ı | DM 1.75 points at MADRS higher (1.28 higher to 2.22 higher) | DOOO Very low |
| Respons | se ≥50% in reduc | tion in baseline M, | ADRS. Follow-up | o 1 day post-do: | se | | | | | | |
| 7 | Randomized trials | Not serious | Not serious | Not serious | Notserious | None | 39/150 (26.0%) | 12/146 (8.2%) | RR 3.14 (1.72-5.74) | 180 fewer per 1,000 (from 260 fewer to 90 fewer) | ⊕⊕⊕⊕ High |
| Respons | se ≥50% in reduc | tion in baseline M, | ADRS. Follow-up | o 8 days, pre-do | se | | | | | | |
| 4 | Randomized trials | Not serious | Not serious | Not serious | Not serious | None | 48/115 (41.7%) | 44/115 (38.3%) | RR 1.09 (0.79-1.50) | 30 fewer per 1,000 (from 160 fewer to 90 more) | ⊕⊕⊕⊕ High |
| Respons | se ≥50% in reduc | tion in baseline M, | ADRS. Follow-up | o 25 days pre-d | ose | | | | | | |
| 2 | Randomized trials | Serious ^a | Not serious | Not serious | Not serious | None | 86/150 (57.3%) | 78/146 (53.4%) | RR 1.07 (0.87-1.31) | 40 fewer per 1,000 (from 150 fewer to 80 more) | ⊕⊕⊕ O Moderate |
| Remissic | on of depression, | , ≤12 points on the | Part MADRS. Follow | v-up 1 day post- | dose | | | | | | |
| 3 | Randomized trials | Not serious | Not serious | Not serious | Not serious | None | 28/264 (10.6%) | 15/258 (5.8%) | RR 1.82 (1.00-9.03) | 50 fewer per 1,000 (from 90 fewer to 0 fewer) | ⊕⊕⊕⊕ High |
| Remissic | on of depression, | ,≤12 points on the | P MADRS. Follow | v-up 8 days pre- | dose | | | | | | |
| 7 | Randomized trials | Serious ^a | Not serious | Not serious | Very serious ^c | None | 58/229 (25.3%) | 46/227 (20.3%) | RR 1.25 (0.89-1.76) | 50 fewer per 1,000 (from 130 fewer to 30 more) | @ 000 Very low |
| Remissic | on of depression, | , ≤12 points on the | e MADRS. 25-da | y pre-dose follc | dn-w | | | | | | |
| c | Randomized trials | Serious ^a | Not serious | Not serious | Notserious | None | 116/264 (43.9%) | 82/258 (31.8%) | RR 1.38 (1.10-1.72) | 120 fewer per 1,000 (from 200 fewer to 40 fewer) | @@@ O Moderate |
| Serious ; | adverse events w | vithin 25 days | | | | | | | | | |
| c | Randomized trials | Serious ^a | Not serious | Not serious | Extremely serious ^c | None | 13/261 (5.0%) | 8/263 (3.0%) | RR 1.62 (0.70-3.73) | 20 fewer per 1,000 (from 50 fewer to 10 more) | BOOO Very low |
| CI: confid | ence interval; MC |): mean difference; | RR: risk ratio. ^a Th | here was no anal | vsis by intention |) of treatment and | d losses >20%. ^b H _t | eterogeneity 89% | 6. °Confidence in | iterval exceeds the nullity line. | There was no |

analysis by intention to treat and losses > 20%. Heterogeneity 89%. Confidence interval crosses the null line.

Patient or population: Patients with major depression and suicidal ideation Context: Efficacy, safety, and tolerability Intervention: Esketamine Comparison: Placebo

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Rev Assoc Med Bras. 2023;69(4):e2023D694

EXCLUDED STUDIES (REASONS)

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New-onset atrial fibrillation after coronary artery bypass graft surgery

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Dear Editor,

We have read with great interest the article entitled "Systemic immune-inflammation index as a novel predictor of atrial fibrillation after off-pump coronary artery bypass grafting" by Topal et al.¹. First of all, we congratulate the authors for their valuable contribution and their successful high-volume off-pump coronary surgeries performed within approximately 5 years in a tertiary referral center. However, we would like to discuss some points about postoperative atrial fibrillation (PoAF), systemic immune-inflammation index (SII), and study design.

The study was performed on patients who underwent an off-pump coronary artery bypass grafting (CABG) operation¹. Did the authors include all consecutive patients in the study during the years they specified? Also, how many operations did they perform in this process? In the exclusion criteria, they have made a definition as "concomitant cardiac operation such as mitral valve surgery were excluded from the study." How many operations did they exclude that they performed off-pump CABG operation at their clinic and performed additional cardiac surgical procedures? In addition, how did they diagnose PoAF in the postoperative period? How long was the atrial fibrillation attack considered as PoAF in their study? Since various durations (60 s, 5 min?) are given in the literature, we believed that it is important to clarify these issues^{2,3}.

Platelet and neutrophil-to-lymphocyte ratio have been the subjects of valuable studies in many fields of medicine^{4,5}. SII, which is obtained by multiplying these parameters, is an important marker that has been recently investigated in various cardiovascular studies^{6,7}. It is also important to note that it is cheap and easily available. Studies have also shown a relationship between SII and the prevalence of atherosclerosis. Peripheral artery disease (PAD) was used as a categorical variable in this study. As an indicator of the extent of coronary artery disease, the number of distal bypasses was given. In the literature, the relationship between SII and SYNTAX score I was shown⁸. Did the authors calculate the SYNTAX score I for the patients in their study? Also, what did they accept the presence of PAD as? The TransAtlantic Inter-Society Consensus II (TASC II) classification is an important indicator of the prevalence of PAD⁹. If the authors have accepted the presence of PAD as having stenosis greater than 50%, the SII value may be higher in patients with a higher TASC II class, which may lead to misleading results¹⁰.

Therefore, PoAF is an important problem. We believe that clarification of the issues that we have mentioned will increase the value of this precious work.

AUTHORS' CONTRIBUTIONS

ME: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. UA: Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YA: Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SY: Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SY: Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none. Received on October 20, 2022. Accepted on January 09, 2023.

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Comment on "Evaluation of pulmonary nodules by magnetic resonance imaging sequences: which sequence will replace computed tomography?"

Aleksandar Georgiev^{1,2*} , Lyubomir Chervenkov¹, Vania Anastasova³, Tanya Kitova^{4,5}

Dear Editor,

We have read with great interest a manuscript entitled "Evaluation of pulmonary nodules by magnetic resonance imaging sequences: which sequence will replace computed tomography?" by Kızıloğlu et al.¹. We fully agree with the authors that magnetic resonance imaging (MRI) is emerging as a promising method for the follow-up of small nonmalignant pulmonary nodules.

Based on our personal experience from the oncological practice and the available data in medical literature, we would like to make some clarifications, which, in our opinion, would contribute to elucidating some of the existing controversial points. Conventional X-rays of the chest are still used for diagnosing pulmonary diseases. Not every patient has immediate access to CT or MRI, especially people living in more rural areas, smaller cities, or less developed countries. As an example, in our country, only the biggest cities have access to MRI. CT scanners have better availability but still not every hospital or medical center has one. Positron emission computed tomography (PET/CT) is the method that is in common use in oncology for staging and restaging as it reveals not only anatomical information but also the metabolic activity of tumors and metastases. Therefore, the hybrid method gives insight into the neoplasm's activity and response to treatment that neither CT nor MRI is capable of. As PET/CT will greatly increase the radiation exposure of patients, the hybrid method does not have the potential to be utilized in the follow-up of benign pulmonary nodules. In general, all other imaging methods represent a better option for the surveillance of pulmonary nodules. PET/CT is also very expensive for both initial investment and running costs. MRI is the slowest method and second most expensive option for both installing and running, followed by CT. X-rays are the fastest and cheapest method available, but this method can visualize nodules in around 50% of the cases². PET/MRI is a novel but still emerging hybrid method, due to the lack of available devices, that will have wider clinical implications for oncological imaging in the future.

The majority of diagnosed small pulmonary nodules are incidental findings³, and globally more than half of lung cancer patients are diagnosed initially in stage IV or more advanced stage⁴. The free survival rate in stage IV and above according to medical literature is approximately 1 year or less, and 5-year survival rates are close to 0%^{5,6}. Are radiation exposure and late related neoplasms from radiation that big of an issue? Do we really have the luxury to choose the method for lung malignancies? In our opinion, we should benefit from every imaging modality that can detect lung cancer and provide our patients a chance for better survival. Patients fully depend on a fast diagnostic process, including x-rays, which can trigger further diagnostic evaluation and biopsy.

From the perspective of oncological imaging, we have to stage and restage lung cancer and metastatic lung disease. For both of these, we need full-body scans with head and neck anatomical regions included in the scan protocol. Common metastatic locations for lung cancer include the brain, bones, suprarenal glands, lymphatic metastases, and bones; therefore, we have to include all the anatomical regions mentioned above. Neoplasms that have invaded the lungs are usually involving other organs or systems. To stage/restage an oncological disease based on a single anatomical region is not advisable as it may compromise the decision for the proper line of therapy.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on January 09, 2023. Accepted on January 10, 2023.

Cancer therapy is based on histology combined with all imaging findings and the presence of local and distant metastases that should be regularly followed up for the progression of the disease. Screening in those cases assesses the need for a second or third line of therapy⁷. The restaging should be based on RECIST 1.1 criteria⁸. For such full-body exams, CT is still the preferred option as MRI is too slow and expensive. MRI has its limitations in more advanced oncological cases because of scanning times, narrower openings, and longer tunnels compared to CT. Patients with full or partial pneumonectomy, for example, will be challenged with MRI's longer apneic pauses. Vascular imaging with CT or MRI, in our experience and available literature, has almost identical clinical value when performed with contrast for both tumor invasion and pulmonary embolism caused by neoplasms⁹. For pulmonary embolism, CT is highly preferred than MRI as it is faster and the patient can receive critical care if needed by using normal hospital equipment. Specialized MRI equipment that is shielded from electromagnetic impulses is very expensive and scarce in many

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hospitals. MRI has the upper hand only in non-contrasted scans. We do agree with the authors that MRI is superior for mediastinum and soft-tissue lesions.

All controversial points that we find are related to lung cancer or lung metastatic disease staging and restaging. We completely agree with the authors that for small or even bigger benign pulmonary nodules, we should advocate for methods that do not rely on radiation exposure. We happily look forward to such innovations. The minor clarifications discussed here will not diminish the immense practical value of the work and publication of Kızıloğlu et al., for which we would like to congratulate them.

AUTHORS' CONTRIBUTIONS

AG: Conceptualization, Data curation, Formal Analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. LC: Conceptualization, Resources, Supervision, Validation. VA: Conceptualization, Supervision, Validation. TK: Conceptualization, Supervision, Validation.

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Comment on "Mutagenic damage among bronchiectasis patients attending in the pulmonology sector of a hospital in southern Brazil"

Andrea Cristina de Moraes Malinverni¹ , Claudia Cristina Alves Pereira², Daniel Araki Ribeiro^{2*}

Dear Editor,

We read the recently published article entitled "Mutagenic damage among bronchiectasis patients attending in the pulmonology sector of a hospital in southern Brazil" by Olmedo et al.¹ in the *Journal of the Brazilian Medical Association*. The results of this study showed no significant differences in the frequency of oral micronucleated cells in bronchiectasis patients. In this regard, some questions are raised below for helping better understanding of the manuscript.

It was written in "Material and Methods" section that "Smears were made on the slides, and these were stained with eosin-methylene blue according to Leishman." It is important to note that Leishman stain is not suitable for micronucleus testing because the dye is not specific for nucleic acids. This is a confounding factor due to the fact that the identification of micronucleus in oral cells is very complicated in this case². Certainly, the approach compromises the expected results. Moreover, it was stated that "the frequency of micronucleus was expressed as the number of micronucleus in 1,000 cells." According to the guidelines by the International Micronucleus Assay Group, the analysis of a minimum 2,000 cells per patient was established². If the authors increase the total number of cells evaluated, the statistical power would improve considerably.

Considering that the aim of this study was the evaluation of the mutagenic potential induced by respiratory disease (bronchiectasis)¹, it is not clear why the authors evaluated the micronucleus test in oral mucosa cells. In the "Discussion" section, the authors mentioned that "Studies have shown that bronchiectasis increases systemic inflammation and arterial stiffness and causes bone thinning, and the inflammatory response plays an essential role in tissue genotoxicity and consequently in tumorogenesis." Following the rationale, it would be more interesting to evaluate if, and that extent, bronchiectasis is able to induce micronucleated cells in lymphocytes as a result of systemic host response.

Another pertinent point refers to the role of cytotoxicity in genotoxicity studies. Cytotoxicity interferes in genotoxicity because micronucleated cells are not detected in this scenario. To mitigate the problem of false-negative data, Tolbert et al.³ have published the analysis of several metanuclear changes as a result of cytotoxicity induced in exfoliated cells, such as karyorrhexis, pyknosis, and karyolysis, in the micronucleus assay. Particularly, the approach is very important in the current study since the inflammatory process induced by bronchiectasis increases the level of several mediators, such as pro-inflammatory cytokines and oxygen reactive species, which are able to induce cellular death in several tissues and organs.

We assumed that such comments are important and necessary for the correct understanding of the relevant study that investigated cytogenetic damage in oral mucosa cells of patients suffering from bronchiectasis.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHORS' CONTRIBUTIONS

ACMM: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **CCAP:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **DAR:** Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: DAR is a recipient of CNPq (Conselho Nacional de Desenvolvimento Clentifico e Tecnologico), grant number #001.

Received on January 04, 2023. Accepted on January 10, 2023.

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Clinical profile of Brazilian patients aged over 50 years at the diagnosis of celiac disease

Lorete Maria da Silva Kotze¹ , Luiz Roberto Kotze¹, Gabriella Mara Arcie², Renato Nisihara^{1,2*}

INTRODUCTION

Celiac disease (CD) is a multisystemic complex immune-mediated disorder (IMD), which is triggered and maintained by gluten in genetically susceptible individuals. Despite the availability of autoantibodies as CD biomarkers and upper endoscopy facilities with duodenal biopsies, most patients with this disorder remain undiagnosed¹. CD is traditionally diagnosed in children and adolescents. However, some authors reported higher detection in the elderly population^{1,2} and that about 25% of celiac patients were first diagnosed in the seventh decade in countries such as Canada, the United States, and Northern Europe².

The heterogeneous mode of clinical presentation, with digestive and extra-digestive manifestations, might be responsible for the delay in the diagnosis, besides the poor awareness by primary care providers or specialists without a high index of suspicion²⁻⁴. The physician should consider the diagnosis, order the correct tests, interpret them, and know when to refer the patient to a gastroenterologist expert in CD. As the CD prevalence in adults occurs in the third and fourth decades of life, patients aged above 50 years can be misdiagnosed with great delay and repercussions in their quality of life (QoL)^{1.3,4}.

This study aimed to evaluate the clinical profile of Brazilian patients aged over 50 years at the diagnosis of CD.

METHODS

This study was approved by the Ethics Committee of the Evangelical Beneficent Society of Curitiba under protocol CAAE 84793318.0.0000.0103. This is a retrospective study conducted through a review of clinical charts. The same physician attended to all patients in a single private practice in the city of Curitiba, Brazil, from 2010 to 2020.

Patients aged 50 years or more diagnosed with CD⁵ were included in this study. A structured questionnaire was used, comprising questions about complaints related to the digestive tract and other systems. Cases with incomplete data were excluded.

The symptoms of the digestive and extra-digestive tract were based on the transcriptions of patients' subjective reports. Gastrointestinal (GI) symptoms, such as aphtha, gastroesophageal reflux, epigastric pain, bloating, indigestion, nausea, vomiting, flatulence, abdominal pain, diarrhea, and constipation, were investigated. Personal comorbidities before this investigation and information regarding drugs currently being used were obtained.

Routine laboratory tests were required. DEXA (dual-energy X-ray absorptiometry) was conducted for bone disease evaluation⁶.

Data on upper endoscopy were collected on all patients, with gastric biopsies performed in cases with macroscopic alterations. Duodenal biopsies were performed based on the recommendations: one or two fragments of the bulb⁷, and four to five specimens from the second portion of the duodenum and classified according to Marsh^{8,9}.

Statistical analysis

The data were tabulated and expressed as median and interquartile ranges (IQR), mean and standard deviations, or frequencies and percentages.

RESULTS

A total of 40 Caucasian patients, 34 (85.0%) female and 6 male, with a median age of 59.5 years were studied (IQR=50–79 years).

Table 1 shows the digestive manifestations in the study patients, with no gender differences. Flatulence and bloating were the more frequent complaints.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on October 05, 2022. Accepted on December 16, 2022.

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| Symptoms | Total n (%) |
|-------------------|-------------|
| Flatulence | 35 (87.5) |
| Bloating | 30 (75) |
| Esophageal reflux | 21 (52.5) |
| Diarrhea | 21 (52.5) |
| Aphtha | 16 (40) |
| Epigastric pain | 16 (40) |
| Abdominal pain | 16 (40) |
| Nausea | 14 (35) |
| Maldigestion | 14 (35) |
| Constipation | 9 (22.5) |
| Vomit | 7 (17.5) |

Table 1. Digestive symptoms and signs referred by the study patients (n=40).

Anemia was observed in 37 (32.4%) patients, with iron deficiency in 12 (34.3%) patients and vitamin B12 deficiency in 7 (20.6%) of the cases. Vitamin D levels decreased in 89.3% of the cases. DEXA was performed in 32 cases, with 53.1% of osteopenia and 37.5% of osteoporosis detected in the femur, and 25.9% of osteopenia and 28.1% of osteoporosis detected in the spinal cord.

Patients mentioned non-drugs that could alter the histological findings at the time of consultation.

Table 2 presents extra-digestive manifestations that can occur alone or along with GI symptoms. Psychiatry diseases were the most frequent, affecting 87.1% of the study patients.

Out of 40 patients, 39 (97.5%) reported at least one IMD before the diagnosis of CD, being autoimmune hypothyroidism observed in 14 (35.9%) and Sjogren's syndrome in 2 (5.1%). IMDs, such as hyperthyroidism, Behçet's disease, type 1 diabetes mellitus, macroamylasemia, lupus erythematosus, juvenile rheumatoid arthritis, scleroderma, vasculitis, multiple sclerosis, common variable immunodeficiency, and asthma, were reported in one patient each.

Table 3 displays the upper endoscopic, ileocolonoscopic, and histological findings in the study patients. Marsh III was observed in 72.5% of patients.

DISCUSSION

Despite the obvious tolerance to gluten ingestion, as emphasized by Beaumont and Mian since 1998, CD is increasingly being identified in later life¹⁰. There are few epidemiological studies on middle-aged and older patients, mainly in Brazil. CD in this population has been underdiagnosed due to the lack of physicians' awareness of CD occurrence in this age

| Table 2. Complaints and main previous comorbidities referred by | the |
|---|-----|
| study patients (n=40). | |

| Comorbities | Total n (%) |
|--------------------------|-------------|
| Psychiatric | |
| Anxiety | 20 (51.3) |
| Depression | 14 (35.9) |
| Musculoskeletal | |
| Arthralgias | 10 (25.0) |
| Fractures | 7 (17.9) |
| Neurological | |
| Migraine | 7 (17.9) |
| Headache | 3 (7.5) |
| Insomnia | 4 (10.2) |
| Cutaneous/mucosal | |
| Dermatitis herpetiformis | 4 (10.2) |
| Oral lichen planus | 2 (5.1) |
| Cardiovascular | |
| Arterial hypertension | 7 (17.5) |
| Respiratory | |
| Respiratory allergy | 5 (12.5) |
| Endocrinological | |
| Hypothiroidism | 14 (35.0) |
| Pancreatic insufficiency | 2 (5.1) |

Table 3. Upper endoscopic and histological findings in the study patients.

| Gastrointestinal segment | n (%) |
|--------------------------|--------------|
| Esophagus | |
| Macroscopy | |
| Normal | 25/40 (62.5) |
| Esophagitis | 14/40 (35.0) |
| Hiatal hernia | 1/40 (2.5) |
| Stomach | |
| Macroscopy | |
| Normal | 16/40 (40.0) |
| Gastritis | 23/40 (57.5) |
| Gastric atrophy | 1/40 (2.5) |
| Microscopy | |
| Normal | 6/14 (42.8) |
| Gastritis | 12/22 (54.5) |
| Lymphocytic gastritis | 2/14 (14.3) |
| Duodenum | |
| Macroscopy | |
| Normal | 10/40 (25.0) |
| Alterations | 30/40 (75.0) |
| Microscopy* | |
| Normal | 0 |
| Marsh I | 2/40 (5) |
| Marsh II | 9/40 (22.5) |

*Marsh classification - Reference 9.

group and the heterogeneity of clinical presentation^{2,11}. Their subtle or atypical symptoms may go undetected by healthcare professionals, and the delay in CD diagnosis can lead these patients to consume gluten for extended periods¹². The CD diagnosis in older patients follows the same guidelines as in young people. However, the clinical diversity and the lower frequency or intensity of symptoms than seen in children or adolescents frequently delay and obscure the CD diagnosis, in particular in patients aged over 50 years, as it is easy to dismiss such symptoms due to "old age"^{2,13}. The GI complaints referred by our patients were similar to those reported in young Brazilian adults by Lima et al., in both genders¹⁴ and to Italian and Finland studies^{1,15}.

In our data, extra-digestive manifestations were highly frequent and reinforce that patients aged over 50 years had symptoms related to all other systems and could be attended to by specialists that cannot be aware of CD as the basic disorder^{1.3,4}.

In our study, psychiatric and neurological symptoms, which are common in this age group, could be part of the CD spectrum of manifestations, similar to those described by other authors^{16,17}

The risk of complications is higher in patients with late recognition of CD because gluten testing is more time-consuming². We observed that anemia and bone disorders were more frequent. Anemia by iron deficiency or vitamin B12 deficiency was detected in one-third of the cases and is similar to that observed in adults from the same geographical area¹⁴. Regarding bone disorders, we detected osteopenia in the femur (53.1%) and osteoporosis in the spinal cord (28.1%), which is consistent with other studies¹. Low bone mineral density (BMD) is a common finding in Brazilian patients with CD, as described previously by the same research group, studying CD patients and healthy controls with similar age, ethnicity, and geographical area^{17,18}. Identifying low BMD is crucial to allow calcium and vitamin D supplementation and reduce the risk of fracture¹⁹.

We observed several IMDs affecting celiac patients, the most common of which is hypothyroidism. Common inflammatory pathways, similar genetic factors, environmental triggers, and pathophysiological mechanisms were reported²⁰. Furthermore, female gender, age at diagnosis, and family history positive for IMDs are recognized risk factors²¹. In our study, at least one IMD had affected practically all patients (39 out of 40). Elli et al., reported a higher prevalence of IMDs in patients with CD compared to the general population (23 vs. 0.4%)²¹ in Italy, which is similar to that reported by Castro et al., in Ireland (31.1%)²². This study, as proposed by Elli et al., implies that patients with CD should also be examined for other IMDs²¹.

At upper endoscopy, in this research, normal mucosa of the esophagus was observed in two-thirds of the cases and non-erosive esophagitis in one-third of the cases. Routine biopsies are not recommended²³, which have no direct correlation with the complaints of gastroesophageal reflux²⁴. Studies reporting the association between CD and gastric disorders indicated conflicting results^{24,25}, and there are controversies if gastric biopsies should be routinely taken during upper endoscopy in CD patients²⁶.

Duodenal biopsies were performed to confirm CD diagnosis in patients ingesting gluten. Complications are unusual after duodenal biopsies even among the elderly patients²⁷. According to the Marsh classification⁹, two-thirds of the patients presented Marsh III. Ciccocioppo et al., after comparing duodenal lesions, reported 86% of Marsh III in childhood vs. 51% in adulthood²⁸. Nonetheless, duodenal biopsy remains an important component in the diagnosis of adult patients with suspected CD^{3,4}.

This study was limited by its retrospective approach and small sample size. However, since all patients were attended to by the same physician, the same clinical and laboratory protocol was applied. Also, the same pathologist analyzed the biopsies, reducing the bias.

Interestingly, some people can consume gluten for 50 years before developing CD, while others consume gluten for only 9 months before being diagnosed. However, why to wait for end-stage celiac disease to occur when it can be prevented by early diagnosis? Early diagnosis and CD treatment can prevent complications in these people²⁹.

In conclusion, our patients diagnosed with CD after 50 years of age had a significant prevalence of IMDs before the diagnosis, as did their family members. Most patients manifested classical CD symptoms and total duodenal atrophy, revealing the severity and difficulty in nutrient absorption.

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 of Faculdade Evangélica Mackenzie de Medicina, Curitiba, PR, Brazil, which can be contacted by telephone number +55 (41) 3240-5570 or by e-mail at comite.etica@fempar.edu.br.

AUTHORS' CONTRIBUTIONS

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Knowledge about human papillomavirus transmission and prevention among physicians in Rio de Janeiro state, Brazil

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SUMMARY

OBJECTIVE: This study aimed to assess physicians' knowledge about human papillomavirus infection and its prevention.

METHODS: Descriptive web-based survey with 15 objective questions targeted to physicians affiliated with the Regional Council of Medicine from Rio de Janeiro state, Brazil. Participants were invited by e-mail and the Council social networks, between January and December 2019.

RESULTS: The study sample had 623 participants, with a median age of 45 years, predominantly women (63%). The most frequent specialties were Obstetrics and Gynecology (21.1%), Pediatrics (11.2%), and Internists (10.5%). Concerning human papillomavirus knowledge, 27.9% of the participants were able to identify accurately all possible forms of transmission, and none of them could recognize all the risk factors of infection. Nevertheless, 95% recognized that asymptomatic infection could occur in both sexes. Regarding knowledge about clinical manifestations, diagnosis, and screening, only 46.5% were able to identify all human papillomavirus-related cancers, 42.6% were aware of the periodicity of Pap smears, and 39.4% indicated that serological test was not adequate for diagnosis. The recommended age group for human papillomavirus vaccination was recognized by 94% of the participants, as well as the need for a Pap smear and the use of condoms, even after vaccination.

CONCLUSIONS: There is good knowledge about prevention and screening for human papillomavirus infections; many gaps were identified regarding transmission, risk factors, and associated diseases among physicians in Rio de Janeiro state.

KEYWORDS: Papillomaviridae. Uterine cervical neoplasms. Genital neoplasms, female. Papillomavirus vaccines. Knowledge. Physicians.

INTRODUCTION

Cervical cancer is a preventable disease, which is also curable if detected early and adequately treated. Nevertheless, it remains the fourth most common cancer among women globally and is expected to increase among young, undereducated women in the world's poorest countries. The World Health Organization (WHO) launched the first global health strategy for the elimination of cervical cancer as a public health problem, and one of the goals is to reduce knowledge gaps concerning HPV infection¹. Additionally, HPV is involved in other cancers, such as anogenital and oropharyngeal ones, all of them susceptible to prevention by vaccine².

The success of HPV prevention programs will depend on whether health care professionals recommend the vaccine to patients. They influence the decision-making of patients and guardians, minimize vaccination barriers, and increase its acceptability³. The knowledge on HPV and related cancers is developed throughout medical education and will be essential to physicians, especially those dealing with HPV malignant lesions at different levels of care—health counseling and education, prevention by vaccination and screening, diagnosis, treatment, and recovery⁴.

In Brazil, cervical cancer is still an important cause of cancer and death⁵. Urgent and bold action is needed to scale up and sustain evidence-based interventions. The identification of knowledge gaps among physicians can support proposals for improving medical education, reduce negative beliefs, and promote adherence to vaccination and other HPV prevention methods, contributing to HPV incidence reduction and cervical cancer control¹.

The objective of the study was to assess physicians' knowledge about HPV infection and its prevention in Rio de Janeiro (RJ) state, Brazil.

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

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Received on October 04, 2022. Accepted on November 14, 2022.

METHODS

The study was approved by the Faculty of Medicine Ethics Committee from UFF (CAAE14660613.2.0000.5243) on May 20, 2013. All respondents were instructed about the goals of the study, and all of them filled out written online-administered informed consent. Participation was anonymous and voluntary, and the confidentiality of data was kept throughout the study. Participants were not involved in the development of this study.

We conducted a survey targeted to all physicians registered on "Conselho Regional de Medicina do RJ (CREMERJ)" between January and December 2019. Participants were invited by e-mail and social networks, such as Facebook.

Sample size calculations were based on a 70% estimated HPV knowledge⁶⁻⁸, according to previous studies⁶⁻⁸, with a 5% precision rate and a 95% confidence level. Considering a population of 60,000 physicians in RJ state⁹, we estimated a sample of 321 participants.

Participants completed a web-based survey (Google Forms) with 15 questions, including demographic data (gender, age), time since graduation, post-graduation (yes or not), university (public or private), and specialty (Internal Medicine, Pediatrics, Obstetrics/Gynecology, Urology, Dermatology, others). There were some closed questions (yes/not) requiring a single answer; others had multiple answers format, and a few had open fields.

Questions about HPV knowledge involved transmission (type of sexual intercourse, transplacental, and delivery routes), risk factors (partnership, toilet items, use of condoms and oral contraceptives, and age at sexarche), clinical presentation (warts and HPV-related cancers), cervical screening (frequency, technique, and interpretation), and HPV-vaccine recommendations (age and need of cervical screening).

Knowledge on HPV transmission, types of cancer, PAP smear, and serology was compared among specialties, and differences in proportions of total hits were tested using chi-square tests.

Data were entered and analyzed using SPSS Statistics version 23. Descriptive analysis used means or median for continuous variables and proportions for categorical ones. We described percentages of correct answers and percentages of total correct items when appropriate.

RESULTS

We obtained 623 answers, representing 1% of RJ physicians. Participants, whose median age was 45 years, were mostly women, with a postgraduate degree, and graduated for more than 10 years. Obstetricians/Gynecologists (OBGyn) comprised the most frequent specialty. A minority declared to be vaccinated against HPV was mostly women (Table 1).

Regarding HPV knowledge, the item on clinical manifestations had the highest percentage of participants who answered all questions correctly. In contrast, none of the participants answered all risk factors correctly. As to transmission, this percentage was 30% (Table 2).

Table 1. Sociodemographic profile, Rio de Janeiro state physicians(n=623), 2019.

| Variables | n (%) | | | |
|-----------------------------|-------------|--|--|--|
| Age | 45 (median) | | | |
| Sex | | | | |
| Female | 392 (63) | | | |
| Male | 230 (37) | | | |
| Graduation | | | | |
| Graduates | 95 (15,3) | | | |
| Postgraduates | 527 (84.7) | | | |
| Time since graduation | | | | |
| 1–4 years | 110 (17.7) | | | |
| 5–10 years | 80 (12.9) | | | |
| >10 years | 432 (69.5) | | | |
| Specialty | | | | |
| Internal medicine | 65 (10.5) | | | |
| Dermatology | 33 (5.3) | | | |
| Gastroenterology | 20 (3.2) | | | |
| Gynecology and obstetrics | 131 (21.1) | | | |
| Pediatrics | 70 (11.2) | | | |
| Urology | 19 (3.1) | | | |
| Others | 285 (45.8) | | | |
| Public universities | | | | |
| UFFª | 96 (15.4) | | | |
| UFRJ [♭] | 98 (15.7) | | | |
| UERJ⊂ | 44 (7.1) | | | |
| UNIRIO ^d | 54 (8.7) | | | |
| Private universities | | | | |
| FTESM ^e | 67 (10.8) | | | |
| Vaccinated against HPV | | | | |
| Yes | 138 (22.2) | | | |
| Complete vaccination scheme | | | | |
| Yes | 121 (19 5) | | | |

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| Aspect of knowledge | Correct answers n (%) |
|---|--------------------------|
| Genital-genital | 612 (98.4) |
| Oral-genital | 541 (87.0) |
| Anal-genital | 572 (92.0) |
| Transmission | 0.12(1.2.1) |
| Manual-genital | 315 (50.6) |
| Transplacental | 512 (82.3) |
| Transvaginal delivery | 438 (70.4) |
| All answers are correct | 185 (29.7) |
| Toilet seat | 567 (91.2) |
| Share underwear and towels | 462 (74.3) |
| Sex without condoms | 613 (98.6) |
| Risk situation | 0.00 (1.010) |
| Oral contraceptives | 605 (97.3) |
| Sex before 18 years old | 0 |
| Share glasses and cutlery | 604 (97 1) |
| Multiple sex partners | 577 (92.8) |
| Partner with multiple partners | 553 (88.9) |
| Pool bath | 619 (99 5) |
| All answers are correct | 0 |
| Pruritus | 590 (94 9) |
| Clinical manifestations | 570(74.77 |
| Bleeding | 605 (97 3) |
| Wart | 600 (96 5) |
| Pain | 600 (96.5) |
| Discharge | 606 (97.4) |
| All apswers are correct | 558 (89.7) |
| | 611 (98.2) |
| Asymptomatic transmission | 594 (95 5) |
| Occurrence in both seves | 620 (99 7) |
| Appl | 400 (79.9) |
| | 470 (70.0) |
| Types of cancer associated | 137 (00.4) |
| Convical | 515 (976) |
| Oronhanzay | J4J (07.0) 125 (60.0) |
| Popilo Dopilo | 433 (07.7) 514 (92.6) |
| Vaginal | 14(02.0) |
| Vaginai | 440 (70.7) |
| | 409 (75.4) |
| | 289 (40.3) |
| Cervical cytology (PAP test) | $E_{40}(0, 0)$ |
| Main strategy for detecting progureer locions | 540 (80.8) |
| and cervical cancer | 563 (90.5) |
| Collection involves peeling the outer and inner surfaces of the cervix | 498 (80.1) |
| Performed by 25- and 64-year-old women who have or had a sexual life | 482 (77.5) |
| After two first annual exams with normal results, perform every 3 years | 327 (52.6) |
| All answers are correct | 265 (42.6) |
| Diagnosis by serology | 245 (39.4) |
| HPV vaccine | |
| Recommended age | 587 (94.4) |
| Need to realize PAP | 618 (99.4) |
| Need to use condoms | 618 (99.4) |

 Table 2. Knowledge about human papillomavirus, among Rio de Janeiro state physicians (n=623), 2019.

Less than half were right about HPV-related cancers. The majority are aware of uterine cervix cancer, and the lowest percentage was of oral cancer (Table 2).

Notably, 60% wrongly considered serological tests for diagnosis. The majority recognized the physiopathological basis of Pap smear. Despite this, only 42.6% correctly answered all the questions. In relation to the HPV vaccine, knowledge about age and recommendations was almost universal (Table 2).

OBGyn physicians performed better on PAP questions, but almost 30% did not answer all the items correctly (p<0.01). Urologists had the best score on HPV-related cancers, followed by OBGyn and dermatologists (p=0.04). OBGyn and urologists had better results than other specialties. There was no difference for transmission questions (p=0.13) (Table 3).

DISCUSSION

In our study, physicians' knowledge about HPV transmission was low, without differences among specialties. Although nearly 75% correctly marked the main routes of transmission, 25% wrongly identified non-related events. Knowledge about risk factors was good, except age at sexarche, but none of the participants could recognize all the risk factors. Most of them were able to identify the main clinical manifestations and the virus pathogenesis. There was a good perception of HPV infection and warts, but less than half of the participants correctly associated all HPV-related cancers, of which oral cancers being the less recognized ones. Finally, for the HPV vaccine, knowledge was almost universal.

Other studies confirmed the understanding of HPV as a sexually transmitted infection (STI) and gaps in knowledge about transmission, related diseases, and vaccination^{4,6-8,10-17}.

It was noteworthy that none of the RJ physicians recognized early sexarche as a risk factor. In New Zealand, this question had a 73.8% score of correct answers⁶. The transplacental route was wrongly assigned by almost 20.0% of participants, a mistake also reported among Italian general practitioners (13.0%)¹².

The relationship between HPV and oral cancers, like our results, had one of the lowest scores in several studies^{10,12,13,15,16}. Besides cervical cancer, knowledge about other HPV-related cancers was also low^{11,12}. In contrast, physicians in RJ know more about warts than those in some other places^{6,11,12,14}.

More than half of the RJ doctors wrongly indicated serological tests for viral diagnosis. We also observed a lack of knowledge about the Brazilian cervical cancer screening protocol. Among ObGyn physicians, we found a better understanding of Pap test and HPV diagnosis, in agreement with Canadian studies^{18,19}.

| Crecialty | Transmission Types of cancer | | PAP smear | Diagnosis by serology |
|---------------------------|------------------------------|------------|------------|-----------------------|
| Specially | n (%) | n (%) | n (%) | n (%) |
| Gynecology and obstetrics | 36 (27.5) | 73 (55.7) | 93 (71.0) | 83 (63.4) |
| Internal medicine | 18 (27.7) | 24 (36.9) | 33 (50.8) | 14 (21.5) |
| Urology | 12 (63.2) | 13 (68.4) | 1 (5.3) | 12 (63.2) |
| Pediatrics | 20 (28.6) | 25 (36.6) | 15 (21.4) | 21 (30.0) |
| Gastroenterology | 5 (27.3) | 5 (36.4) | 3 (18.2) | 7 (36.4) |
| Dermatology | 11 (33.3) | 17 (51.5) | 8 (24.2) | 13 (39.4) |
| Others | 83 (29.1) | 129 (45.3) | 110 (38.6) | 96 (33.7) |
| p-value | 0.13 | 0.04* | <0.01* | <0.01* |

Table 3. Comparison of the number of correct answers about human papillomavirus outcomes, prevention, and diagnosis according to the specialties, Rio de Janeiro state physicians (n=623), 2019.

*Bold indicates statistically significant p-values.

As to the HPV vaccine, 94.4% of RJ physicians were aware of the recommended age, while other studies showed lower scores: in Polonia, only 24.9%¹³; in Liguria, Italy, 73.7%⁷; in Italy, among general practitioners, 87.0%¹²; in Lebanon, 81.5%²⁰; and in the USA, 56.0% (family physicians) and 85.0% (pediatricians)²¹. Like our results, more than 90% of Irish physicians know that cervical cancer screening must continue in vaccinated women¹¹, but, in a study from Saudi Arabia, only 59.0% had this knowledge¹⁷.

Health care providers (HCPs) disseminate sexual health and prevention information to patients and their parents, especially concerning vaccination. Educational interventions are primarily directed at patients and parents rather than HCPs, despite evidence that provider recommendation is a key determinant of vaccine uptake¹⁰.

Along with cervical screening programs implemented by the Brazilian government, two vaccines, a bivalent and a quadrivalent one, are available in the National Immunization Program for females (9–14 years old) and males (11–14 years old) in a two-dose schedule²². However, a decrease in uptake has been observed: in 2014, 87% of Brazilian municipalities reached the target for the first dose but only 32% for the second dose²³.

The identification of knowledge gaps can support proposals for improving medical education content¹⁰. Students from health care courses in RJ state had difficulty to recognize all risk factors of HPV infection²⁴. We recommend additional education about HPV infection and prevention. Medical societies are recommended to offer continuous education for graduated professionals²¹.

Considering the study limitations, the sample represented only 1% of the RJ medical population, i.e., 59,366 professionals⁹.

Mean age was similar, but females had a higher frequency (63%) than that of the State (50.8%). The sample size was adequate, but it was not random, allowing selection biases.

Our questionnaire used a closed question for specialties, offering five options, including "other", which represented 45.8% of the answers. The four most common specialties in Brazil are Internal Medicine (11.2%), Pediatrics (10.3%), General Surgery (8.9%), and ObGyn (8%), while Dermatology represented 2.2% and Urology 1.4%⁹. Our sample distribution was adequate for Internal Medicine and Pediatrics, but ObGyn was overrepresented.

Although partially limited by selection and participation biases, this study confirmed gaps in HPV knowledge.

CONCLUSION

There is good knowledge about prevention and screening for HPV infections. Many gaps were identified regarding transmission, risk factors, and associated diseases among physicians in RJ state.

ACKNOWLEDGMENTS

We thank Conselho Regional de Medicina do Estado do Rio de Janeiro (CREMERJ) for publicizing our study *online* for the Rio de Janeiro physicians and associations.

AUTHORS' CONTRIBUTIONS

VMSM: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **VCGS:** Formal Analysis, Writing – original draft, Writing – review & editing. **ADB:** Formal Analysis, Writing – original draft, Writing – review & editing. **SCF:** Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. **CAF:** Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. **CLV:** Conceptualization, Data curation, Formal Analysis, Project administration, Supervision, Writing – original draft, Writing – review & editing. **SC:** Conceptualization, Data curation, Formal Analysis, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Treatment results of carotid artery stenting in a developing country

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SUMMARY

OBJECTIVE: The purpose of this study was to investigate the details of minor complications of carotid artery stenting in a developing country. **METHODS:** This was a retrospective, single-center study conducted on the target group consisting of 65 symptomatic patients who underwent carotid artery stenting. We assessed technical success rate, periprocedural complication within 30 days (hypotension, bradycardia, acute kidney injury, vasospasm, a transient ischemic attack, stroke, myocardial infarction, and death), and the differences between groups with and without complications. **RESULTS:** Minor periprocedural complications occurred in 15 patients. In all, 8 (12.3%) had transient hypotension, 6 (9.2%) had bradycardia, 7 (10.7%) had acute kidney injury, 2 (3.1%) had vasospasm, and 1 (1.5%) had transient ischemic attack. A greater rate of minor complications was observed in women (p=0.051).

CONCLUSION: The results of the carotid artery stenting procedures performed in a developing country were acceptable. **KEYWORDS:** Risk. Complications. Carotid artery diseases. Stents.

INTRODUCTION

Carotid artery stenting (CAS) is considered an alternative to carotid endarterectomy (CEA) for symptomatic patients when the rate of periprocedural stroke or death is <6%, the risk of complications is considered to be at average or low, and the stenosis of the internal carotid artery (ICA) is more than 50% by digital subtraction angiography or noninvasive neuroimaging, according to the American Heart Association/ American Stroke Association guidelines (Recommendation Class IIa, Level B)¹.

Therefore, to perform CAS as an intervention to prevent recurrent strokes, it is necessary to determine whether the risk of periprocedural stroke or death is <6% within the center where the procedure will be carried out. Most of the information about the risks of CAS originates from studies conducted in developed countries, and there is a gap in information about rates of complications in developing countries²⁻⁸.

Previously, we reported the rates of major and minor periprocedural complications of CAS in 65 patients with symptomatic carotid stenosis at a reference academic hospital in São Paulo, Brazil⁹. The rate of stroke, myocardial infarction (MI), or death was 4.6%, similar to reports in the real-world series or clinical trials (2–9%)^{5,6,10}. So far, few studies reported the details of treatment results after CAS in developing or developed countries^{5,8,11}.

We extended our investigation by explaining, in the same dataset, the types of minor complications. Also, we compared demographic characteristics, risk factors, use of antithrombotic drugs, and types of cerebrovascular events between patients with and without major or minor complications.

METHODS

Study design

This is a retrospective, single-center study that evaluated medical records of consecutive patients submitted to CAS for the treatment of symptomatic carotid stenosis at a university hospital in a developing country.

Subjects

Inclusion criteria include age 18 years or above, CAS performed according to the institutional protocol (see Supplementary material) and follow-up by neurologists.

Exclusion criterion includes a lack of follow-up by neurologists.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on January 09, 2023. Accepted on January 11, 2023.

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Information retrieved from medical records were as follows: age, gender, ethnicity, comorbidities (hypertension, diabetes, hypercholesterolemia, cardiopathy, coagulopathy, smoking, prior stroke); days between the onset of symptoms and the procedure; the use of antiplatelet or anticoagulant drugs; the type of cerebrovascular event (stroke or TIA); and the National Institutes of Health Stroke Scale (NIHSS) scores. These scores, if not recorded in medical records, were calculated based on the neurological examination described in medical records¹².

Outcomes

We described the rates of different types of minor complications after the procedure: TIA, hypotension, vasospasm, bradycardia, ICA dissection, and acute kidney injury (AKI) (creatinine blood levels>1.5×baseline)¹³ during the first 96 h after the procedure. The severity of AKI was classified according to the Acute Kidney Injury Network (AKIN)¹³. Complications were assessed according to notes from medical records, until hospital discharge. Major complications were stroke, MI, or death during the periprocedural period¹.

In addition, we compared demographic characteristics; risk factors; the use of aspirin, clopidogrel, or anticoagulants prior to the procedure; and types of cerebrovascular events (stroke or TIA) in patients with or without minor or major complications. Post-hoc comparisons were performed in patients with and without AKI with regard to baseline creatinine, glomerular filtration rate according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, administration of intravenous hydration, or N-acetylcysteine before or after the intervention.

Ethics

The study was approved by the institutional Ethics Committee (protocol 1.981.536). Informed consent was waived because data were obtained from medical records.

Data analysis

Continuous variables are presented as mean, medians, standard deviations (SD), and minimum and maximum values. Percentages of complications were calculated. Comparisons between characteristics of the groups of patients with and without major or minor complications were performed with unpaired t-test, chi-square test, or Fisher's exact test. Fisher's exact test was used instead of chi-square tests when at least one cell had counts less than 5. Unplanned, post-hoc comparisons were performed using the chi-square test, Fisher's exact test, unpaired t-test, or Mann-Whitney U test, according to the nature and distribution of the data. Multivariate regression was planned in order to analyze predictors of minor complications, in case between-group differences were observed in bivariate analysis, regarding more than one variable.

Carotid artery stenting and follow-up

The recommended antiplatelet regimen is aspirin (100 mg qd) and clopidogrel (75 mg qd) at least 5 days before treatment or aspirin (300 mg) and clopidogrel (300 mg) at least 4 h before CAS. These drugs are continued for at least 1 month later. When an anticoagulant is indicated for secondary stroke prevention, only 100 mg daily aspirin is maintained. Double antiplatelet in combination with anticoagulants is never prescribed. The time to discharge depends on the follow-up, but patients typically remain in the hospital from 24 to 96 h after the procedure. According to the institutional protocol, cardiac biomarkers and creatinine are measured within this time frame.

On average, 20 CAS procedures are performed for symptomatic ICA stenosis per year in our institution. All procedures are performed by a high-volume interventional neuroradiologist (>20 procedures per year)¹⁴. The chief in the procedure is always an attending physician, with the assistance of a fellow. Cerebral embolic protection devices are used whenever possible, and the amount of contrast varies between 60 and 150 mL, depending on the characteristics of the artery. ICA tortuosity and calcifications render the intervention more difficult, increasing the length of the procedure and requiring a greater volume of contrast. In general, a low osmolality nonionic contrast (Ultravist) is administered, but for patients with prior renal failure an isosmolar agent (Vasipaque) is preferred. An embolic protection device (EZ filter, Boston Scientific) was used for protection in all patients.

RESULTS

A total of 73 patients who underwent CAS were identified, of whom 8 were excluded due to a lack of follow-up by neurologists. The mean±SD age was 67.7±9.9 years. Only 10 (15.3%) patients were ≥80 years. The mean NIHSS score was 2.5 (range 0–10, median 2). Other baseline characteristics are shown in Table 1. Patients were followed up until the end of hospital admission, ranging from 4 to 42 days (18.6±7.1). The median interval between cerebrovascular event and procedure was 20 days (range 3–193 days).

Primary outcome

The rate of any minor complication was 15 (23.1%) of 65. Some patients had more than one minor complication, so the

overall rate of all minor complications was 36.9% (24/65). Among minor complications, 8 (12.3%) patients had transient hypotension, 6 (9.2%) had bradycardia, 7 (10.7%) had AKI, and 2 (3.1%) had vasospasm.

| Table 1. Characteristics of | the | patients. |
|-----------------------------|-----|-----------|
|-----------------------------|-----|-----------|

| Characteristics | n (%) |
|---------------------------|-----------|
| Male | 40 (61.5) |
| Ethnicity | |
| White | 46 (70.7) |
| Black | 14(21.5) |
| No information | 5 (7.7) |
| Arterial hypertension | 50 (76.9) |
| Diabetes mellitus | 25 (38.5) |
| Cardiopathy | 22 (33.8) |
| Hypercholesterolemia | 32 (49.2) |
| Smoking | 28 (43) |
| Carotid-related stroke | 55 (84.6) |
| Transient ischemic attack | 10 (15.4) |

Creatinine was measured in all patients up to 96 h post-CAS (7.7% up to 24 h after the procedure, 40% between 24 and 48 h, 52.3% between 48 and 96 h). In the seven patients who had AKI, the severity was AKIN grade 1, and the patients do not require hemodialysis. We could not retrieve the creatinine data of two patients in the study.

One (1.5%) patient had a TIA, with no evidence of stroke in a computed tomography (CT) performed 24 h after the onset of the symptoms. Magnetic resonance imaging (MRI) was not performed. This patient also presented hypotension.

Secondary outcomes

There were no significant differences in age between groups with $(64.6\pm21.5 \text{ years})$ and without $(67.9\pm9.3 \text{ years})$ major complications (p=0.589), or between the groups with $(64.7\pm12.3 \text{ years})$ and without $(68.6\pm9.1 \text{ years})$ minor complications (p=0.185).

Minor complications were more common in women than in men (p=0.051) (Table 2).

Baseline creatinine levels were higher in patients with AKI than in those without, but the between-group difference in this variable did not reach statistical significance (Table 3). The difference between creatinine levels on the first day after CAS,

| | Subgroups according to major complications | | | Subgroups a minor com | according to aplications | | |
|-----------------------|---|-----------------------|----------|-----------------------|-----------------------------|----------|--|
| Characteristics | With (%) (n=3) | Without (%) (n=62) | p-valueª | With (%) (n=15) | Without (%) (n=50) | p-valueª | |
| Sex (male) | 33.3 | 62.9 | 0.55 | 40 | 68 | 0.051 | |
| Ethnicity (non-white) | 33.3 | 22.8 | 0.55 | 21.4 | 23.9 | 1.0 | |
| Arterial hypertension | 66.7 | 77.4 | 0.55 | 80 | 76 | 1.0 | |
| Diabetes mellitus | 33.3 | 38.7 | 1.0 | 46.7 | 36 | 0.46 | |
| Cardiopathy | 33.3 | 33.8 | 1.0 | 33.3 | 34 | 0.96 | |
| Dyslipidemia | 33.3 | 50 | 1.0 | 60 | 46 | 0.34 | |
| Smoking | 33.3 | 43.5 | 1.0 | 60 | 38 | 0.13 | |
| Previous TIA | 33.3 | 9.7 | 0.3 | 6.7 | 12 | 1.0 | |
| Previous stroke | 33.3 | 25.8 | 1.0 | 20 | 28 | 0.74 | |
| Blood dyscrasia | 33.3 | 3.2 | 0.13 | 6.7 | 2 | 0.52 | |
| Aspirin | 66.7 | 96.8 | 0.13 | 93.3 | 96 | 0.55 | |
| Clopidogrel | 66.7 | 96.8 | 0.13 | 86.7 | 98 | 0.13 | |
| Anticoagulation | 50 | 6.4 | 0.22 | 13.3 | 6 | 0.32 | |
| Type of event | | | | | | | |
| Stroke | 100 | 83.9 | 1.0 | 86.7 | 84 | 1.0 | |
| TIA | 0 | 16.1 | 1.0 | 13.3 | 16 | 1.0 | |

Table 2. Characteristics of subgroups of patients with or without major and minor complications.

TIA: transient ischemic attack. ^aChi-square or Fisher's exact test.
| | Worsening in renal function | | | |
|---|-----------------------------|-----------|--------------------|--|
| | Yes (n=7) | No (n=56) | p-value | |
| Hydration before intervention (%) | 85.7 | 78.6 | 1.0ª | |
| Hydration after intervention (%) | 71.4 | 53.6 | 0.448ª | |
| Treatment with N-acetylcysteine (%) | 0 | 23.2 | 0.328ª | |
| Creatinine at admission (average±standard deviation) (mg/dL) | 1.21±1.2 | 1.02±0.3 | 0.088 ^b | |
| Glomerular filtration rate calculated according to CKD-EPI equations, mL/ min/1.73 m ² (average±standard deviation) | 75.3±30.5 | 71.7±18.9 | 0.653 | |

Table 3. Comparisons mong patients with or without transient acute kidney injury.

^aFisher's exact test. ^bMann-Whitney U test. ^cUnpaired t-test.

compared to creatinine at admission, was -0.03 ± 0.17 mg/dL (range, -0.48 to 0.38 mg/dL) in patients who did not present worsening in renal function and 0.68 ± 0.7 mg/dL (range, 0.22-2.21 mg/dL) in those who did (p=0.056).

Post-hoc assessment of the time from the onset of neurologic symptoms and CAS showed no significant difference (p=0.9) between patients who presented hypotension (n=8; mean=28.8; SD±25.1) or bradycardia (n=6; mean=26.8; SD±22.0; p=1.0) and those who did not (without hypotension: n=57; mean=28.9; SD±29.4; without bradycardia: n=59; mean=29.1; SD±29.4).

DISCUSSION

To the best of our knowledge, this is the first study to address specifically different types of minor complications after CAS. The most common minor complications were hypotension and bradycardia. The main strengths of this study were the detailed assessment of consecutive patients and evaluation of different minor complications.

Overall, major complication rates, previously published by our group¹⁰, were low, meeting international recommendations. Cerebral infarction as a perioperative complication related to CAS is an issue, and previous studies reported that risk factors for cerebral infarction included protection devices, operator's skill, patient age, plaque properties, stent design, and statin use. Kotsugi et al. reported that plaque protrusion (PP), as a new risk factor, was strongly associated with cerebral infarction¹⁵⁻¹⁷.

The good results obtained in this study may be explained by the use of embolic protection devices, double antiplatelet regimen, and performance of procedures by experienced neurointerventional radiologists¹⁸. This result may not be externally valid for low-volume centers in Brazil or other countries.

Our rates of hypotension (12.3%) and bradycardia (9.2%) are within the wide range of reported rates (6.8–75.9% and 2.3–47.6%, respectively)^{8,19-24}. These effects, expected to be transient,

are explained by mechanical dilation of the carotid artery bulb during the procedure, leading to decreased sympathetic output and, possibly, increased parasympathetic discharge²²⁻²⁴. Alcade-Lopez et al reported low rates of hypotension (3.6%) and bradycardia (4.4%)⁸. The authors suggested that early CAS (<14 days after the event) is associated with fewer transient hemodynamic events. Our results do not support this hypothesis because we found no significant differences in the timing of CAS in patients with or without these minor complications.

As for the rate of AKI found in our study (10.7%), it was 2-10 times greater than rates previously reported in patients receiving greater (250 mL)²⁵ or the same (150 mL)²⁶ volume of contrast. All but one of the seven patients with AKI in our series received intravenous fluids before the procedure. None of the patients received sodium bicarbonate or N-acetylcysteine, which have already been considered inefficient to prevent contrast-associated AKI²⁷. Baseline creatinine levels were higher in patients with AKI; therefore, these had a greater risk for this outcome and could benefit from the use of low osmolarity contrast media²⁸. However, we could not retrieve information about the type of contrast media used in these patients. Still, there were no cases of permanent renal damage. As expected, the change in creatinine levels after CAS was greater in subjects who developed kidney injury than in patients without, but the difference did not reach statistical significance. However, glomerular filtration rates before CAS were similar in these two subgroups of patients.

Vasospasm is a possible reaction to the use of distal protection devices used in the CAS procedure. The device's basket and its movement might cause endothelial injury, leading to vasospasm, which may cause neurological symptoms²⁹. Our vasospasm rate (3.1%) was low, when compared to the one reported by Alcade-Lopez et al (15.8%)⁸. Intra-arterial administration of nitroglycerin may be used to treat vasospasm, but not for prophylaxis, because it increases the risk of hypotension²⁹. We found no significant differences in the age of subjects who presented and those who did not present complications, in contrast with the concept that older age is a predictor of the occurrence of complications after CAS²⁴. The reason for this result is unclear, and the relatively small sample size of this study may have influenced, as well as the trend for a greater proportion of women in the group who had minor complications.

This study has some limitations: sample size, retrospective design, and relatively short-term follow-up. Still, it demonstrates that, in a high-volume center in a developing country, minor complications were more frequent than major. These findings are useful to inform patients before CAS procedures. In centers and patients with a comparable profile, considering the high risks of stroke recurrence in patients with carotid stenosis \geq 70%¹, the overall risk-benefit of CAS is highly favorable. Future studies may compare rates of minor complications in different settings, such as low- and high-volume centers in

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different parts of the world, and assess the effects of these complications on patient-reported outcomes.

CONCLUSION

Our treatment result of CAS seemed to be acceptable compared with previously published articles regarding CAS in developed countries. In addition, these findings reinforce the safety of CAS in a high-volume reference center.

AUTHORS' CONTRIBUTIONS

ISM: Data curation, Formal Analysis, Writing – original draft. **RAA:** Conceptualization, Data curation. **LSV:** Conceptualization, Data curation. **PPJ**: Supervision, Validation. **ABC:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Criteria for selection and classification of studies in medical events

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the impact of study methodology and evaluation type on the selection of studies during the presentation of scientific events.

METHODS: A prospective, observational, transversal approach was applied to a cohort of studies that were submitted for presentation at the 2021 Brazilian Breast Cancer Symposium. Three forms of criteria (CR) were presented. CR1 was based on six criteria (method, ethics, design, originality, promotion, and social contribution); CR2 graded the studies from 0 to 10 for each study, and CR3 was based on five criteria (presentation, method, originality, scientific knowledge, and social contribution). To evaluate the item correlation, Cronbach's alpha and factorial analysis were performed. For the evaluation of differences between the tests, we used the Kruskal-Wallis and *post-hoc* Dunn tests. To determine the differences in the study classifications, we used the Friedman test and Namenyi's all-pairs comparisons.

RESULTS: A total of 122 studies were evaluated. There was also a good correlation with the items concerning criterion 1 (α =0.730) and 3 (α =0.937). Evaluating CR1 methodology, study design and social contribution (p=0.741) represents the main factor and CR3 methodology, and the scientific contribution (p=0.994) represents the main factor. The Kruskal-Wallis test showed differences in the results (p<0.001) for all the criteria that were used [CR1-CR2 (p<0.001), CR1-CR3 (p<0.001), and CR2-CR3 (p=0.004)]. The Friedman test showed differences in the ranking of the studies (p<0.001) for all studies (p<0.001).

CONCLUSION: Methodologies that use multiple criteria show good correlation and should be taken into account when ranking the best studies. **KEYWORDS:** Planning techniques. Congress. Meeting abstract. Societies, scientific. Methods.

INTRODUCTION

Medical scientific events (MSEs) are spaces for the recycling of scientific knowledge where updates are presented on changing trends in basic science, diagnosis, or treatment. In addition, they allow the strengthening of medical societies and the presentation of new inputs and novel technologies¹.

The refinement observed in the selection criteria of articles is not extended to scientific events. The size of an abstract limits the details involved in a study. The quality of the abstract presentation influences the acceptance rate^{1,2}.

Generally, studies in progress are presented, but only some are published³⁻⁵. Oral presentations (OP)⁵, the region of origin of the study⁶ or the institutions involved, the sample size, the presence of positive results, or the level of evidence have a positive impact on publication⁷. Several factors can influence the selection and classification of studies, including the quality of a study, the form of presentation of its abstract,² and its methodology. Regarding the evaluation committee, relevant factors include the training of evaluators (basic science or clinical practice)⁸, the criteria used⁸, the area of the study⁹, the form of analysis (structured evaluation)¹⁰, the blinding of the evaluators¹¹, the methodology used during agreements or disagreements among the evaluators⁹, and the concordance between the evaluators⁹.

There are criteria for the selection of the studies and criteria for ranking them. For initial selection, simple criteria can

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Conflict of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on November 20, 2022. Accepted on December 19, 2022.

be used, such as a Likert scale ranking (minor=worst; maximum=best)¹⁰, adding criteria for accepting (e.g., reject, unsure, accept)^{9,10}, or adding abstract items (abstract's clarity, significance of learning objectives, relevance in clinical practice, grouping it in a Likert Scale)¹². Limited studies presented the criteria used for selecting abstracts at scientific events^{12,13,8}, justifying the present study.

METHODS

The present study did not involve human beings, so it did not require evaluation by the Brazilian Research Ethics Committee. We conducted an observational, prospective, and blind study to evaluate the influence of the criteria used for the evaluation of studies and their relationship with the order of their classification in scientific events. We used an event in the area of mastology as our basis. The criteria that were used for the evaluation of the abstracts followed a recently published model⁸.

The study was conducted at the 2021 Brazilian Breast Cancer Symposium (BBCS). The members of the scientific committee were invited to participate in the study. Only members who completed the evaluation of all studies and evaluated them according to the three criteria participated in this research. To the committee, the studies were presented in a Microsoft Excel® spreadsheet in a blind manner, and three columns were presented for their evaluation of the different criteria. Clinical studies were separated from case reports. The first criterion (CR1) was based on six criteria (method, ethics, design, originality, promotion, and social contribution). The sum for each study resulted in 10 points, representing the event pattern⁸. For each factor, the score was predefined. In the second criterion (CR2), the evaluator rated the study from 0 to 10. The third criterion (CR3) was based on previous mastology meetings, considering 5 criteria (presentation, method, originality, scientific and social contribution), scored from 0 to 10 (free score), with the sum divided by 5, representing the final score based on the mean evaluation. If the evaluator participated in one research, we opted to use the mean of the other evaluators. Table 1 specifies the criteria used. Subsequently, the classification of the studies was evaluated using the criterion used in the event (CR1) as a standard, and the 10 best potential studies were identified. For analysis, we consider the best studies considered by the study evaluators.

Statistics

We sought to evaluate whether the medians of the tests were equal. For this purpose, the Kruskal-Wallis test was used. When there were changes between the tests, a *post hoc* evaluation was performed using the Dunn test to determine the tests where there was a difference. To demonstrate whether there was a difference in the classification position between the studies, the Friedman test was used.

When there were changes between the tests, a *post hoc* evaluation was performed using Nemenyi's all-pairs comparisons test to identify which tests showed differences. In these evaluations, we used the program "R".

We attempted to quantify the relationship between the results of these methods using multiple evaluation methodologies (CR1 and CR3) using Cronbach's alpha. To determine the best methodology and the smallest number of items that could determine the same results, factor analysis was performed (Table 2). The minimum sample size necessary for factorial analysis was 100 patients¹⁴. To compare the evaluation methodologies, the IBM SPSS[®] software for Mac[®] was used.

RESULTS

All 20 professors on the scientific committee were invited to participate in this research, allowing us to observe the adherence of five members in all evaluations, all senior professionals, and from different services. Among the evaluators, the mean age was 58 years (range 49–71 years), with an average of 25.4 years (range 18–36 years) of activity in mastology and 13.8 years (range 7–20 years) of participation on scientific congress committees. All of them had completed medical residencies, with four doctors (Ph.D.) and one master (M.Sc.). All of them advocated the separation of studies into clinical articles, molecular biology research, and case reports. When asked about the criteria, 4 of 5 evaluators considered it important to use predefined criteria in the evaluation of studies. The researchers were unanimous in their identification of study design, method, originality, ethics, and clinical relevance as important criteria.

Approximately 122 studies were evaluated, including 94 original studies and 28 case reports. Regarding the criteria used in the event (mean±standard deviation), CR1 indicates that original studies (5.62 ± 0.92) received better scores than case reports (3.64 ± 0.84). Evaluating the original studies and the type of criteria, CR2 presented higher scores [CR2 (6.43 ± 0.72) > CR1 (5.62 ± 0.92) > CR3 (4.61 ± 0.84)].

Binary comparisons (CR1/CR3, CR1/CR2, and CR2/CR3) were performed. The Kruskal–Wallis test showed that there was a difference in the medians between the tests (p<0.001). There was a difference between the CR1-CR2 criteria (p<0.001), CR1-CR3 criteria (p<0.001), and CR2-CR3 criteria (p=0.004). According to the Friedman test, there was also a significant difference in the classification of the studies. Nemenyi's all-pairs

Table 1. Criteria used in the study.

| | Criterion 1 – Single criteria adapted from Mastology ⁸ | | | | | | |
|-------|--|--|--|--|--|--|--|
| Malua | Criteria | | | | | | |
| value | Study method | | | | | | |
| 2.8 | Systematic review of randomized studies with or without a meta-analysis. Molecular: Omics studies (genomics, transcriptomics, proteomics) | | | | | | |
| 2.4 | Randomized experimental studies. Molecular - Functional studies (in vitro/in vivo) | | | | | | |
| 2.0 | Cohort Studies. Molecular: The identification of biomarkers (with validation methodology) | | | | | | |
| 1.6 | Case control studies | | | | | | |
| 1.2 | Case series. Molecular: Descriptive studies without validation or without a control group | | | | | | |
| 0.8 | Case report | | | | | | |
| 0.4 | Expert opinions | | | | | | |
| | Ethics in research | | | | | | |
| 1.0 | Approval from the ethics committee | | | | | | |
| 1.0 | No need for a Research Ethics Committee under Resolution No. 466 | | | | | | |
| 0.0 | No description or evaluation by the ethics committee | | | | | | |
| | Design/Study presentation | | | | | | |
| 2.5 | Adequate description of the study with clear, reproducible methodology, consistent results and adequate conclusion that is compatible with the data presented. Approved through ClinicalTrials/ReBEC or something similar. | | | | | | |
| 2.0 | Adequate description of the study with clear, reproducible methodology, consistent results and adequate conclusion that is compatible with the data presented. | | | | | | |
| 1.5 | Adequate description of the study, however the methodology is weak (not reproducible), consistent results and adequate conclusion that is compatible with the data presented. | | | | | | |
| 1.0 | Adequate description of the study, however the methodology is weak (not reproducible), and the results and/or conclusions were not adequate for the data presented. | | | | | | |
| 0.5 | Severe failures in the introduction, methodology, results and conclusions. | | | | | | |
| 0.0 | Does not apply. Methodology and results not described. | | | | | | |
| | Originality | | | | | | |
| 1.7 | Unprecedented - new interpretation of the concept | | | | | | |
| 1.2 | Ratifies a known concept that is optional | | | | | | |
| 0.7 | Ratifies a classic concept that is used everyday | | | | | | |
| 0.4 | Does not introduce a new concept | | | | | | |
| | Grant/Promotion | | | | | | |
| 1.0 | Promotion from a public agency | | | | | | |
| 0.5 | Promotion from a private agency | | | | | | |
| 0.0 | Self-promotion or no promotion | | | | | | |
| | Clinical/Social contribution | | | | | | |
| 1.0 | In clinical practice and/or social practice | | | | | | |
| 0.5 | In the study subgroup | | | | | | |
| 0.0 | No clinical applicability or does not fit | | | | | | |
| | Criterion 2 - Simple assessment of Abstracts - Grade from 0 to 10 for the study. | | | | | | |
| | Criterion 3 – Criteria used in past Congresses – Grade from 0 to 10 for each of the item. | | | | | | |
| | Presentation – Method – Originality – Social Contribution – Scientific Contribution | | | | | | |

Table 2. Factor analysis results*.

| Orden | Criteria 1 | | Criteria 3 | | |
|-------|---------------------|-------|-------------------------|-------|--|
| Order | Category | Value | Category | Value | |
| 1 | Method | 0.868 | Scientific contribution | 0.944 | |
| 2 | Study design | 0.843 | Presentation | 0.934 | |
| 3 | Social contribution | 0.741 | Originality | 0.922 | |
| 4 | Originality | 0.588 | Method | 0.914 | |
| 5 | Ethics | 0.449 | Social contribution | 0.836 | |
| 6 | Grant | 0.438 | _ | - | |

*In the criteria 1, the scores were pre-defined for each type of assessment, and in criterion 3, the evaluator was free to give a score within the question.

comparisons *post hoc* test indicated differences (p<0.01) for all comparison pairs. When exclusively evaluating the top 10 (Figure 1), the Friedman test showed a difference between the rank of the abstract in relation to the different criteria used (p<0.001), and Nemenyi's all-pairs test showed no difference between the CR1×CR2 criteria (p=0.17) and CR1×CR3 criteria (p=0.06), although the CR2×CR3 criteria were very different (p=0.01).

The correlation between the items observed in CR1 was evaluated, demonstrating a good correlation (α =0.730), whereas factorial analysis showed that only three criteria would best represent the evaluation, namely, study method, study design, and social relevance (Table 2). The correlation between the items observed in CR3 was evaluated, showing an excellent correlation (α =0.937), whereas factor analysis showed that only one criterion would best represent the evaluation, namely, scientific contribution (Table 2).

DISCUSSION

Studies at scientific events have greater flexibility since they constitute a space where several professionals from the same specialty are gathered, and there is also space for the presentation of institutions or infrequent situations. The type of scientific event influences the quality of the studies presented, with international specialty events at the top of this hierarchy, associated with abstracts in high-impact factor journals, followed by other international events and then national, regional, and local events. Depending on the event, these selected studies are published in impact factor journals or event supplements.

Between the presentation of a study at a medical event and its final publication, there is a period that should be considered. This path is long, and many studies have never been published. The publication rate varies from 7.9⁴ to 57%⁵, a fact influenced by the regularity and hierarchy of medical events, the occurrence of concurrent events with the same specialty and type of specialty, or the acceptance of previously published studies⁶.



Figure 1. Adjusted variation of position among the 10 best studies.

The average time for publication is 2 years ^{3,5}, and most studies are published in 5 years⁵. In Brazil, the number of studies published in public services is higher^{4,6}, with most of these published in national and specialty journals^{4,7}. Among the reasons for nonpublication are time, reluctance to publish incomplete findings, no attempt at publication, the need to increase casuistry, the responsibility of another author, and rejected study³.

To select the best abstracts, we evaluated three different methodologies. After evaluating the scores, a factor analysis was performed to determine the main factors associated with the studies by employing methodology, design/presentation, and social relevance as multiple criteria and scientific contribution as a single criterion. This method should be considered during the future selection and classification of abstracts. There is less description in the literature regarding the criteria used in the selection of abstracts. It is important to consider the description of clinical applicability, innovation, clarity in the description of findings (objective, hypothesis, description of findings, and discussion), and quality of the method¹⁵. Based on the quality of study evidence, one study suggested quality scores² and the other suggested criteria to increase the study description, given transparency, and integrity for publications submitted to conference¹. We previously created clear and reproducible criteria⁸. However, these were grouped to facilitate the evaluation of clinical and basic studies, and therefore a lower score was used for case reports.

In the literature, the number of evaluators reported was 3², 5¹³, 9⁹, or 10¹⁰. But we have to evaluate the number of abstracts evaluated by each evaluator, and the evaluator's characteristics. One publication reviewed 938 abstracts, 70–100 members, and 20–30 abstracts/evaluators¹². Another considered from 17,205 abstracts, 1,000 were selected, and 100 were evaluated in the study by three researchers, creating a potential criteria for quality². New members in the association evaluated the abstracts (n=194) of one study¹³. Although reliability generally increases with the number of reviewers, the annual increase in abstracts submitted may require a decrease in the number of reviewers for each abstract, a fact that difficult studies in this area¹⁰. Our study included five senior professionals (four PhDs and one MSc).

Different methods were used to choose the abstract, varying the Likert scale with or without other criteria^{9,10,12}. Likert scales have different ranges (-6 to +6¹⁰, 1 to 7¹², and 1 to 5⁹), and we chose 0–10. For quality criteria, the literature is not uniform in relation to abstract items,¹² and one publication suggests 14 important items for evaluation². We used three models, namely, criteria+scale (CR1), Likert (CR2), and criteria+Likert (CR3). Model CR1 used six predetermined criteria,⁸ and CR3 used a Likert scale (0–10) in five situations. Factorial analysis selected the main items for CR1 that were method, design, and social relevance, so the quality of the study and relevance in clinical practice were important for the abstract evaluation. When the evaluation of CR3's scientific contribution was considered, multiple criteria reduce the subjectivity of the evaluation and help the evaluator.

The BBCS has established itself as the main event for clinical and basic research in mastology in Brazil, and it is currently in its tenth edition. For the selection of the studies, we took some care to avoid possible bias, as the form of evaluation (blind or not blind) interferes with the acceptance of studies and programming¹¹. To avoid biases related to the participation of the study (detection bias), we opted to use the mean of the other four evaluators, a fact that occurred in 8 abstracts (6.5%). To prevent biases among the evaluators, national researchers with different services and high experience (senior) in the field of mastology were invited. In our study, the high experience of the committee may have entailed a certain bias in the evaluations; when using CR1, three factors were found to be representative because the committee was comprised of professionals with primarily clinical activity. To avoid biases related to the evaluators (attrition bias), we chose to evaluate similar situations and compare the results, and we stopped the evaluation based on the five evaluators, using the same methodology in the same sample.

We do not compare our results with the final classification of the BBCS, as 20 researchers classify the abstracts. We evaluated the results related to our five reviewers. Concerning only the 10 top-ranked studies selected from the event (CR1), there was a difference in their order of classification in relation to the other criteria (Figure 1). We thus observed that the top study, due to its quality, remained in the first place, independent of classification.

The use of a structured questionnaire can be useful in the objective evaluation of abstracts during a scientific meeting and can facilitate the comparison of abstracts. The meritocratic distribution of abstracts among reviewers is thus advocated, and more studies are necessary to improve the reliability of their classification, justifying future studies.

CONCLUSION

The original studies received better scores. Methodologies that used many criteria showed a good correlation, which was the preference of the evaluators. The methodology used in the evaluation of studies thus influences the classification of the best studies. In the selection of criteria, a detailed method, study design, and scientific contribution were relevant.

ACKNOWLEDGMENTS

We thank Flavio Ferraz Vieira for his help in the statistical evaluation.

AUTHORS' CONTRIBUTIONS

RACC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **RRP**: Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **FFOR**: Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **MARM**: Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **RC**: Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **RC**: Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **FCP**: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **RMSR**: Resources, Visualization, Writing – original draft, Writing – review & editing. **GF**: Conceptualization, Methodology, Validation, Visualization, Writing – original draft, Writing – review &

editing. **RFJ**: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing.

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Transjugular intrahepatic portosystemic shunt in decompensated cirrhotic patients in a tertiary hospital in southern Brazil

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SUMMARY

OBJECTIVE: The aim of the present study was to evaluate the outcomes of cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt. **METHODS:** A retrospective longitudinal observational study was carried out evaluating 38 cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt. The outcomes were evaluated in an outpatient follow-up period of 3 months. The assumed significance level was 5%.

RESULTS: The indications for transjugular intrahepatic portosystemic shunt were refractory ascites in 21 (55.3%), variceal hemorrhage in 13 (34.2%), and hydrothorax in 4 (10.5%) patients. There was development of hepatic encephalopathy in 10 (35.7%) patients after transjugular intrahepatic portosystemic shunt. From the 21 patients with refractory ascites, resolution was observed in 1 (3.1%) patient, and in 16 (50.0%) patients, there was ascites control. Regarding transjugular intrahepatic portosystemic shunt after variceal bleeding, 10 (76.9%) patients remained without new bleeding or hospitalizations in the follow-up period. The global survival in the follow-up period in patients with and without hepatic encephalopathy was 60 vs. 82%, respectively (p=0.032).

CONCLUSION: Transjugular intrahepatic portosystemic shunt can be considered in decompensated cirrhotic patients; however, the development of hepatic encephalopathy which can shorten survival should be focused.

KEYWORDS: Hypertension, portal. Ascites. Gastrointestinal hemorrhage. Hydrothorax.

INTRODUCTION

The final stage common to liver diseases of different etiologies is cirrhosis, resulting in portal venous hypertension (PVH), which determines important clinical consequences^{1,2}.

In an attempt to control PVH and its consequences globally, drug therapy seeks to correct the increase in portal blood flow through the use of splanchnic vasoconstrictors, reducing the hepatic venous pressure gradient, and, therefore, attenuating or avoiding these complications²⁻⁴.

The transjugular intrahepatic portosystemic shunt (TIPS) appears as an element of this therapeutic arsenal. TIPS is a procedure of proven effectiveness for the management of complications of PVH, and aims to decompress the portal venous system⁵⁻⁸. It reduces the pressure gradient within the portal venous system in about 90% of patients, improving the complications of PVH. The most strongly supported indications for TIPS, as recently revised, are the management of refractory ascites and variceal gastrointestinal bleeding¹⁻⁴.

Given the relevant role of this procedure in the management of PVH and especially considering the very recent updates on the subject^{1-4,9}, the objective of the present study was to evaluate the main clinical outcomes of cirrhotic patients undergoing TIPS.

METHODS

This is a retrospective longitudinal observational study where the medical records of all cirrhotic patients undergoing TIPS between 2012 and 2020 were analyzed.

TIPS was formally indicated according to the recommendations of the current guidelines^{1-4,10,11}, and consent of the patients or guardians was obtained. Those patients who did not register of the indication for TIPS installation and the outcomes were excluded from the study.

The study involved patients from the gastroenterology unit of Hospital Nossa Senhora da Conceição (HNSC), a public tertiary care hospital in southern Brazil. All the procedures were performed by physicians from the Interventional Radiology Unit of the HNSC with expertise in the area.

Data were collected regarding the etiology of cirrhosis, TIPS indication, and Child and MELD scores. Clinical outcomes related to the resolution of ascites, hydrothorax, and variceal bleeding

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on January 12, 2023. Accepted on January 13, 2023.

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were evaluated. Regarding ascites after TIPS, patients were classified as having persistent ascites (requiring paracentesis after TIPS), having ascites controlled (without the need of paracentesis), or having complete resolution of ascites¹². In addition, the onset of hepatic encephalopathy (HE) and death were recorded. HE was diagnosed and classified according the EASL guideline¹³.

TIPS were performed under anesthesia, using the Philips Allura XP® angiograph, Rösch-Uchida® (Cook) access set and noncovered prosthesis, according to the classic technique¹⁴, except at the puncture of the portal branch, when abdominal ultrasound (Sonosite®) was performed to assist the correct positioning¹⁵. Once the hepatic vein was already catheterized and the portal venous branch was identified, the path of the puncture needle was followed from the hepatic vein along its way in the parenchyma until it reached the portal vein branch in real time, adjusting its direction as required. Dilatation of the parenchymal tract between the hepatic and portal veins was performed using an 8-mm angioplasty balloon (Armada®, Abbott). A 10-mm Wallstent® (Boston) was then deployed and further dilated with the same balloon. In some cases, it was necessary to perform an additional procedure along with TIPS, such as gastroesophageal varices embolization and vascular recanalization.

The portosystemic pressure gradient was calculated as the difference between the pressures of the portal vein and the inferior vena cava, measured through a catheter positioned freely inside the veins and attached to a pressure transducer. TIPS execution time and the fluoroscopy time were evaluated.

All outcomes were evaluated pre-TIPS and in an outpatient follow-up period of up to 3 months afterward (post-AMB).

The research project was carried out in accordance with resolution 466 of 2012, which regulates the conduct of research in human beings, and was approved by the Research Ethics Committee of HNSC under number 5.218.265.

Data were exported to the Statistical Package for the Social Sciences (SPSS) version 20.0 of Windows for statistical analysis and were presented as mean and standard deviation, median and interquartile range (IQR), or frequency and percentage. Associations between categorical variables were tested using Pearson's χ^2 test, and those between moments were tested using McNemar's test. To compare continuous variables between groups, the Student's t-test was used for variables with a normal distribution or the Mann-Whitney U test for asymmetric distributions. For intragroup comparisons, the method of generalized estimation equations with Bonferroni adjustment was used in the multiple comparisons for laboratory variables. Child and MELD scores were compared using the Wilcoxon test. In the case of dichotomous variables (HE), the Cochran test was used. For analysis of ordinal variables (degree of ascites), the

Friedman test (nonparametric test) was used. Overall survival up to 3 months (post-AMB) was assessed using the Kaplan-Meyer curve, comparing patients with and without HE and also patients with ascites using the log-rank test. The assumed significance level was 5%.

RESULTS

Among 51 cirrhotic patients undergoing TIPS, data were obtained from 38 patients.

The mean age was 59 years, the majority was male, and the most frequent etiology of cirrhosis was the abusive use of alcohol associated or not associated with hepatitis B and/or C viruses. Comorbidities were observed in more than half of the cases, with metabolic syndrome and the presence of cardiovascular diseases being the most frequent (Table 1). Three (7.9%) patients presented hepatocellular carcinoma at the time of TIPS's indication.

 Table 1. Demographic data, clinical baseline characteristics of the patients, and indication for transjugular intrahepatic portosystemic shunt (n=38).

| Parameters | |
|----------------------------|----------------|
| Age - years; md (IQR) | 59 (52.5-69.5) |
| Male sex; n (%) | 23 (60.5) |
| Etiology; n (%) | ` |
| Alcohol | 15 (39.5) |
| Hepatitis B/C virus | 08 (21.0) |
| NAFLD | 02 (5.3) |
| Miscellaneous | 13 (34.2) |
| Comorbidities; n (%) | |
| MetS | 19 (50.0) |
| CVD | 04 (10.5) |
| Other | 06 (15.8) |
| None | 12 (31.6) |
| Indication for TIPS; n (%) | |
| Refractory ascites | 21 (55.3) |
| Variceal bleeding | 13 (34.2) |
| Hydrothorax | 04 (10.5) |
| Child pre-TIPS; n (%) | |
| А | 05 (13.2) |
| В | 29 (76.3) |
| С | 04 (10.5) |
| MELD pre-TIPS; md (IQR) | 12 (10-17) |

md: median; IQR: interquartile range; n: number; NAFLD: nonalcoholic fatty liver disease; MetS: metabolic syndrome; CVD: cardiovascular disease; TIPS: transjugular intrahepatic portosystemic shunt. Indications for TIPS insertion were refractory ascites in 21 (55.3%) patients, variceal hemorrhage that did not respond to initial endoscopic/pharmacological management in 13 (34.2%) patients, and hydrothorax in 4 (10.5%) patients. The vast majority of patients were Child A or B (34; 89.5%). The mean MELD score was 12 (Table 1).

Regarding indications for TIPS, there was no difference between age (p=0.406), sex (p=0.630), etiology of cirrhosis (p=0.484), comorbidities (MetS p=0.531, cardiovascular disease p=0.226; none p=0.353); Child score (p=0.060), and MELD score (p=0.441).

There was no difference between the two periods observed (pre-TIPS and post-AMB) regarding the levels of hemoglobin, platelets, and albumin. However, there was a statistically significant worsening in the International Normalized Index (INR) and total bilirubin, as well as a reduction in serum creatinine levels (Table 2) after TIPS.

In all, 32 patients had pre-TIPS ascites, although only 21 patients were considered to have refractory ascites and were indicated for TIPS insertion. Complete resolution of ascites was observed in 1 (3.1%) patient and control in 16 (50.0%) patients when considering the post-AMB period.

Regarding the control of variceal bleeding, 10 (76.9%) patients remained without new bleeding or hospitalizations in the post-AMB period.

Regarding hydrothorax, there was resolution in one patient in the post-AMB period. There was loss to follow-up in the other two patients.

There was no statistically significant difference when evaluating the median values for MELD (12 vs. 13; p=0.568) and Child (8 vs. 8; p=0.403) scores pre- and post-TIPS, respectively.

There was a development of HE in 10 (34.5%) patients when evaluated in the post-AMB period (Table 2). There was no statistical difference between all the indications for TIPS and the development of HE (p=0.484). The insertion of TIPS was successful in all cases. After its performance, a reduction in the portosystemic pressure gradient was observed (initial gradient of 18.8 ± 3.6 mmHg and final gradient of 9.2 ± 2.2 mmHg). The mean time for TIPS execution was 65.2 ± 46.7 min, and the mean fluoroscopy time was 25.0 ± 14.1 min. More than half of the patients (51.2%) required an additional procedure during TIPS (gastroesophageal varices embolization or vascular recanalization). There were no complications related to the inadvertent puncture of nontarget structures (the biliary tree and arterial branches) during the procedure, and no deaths resulted directly from this procedure.

As for the outcomes related to the installation of TIPS, thrombosis was observed in 6 (15.8%) patients, and 9 (23.7%) deaths occurred in the post-AMB period (5 due to sepsis, 2 due to stroke, 1 for bleeding from small bowel varices, and 1 for advanced extrahepatic neoplasia). The majority of deaths (5; 13.1%) occurred in the group of ascites; also, there were 3 (7.9%) deaths in the variceal bleeding group and 1 (2.6%) death in the hydrothorax group.

Overall survival at 3 months in patients with and without HE can be seen in Figure 1. The probability of overall survival at 3 months in patients with and without HE was 60 vs. 82%, respectively (p=0.032; hazard ratio [HR]=3.04).

The probability of survival of patients with ascites was 76.2% (Figure 2).

Age was significant for survival time—the older the individual, the higher the risk of death (p=0.028; HR=1.08).

DISCUSSION

TIPS has been shown to be the best rescue therapy for controlling variceal bleeding, and some reports have shown it to be superior to large-volume paracentesis in controlling ascites, reducing or eliminating the need for paracentesis by 50–90%,

| Characteristics | PRE (n=38) | POST-AMB (n=29) | p-value |
|----------------------------------|-------------------|-------------------|---------|
| Hemoglobin (g/dL); m (SD) | 9.1 (1.9) | 9.9 (2.2) | 0.122 |
| Platelets (×10°); median (IQR) | 95.5 (61.2-178.0) | 90.0 (71.0-148.0) | 0.272 |
| INR; median (IQR) | 1.36 (1.2–1.5) | 1.49 (1.22-1.6) | <0.001 |
| Creatinine (mg/dL); median (IQR) | 1.2 (0.7–1.5) | 0.95 (0.75-1.23) | 0.017 |
| Albumin (g/dL); m (SD) | 3.2 (0.8) | 3.3 (0.7) | 0.132 |
| Bilirubin (mg/dL); median (IQR) | 0.9 (0.5–1.4) | 1.3 (1.0-1.9) | 0.007 |
| HE; n (%) | O (O) | 10 (34.5) | 0.002 |

Table 2. Laboratory characteristics and rate of hepatic encephalopathy pre- and post-transjugular intrahepatic portosystemic shunt.

m: mean; SD: standard deviation; IQR: interquartile range; INR: International Normalized Index; HE: hepatic encephalopathy.



Figure 1. Overall survival at 3 months post-transjugular intrahepatic portosystemic shunt according to the presence or absence of hepatic encephalopathy. Kaplan-Meyer curve: p=0.032; hazard ratio=3.04 (95% confidence interval: 1.02–9.08).



Figure 2. Kaplan-Meyer curve to assess the survival of patients with ascites at 3 months post-transjugular intrahepatic portosystemic shunt.

and improving the liver transplantation-free survival in cirrhotic patients with refractory ascites^{1-4,9-11}.

In Brazil, there are few reports on the use of TIPS in transplantation centers¹⁶⁻¹⁸: one of them¹⁶ is the description of the first case in Brazil in 1996, and the other two are from the same group and they focused on complications^{17,18}.

The present study evaluated 38 cirrhotic patients who received TIPS in real life, and the indication followed the international recommendations: refractory ascites, gastrointestinal bleeding from varices, and hydrothorax^{1-4,9-11}. TIPS was related to the improvement in the control of ascites, variceal bleeding, and hydrothorax in a reasonable portion of the cases. However, it promoted the development of HE in 34.5% of the patients in the follow-up period, in agreement with that observed in the literature¹⁹⁻²¹.

It was also observed a worsening of the MELD and Child scores in more than 50 and 30% of the patients, respectively. However, there was no statistically significant difference in the observed mean values. It has been described that most patients who underwent TIPS are Child B^{17,22}. This is in agreement with

the present study, configuring patients with moderate-to-severe hepatic dysfunction who often undergo TIPS as a bridge to liver transplantation, and worsening of liver function may also be observed after TIPS. Additionally, it has previously been shown that liver function worsens during the first month after TIPS, followed by progressive improvement at 6 and 12 months²³. Unfortunately, it was not possible to have an extended follow-up period in the present study beyond 3 months.

Complications directly related to the procedure were mainly shunt thrombosis, with a rate similar to that found in the literature—ranging from 8 to 15%^{10,17,22,24}. Probably if covered TIPS were used, a decrease on this complication rate should be observed²⁵. Unfortunately, the public health system in Brazil only offers the uncovered TIPS. In this study, deaths were not directly related to the installation of TIPS, which is also observed in the literature²⁶.

Despite the current evidence recommending the implementation of preemptive TIPS in patients with variceal bleeding, it has been previously demonstrated that only 7–13% of eligible patients are currently treated with preemptive TIPS in real-world practice²⁷.

The 3-month survival was higher in patients who did not have HE, and patients without HE were three times more likely to survive at 3 months than those with HE. Funes et al.¹⁸ found a global mortality rate of 60.3% and observed that Child and MELD were predictors of mortality, with HE developing at a high incidence (58.3%). Silva et al.¹⁷ evaluated 47 patients and observed a mortality rate of 32% over 3 months, while HE was observed in 49%. Other authors did not evaluate HE as a predictor of survival²⁶.

As potential limitations, we highlight the fact that the study was carried out at a single center and was retrospective. Because of the retrospective nature of the study, some data were not recovered in the follow-up period. However, we can say that only one center has published studies with similar or greater experience within the country^{17,18}, and most public hospitals do not offer this alternative treatment. The follow-up period of 3 months may also be considered a limitation. However, data loss could be greater if a longer period was evaluated, and therefore, a shorter period was defined. In addition, it must be emphasized that many studies on the literature consider the period of 3 months on the follow-up^{7,14,17,22,24,26}.

We should consider that this is a successful experience, showing that the procedure is safe and effective in the management of decompensated cirrhosis even when using the noncovered stent, which can be cost-effective in public health.

In conclusion, TIPS is a procedure that can be considered a good alternative in the management of refractory ascites, gastrointestinal bleeding secondary to varices, and hydrothorax, helping to control symptoms even when using the noncovered stent. However, attention must be paid to the development of HE, which can shorten patient survival.

AUTHORS' CONTRIBUTIONS

CVT: Conceptualization, Formal Analysis, Project administration, Supervision, Investigation, Methodology, Writing – original draft, Writing – review & editing. **AAM:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **CMT:** Data curation, Formal Analysis,

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Magnetic resonance arthrographic demonstration of extension of labral defects in paraglenoid labral cysts

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SUMMARY

OBJECTIVE: This study aimed to investigate the extension of labral tears associated with paraglenoid labral cysts by magnetic resonance arthrography. **METHODS:** The magnetic resonance and magnetic resonance arthrography images of patients with paraglenoid labral cysts who presented to our clinic between 2016 and 2018 were examined. In patients with paraglenoid labral cysts, the location of the cysts, the relation between the cyst and the labrum, the location and extent of glenoid labrum damage, and whether there was contrast medium passage into the cysts were investigated. The accuracy of magnetic resonance arthrographic information was evaluated in patients undergoing arthroscopy.

RESULTS: In this prospective study, a paraglenoid labral cyst was detected in 20 patients. In 16 patients, there was a defect in the labrum adjacent to the cyst. Seven of these cysts were adjacent to the posterior superior labrum. In 13 patients, there were contrast solution leak into the cyst. For the remaining seven patients, no contrast-medium passage was observed in the cyst. Three patients had sublabral recess anomalies. Two patients had rotator cuff muscle denervation atrophy accompanying the cysts. The cysts of these patients were larger compared to those of the other patients. **CONCLUSION:** Paraglenoid labral cysts are frequently associated with the rupture of the adjacent labrum. In these patients, symptoms are generally accompanied by secondary labral pathologies. Magnetic resonance arthrography can be successfully used not only to demonstrate the association of the cyst with the joint capsule and labrum, but also to reliably demonstrate the presence and extension of labral defects. **KEYWORDS:** Shoulder joint. Magnetic resonance imaging. Glenoid cavity.

INTRODUCTION

Paralabral cysts are pericapsular loculated fluid collections associated with labral tears. While cysts near the anterior labrum are often related to anterior instability, those near the posterior labrum are associated with posterior instability and those near the superior labrum are associated with SLAP lesions. Paralabral cysts can have a mass effect and cause nerve compression in the shoulder. These cysts appear as lesions with fluid intensities on magnetic resonance (MR) imaging¹. In a study performed by Tung et al., only 2.3% of 2,000 shoulder MR images taken for shoulder pain revealed paralabral cysts².

Large paralabral cysts may compress the suprascapular or axillary nerve, causing shoulder weakness and denervation of the external rotator muscles^{1,3-5}. MR arthrography (MRA) plays an important role in detecting superior labrum from anterior to posterior tears (SLAP lesions), impingement syndromes, and instability accompanying paraglenoid labral cysts^{2,4,6,7}.

If there are no symptoms in patients with paralabral cysts, clinicians usually monitor these patients by performing rest and movement exercises without surgery. However, symptomatic patients with paralabral cysts often have accompanying labral tears, and these tears often require surgical intervention⁸. In this study, we aimed to evaluate the incidence and extent of accompanying labral tears in paraglenoid labral cysts by MRA. These tears may be overlooked on conventional MR imaging when not carefully examined. Our secondary aim was to increase the success of the operation by providing surgeons with more concrete data for this patient group.

METHODS

Between 2016 and 2018, 350 patients with shoulder pain and limitations of movement presented to the Department of Orthopedics and Traumatology of the Atatürk University Medicine Faculty, and they underwent MR and MRA.

MRA and conventional MR examinations were performed using a 3-T MR scanner (MAGNETOM Skyra, Siemens Healthcare). A 16-channel coil was used in all MR procedures.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on October 29, 2022. Accepted on January 03, 2023.

For routine MR imaging, the following sequences were used: T2-weighted imaging in the axial plane (repetition time/time to echo [TR/TE]=3,800/72 ms), proton density imaging in the oblique coronal plane (TR/TE=4,000/24 ms), and T1-weighted imaging in the axial and oblique sagittal planes (TR/TE=650/15 ms). The field of view (FOV) was selected as 18 cm, matrix as 256×256, sectional thickness as 4 mm, and sectional range as 0.1 mm. MRA images were obtained in the axial, oblique sagittal, and oblique coronal planes using 16-channel shoulder coils. For the MRA examinations, T1-weighted spin echo (fat-suppressed) imaging was performed in the transverse, oblique coronal, and oblique sagittal planes (TR/TE=650/15, section thickness=3 mm, spacing=0.3 mm, FOV=16 cm, and matrix=256×250).

The images were retrospectively reviewed by two musculoskeletal radiologists with 12 and 2.5 years of experience, respectively. The localization of the cysts adjacent to the labrum, T1and T2-weighted image characteristics, the dimensions, and signal characteristics of the adjacent labrum were evaluated on MR scans. In MRA, it was determined whether there was a rupture of the labrum adjacent to the cysts localized by MR imaging. In cases of a rupture, it was determined whether the rupture continued along the labrum and if there was leakage of contrast material into the cyst. The MRA images were also evaluated for labral variations. All findings were clarified based on the consensus of the two radiologists. All arthroscopies were performed by a single orthopedist with 7 years of experience in shoulder joint arthroscopy. In arthroscopic cases, the orthopedist removed the cyst and repaired the adjacent joint capsule and labrum. In Figure 1, the labrum is presented as a clock dial, showing the points where the tears in the labrum begin and end and the locations of the cysts.



Figure 1. Schematic representation of the tears in the labrum. As: anterior-superior; Ai: anterior-inferior; Ps: posterior-superior; Pi: posterior-inferior.

RESULTS

Of the 350 patients who underwent MRA, 20 (5.7%) were included in the study. Of them, 16 (80%) patients were male and 4 (20%) were female. The right shoulder was examined in 10 cases, and the left shoulder was examined in 10 cases. The age range of the patients was 21–70 years, and the mean age was 37.4 ± 10.4 years. Only one patient had two cysts on one shoulder, whereas the remaining cases had one. On MR imaging, the smallest size of the cysts was determined as $5\times5\times5$ mm and the largest as $50\times16\times36$ mm.

A total of 21 paraglenoid labral cysts were diagnosed in the 20 patients included in the study. Notably, 7 (33%) of the cysts were adjacent to the posterior superior labrum, 6 (28%) were adjacent to the posterior labrum, 3 (14%) were adjacent to the anterior superior labrum, 2 (9%) were adjacent to the posterior inferior labrum, 2 (9%) were adjacent to the superior labrum, and 1 (4%) was adjacent to the inferior labrum. The localization of the paraglenoid cysts and the extent of the accompanying labral tears are summarized in Figure 1. On MR imaging, 18 (90%) of the 20 patients had pathological signal enhancement in the labrum adjacent to the cyst and a suspected labral rupture (Figure 2). The MRA revealed the rupture of the labrum in 16 (80%) of these patients (Figure 3) and the sublabral recess or cleft anomaly adjacent to the labrum in 2 (10%) patients. There were no accompanying labral pathologies or sublabral variations on MRA in two (5%) patients without a pathological labral signal on MR imaging. Eight (40%) patients had no additional pathology associated with



Figure 2. Oblique coronal fat-saturated PD magnetic resonance image showing a cyst (star) with high signal intensity near the posterior superior labrum.



Figure 3. In the same patients mentioned in Figure 2, oblique coronal fat-saturated T1-weighted magnetic resonance arthrography image showing extravasation into a superior labral anterior posterior lesion and paralabral cyst (star).

the paralabral cyst or labrum pathology. Hill-Sachs deformities were observed in four patients. One case presented with a reverse Hill-Sachs deformity and biceps tendon dislocation. In addition, adhesive capsulitis, synovial osteochondromatosis, and supraspinatus and infraspinatus muscle atrophy were observed in one patient each. Finally, a cartilage defect in the humeral head was present in one patient, and supraspinatus tendinitis was observed in another patient.

The passage of contrast material was observed in 14 (66%) cysts in MRA. In the remaining 7 (33%) cysts, no contrast material passage was observed. As late images were not obtained, the filling rates of the cysts with contrast medium could not be demonstrated. The cyst lumen was not completely filled with contrast media in any of the patients. The atrophy of the infraspinatus muscle was observed in one patient, and the atrophy of both the supraspinatus and infraspinatus muscles was observed in another case secondary to cyst pressure. Arthroscopic surgery was performed in three patients, for whom the MRA findings were arthroscopically confirmed. The cysts were removed.

DISCUSSION

Conventional MR imaging sequences are widely used in musculoskeletal pathologies because of their high soft tissue resolution. However, conventional MR imaging may fail to evaluate the hyaline cartilage, capsule, fibrocartilage structures such as the labrum, and undersurface of the tendons. These limitations have resulted in the development of new imaging modalities, such as MRA and computed tomography arthrography (CTA). The accurate detection of labral tears in the shoulder is important for the treatment of patients. However, common labral and sublabral anatomical variations in the shoulder joint may also be inadvertently diagnosed with labral tears, resulting in unnecessary surgical procedures. MRA and CTA allow for the accurate identification of labral and perilabral variations and facilitate the diagnosis of labral tears¹⁰.

There are several studies in the literature evaluating the efficacy of conventional MR imaging, MRA, and CTA in the identification of labral lesions. Chandnani et al. compared these three imaging methods in the detection of labral tears in 30 cases by correlating them with the surgical results. In that study, the sensitivity and specificity in detecting labral ruptures were found to be 93 and 46%, respectively, for conventional MR imaging, 73 and 52%, respectively, for CTA, and 96 and 96%, respectively, for MRA. The authors concluded that MRA was the best imaging modality in the detection of labral pathologies¹¹. In another study, Palmer and Caslowitz found that MRA had 91% sensitivity and 93% specificity in the identification of labral lesions in patients with anterior instability and concluded that MRA could be used with high accuracy in the diagnosis of these lesions¹².

Paraglenoid labral cysts are easily seen on T2- or PD-weighted fluid-sensitive MR sequences, and if MRA is performed alone, these cysts may be overlooked. Therefore, we applied conventional MR imaging sequences before MRA to each patient we included in the study.

In this study, 16 of the 20 patients had labral tears adjacent to the cyst. In a study of 46 patients by Tung et al., the researchers found ruptures on the conventional MR images of 27 patients². Our labral tear detection rate was higher because we performed MRA in all patients. Not only labral tears but also other factors play a role in the mechanism of cyst formation. In the current study, we did not see labral tears in four patients, probably due to the spontaneous healing of pre-existing labral tears¹. In some studies, labral diseases have been implicated in the mechanism of cyst formation. A good example is the presence of meniscal cysts in osteoarthritis and calcium pyrophosphate storage disorders in the knee¹³. As earlier, other examples include spontaneous primary ganglion cysts in the joint capsule, bursa, or tendon sheath without labral tears^{14,15}.

In MRA, intracystic contrast agent extravasation is a direct evidence of the relationship between the cysts and the joint space. In our series, we did not detect contrast agent penetration into

the cyst on the MRA images of 7 of the 20 patients, but there was no contrast material passage in the remaining 13 patients. Tung et al. performed MRA in only 5 of the 46 patients with paraglabral cysts. The authors showed contrast agent extravasation into the cyst in one patient². In another study, Malghem et al. retrospectively screened 20 patients with knee-related cysts. The direct radiogram images were obtained in early and late series, and CTA was performed. The radiographs took 20 min after arthrography showed cyst opacification in only 2 patients, while in late series, cyst opacification was seen in 10 patients. As a result, the authors concluded that the late images taken an hour after arthrography better showed the relationship between the cyst and the joint¹⁶. In our patients, we performed imaging within half an hour and did not wait for late series. It is possible that the rate of contrast agent extravasation would have been higher in later image series. However, in delayed series, synovial absorption and dilution of intraarticular contrast media would have potentially caused difficulties in interpretation.

In the present study, we found infraspinatus atrophy in one patient and the atrophy of both infraspinatus and supraspinatus muscles in another patient. In both of these patients, the cysts were located in the adjacent posterior labrum. The dimensions of the cysts were measured as 50×39×32 mm and 50×36×16 mm, respectively, and were the largest cysts in the series. These cysts extended to the spinoglenoid notch. In the study performed by Tung et al., the mean diameter of the cysts associated with muscle denervation was measured as 3.1 cm, and the cysts were smaller in patients without muscle denervation². The findings in our study are in agreement with these data. In the present study, 7 of the 21 cysts were localized to the posterior superior labrum, and the majority of the cysts were found in this area. Tirman et al. reported that the majority of the cysts were located adjacent to the posterior superior labrum¹, which is consistent with the findings obtained from our series. These results are probably due to the posterior superior capsule being located above the posterior band of inferior glenohumeral ligament, which is weaker than the thick anterior capsule.

There are several limitations to this study. The first concerns the relatively small number of patients, which did not allow for statistical analysis. Second, we were not able to make a surgical correlation in all of our cases. In only three cases, we confirmed our arthrographic findings with the gold standard method (arthroscopy). As there was no surgical correlation, we could not compare the diagnostic efficacy of conventional MR imaging and MRA. Finally, we cannot assess the true frequency of intracystic contrast material extravasation in late series.

In conclusion, the diagnosis of paralabral cysts can be made easily by conventional MR imaging. However, conventional MR sequences may be inadequate in the diagnosis of the accompanying labral tears and in the determination of the actual size of these tears. MRA can be successfully used to diagnose labral tears accompanying paraglenoid labral cysts and to determine the actual size of the tears before surgery. The results of this study suggest that MRA provides more data for the surgeon in the surgical planning of symptomatic paraglabral cysts located in the shoulder joint and may increase the rate of operative success.

ETHICAL APPROVAL

No animal was used in this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the Institutional Review Board for Human Subjects Research and Ethics Committee of Ataturk University Medical Faculty (2016).

AUTHORS' CONTRIBUTIONS

HO: Conceptualization, Data curation, Formal Analysis, Investigation, Writing – original draft. SK: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. AKOK: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. AKOR: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. AKI: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. MK: Conceptualization, Data curation, Formal Analysis, Writing – review & editing.

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CHAMPS score in predicting mortality of patients with acute nonvariceal upper gastrointestinal bleeding

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the performance of the Charlson Comorbidity Index ≥ 2 , in-hospital onset, albumin < 2.5 g/dL, altered mental status, Eastern Cooperative Oncology Group performance status ≥ 2 , steroid use score in predicting mortality in patients with nonvariceal upper gastrointestinal bleeding and compare it with the Glasgow-Blatchford score; the albumin, international normalized ratio; alteration in mental status, systolic blood pressure, and age 65 score; the age, blood tests, and comorbidities score; and Complete Rockall score.

METHODS: The data of patients with acute upper gastrointestinal bleeding who visited the emergency department during the study period were obtained from the hospital automation system by using the classification of disease codes and analyzed in this retrospective study. Adult patients with endoscopically confirmed nonvariceal upper gastrointestinal bleeding were included in the study. Patients with bleeding from the tumor, bleeding after endoscopic resection, or missing data were excluded. The prediction accuracy of the Charlson Comorbidity Index ≥ 2 , in-hospital onset, albumin < 2.5 g/ dL, altered mental status, Eastern Cooperative Oncology Group performance status ≥ 2 , steroid use score was calculated using the area under the receiver operating characteristic curve and compared with that of Glasgow-Blatchford score, the albumin, international normalized ratio; alteration in mental status, systolic blood pressure, and age 65 score, the age, blood tests, and comorbidities score, and Complete Rockall score.

RESULTS: A total of 805 patients were included in the study, and the in-hospital mortality rate was 6.6%. The performance of the Charlson Comorbidity Index \geq 2, in-hospital onset, albumin < 2.5 g/dL, altered mental status, Eastern Cooperative Oncology Group performance status \geq 2, steroid use score (area under the receiver operating characteristic curve 0.812, 95%CI 0.783–0.839) was better than Glasgow-Blatchford score (area under the receiver operating characteristic curve 0.683, 95%CI 0.650–0.713, p=0.008), and similar to the the age, blood tests, and comorbidities score (area under the receiver operating characteristic curve 0.829, 95%CI 0.801–0.854, p=0.563), the albumin, international normalized ratio; alteration in mental status, systolic blood pressure, and age 65 score (area under the receiver operating characteristic curve 0.761, 95%CI 0.730–0.790, p=0.106).

CONCLUSION: The performance of the Charlson Comorbidity Index ≥ 2 , in-hospital onset, albumin < 2.5 g/dL, altered mental status, Eastern Cooperative Oncology Group performance status ≥ 2 , steroid use score in predicting in-hospital mortality for our study population is better than Glasgow-Blatchford score and similar to the the age, blood tests, and comorbidities score, the albumin, international normalized ratio; alteration in mental status, systolic blood pressure, and age 65 score, and Complete Rockall score.

KEYWORDS: Peptic ulcer hemorrhage. Upper gastrointestinal tract. Critical care. Gastrointestinal hemorrhage. Melena.

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is an important emergency with high mortality and morbidity rates^{1,2}. Despite the improvements in pharmacological and endoscopic treatments, the mortality rate in UGIB cases is estimated to be $2-10\%^{3.4}$.

An important issue for emergency department (ED) physicians is to determine hospitalization and intervention needs when an acute UGIB patient visits the ED. Nonvariceal UGIB guidelines recommend using risk scores to aid clinical decision-making^{5,6}. Conventional scoring systems for assessing the prognosis of patients with nonvariceal UGIB mainly include the Rockall score (RS); Glasgow-Blatchford score (GBS); the albumin, INR, alteration in mental status, systolic blood pressure, and age 65 (AIMS65) score; and age, blood tests, and comorbidities (ABC) score⁷⁻¹⁰.

In 2021, Matsuhashi et al. developed a new score called Charlson Comorbidity Index ≥ 2 , in-hospital onset, albumin < 2.5 g/dL, altered mental status, Eastern Cooperative Oncology Group performance status ≥ 2 , steroid use (CHAMPS) to predict mortality in nonvariceal UGIB patients¹¹. In that study, the CHAMPS score had a significantly higher discriminating ability from GBS, AIMS65, ABC score, and pre-endoscopic RS in predicting low-risk patients in nonvariceal UGIB patients¹¹. For this reason, they reported that it could

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on January 09, 2023. Accepted on January 10, 2023.

be a more effective score in terms of safe discharge. However, a study on the effectiveness of the new CHAMPS score in risk stratification or predicting mortality in different populations has not yet been presented.

The aim of this study was to evaluate the performance of the CHAMPS score in predicting in-hospital mortality in patients who visited the ED with nonvariceal UGIB and compare it with that of GBS, AIMS65, ABC score, and complete RS (CRS).

METHODS

This study was approved by the ethics committee of the research institution (date: 07.03.2022, protocol number: 2022/80). It was made in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived; however, informed consent about the risks of UGIB and all treatment modalities was obtained from all patients at their first visit. In addition, all individual information was securely protected and made available to researchers only. In addition, all data were analyzed anonymously. Finally, our report was organized by using the components of the STROBE checklist¹².

Study design

This single-center retrospective observational study was conducted involving patients diagnosed with nonvariceal UGIB in the ED of a tertiary training and research hospital. The hospital where the study was conducted is a center located in a region with a population of approximately 5 million, where endoscopy is performed on a 24-h basis and patients with suspected UGIB from other health centers in the region are referred.

Study participants

This study was carried out with adult patients diagnosed with nonvariceal UGIB who visited the ED of Bakırköy Dr. Sadi Konuk Training and Research Hospital between January 1, 2017, and March 1, 2022. Nonvariceal UGIB was defined as a disease confirmed by endoscopy with one of the following findings: vomiting of fresh blood, melena, or a decrease in hemoglobin levels of ≥ 2 g/dL from a prior examination. Exclusion criteria were as follows: (1) bleeding from the tumor, (2) bleeding after endoscopic resection, and (3) patients whose data were missing to calculate the relevant risk classification scores (Figure 1).

Data collection and definitions

All patients between the study dates were scanned from the electronic medical record system. The medical records of all patients diagnosed with nonvariceal UGIB were reviewed, and



Figure 1. Flowchart of the study.

data were recorded in the predesigned study form. Data collection in the form was as follows: patient demographics (age, gender, and comorbidity), symptoms of visiting ED (hematemesis, melena, syncope, and change in mentality), in-hospital/ out-of-hospital onset, cause of bleeding (gastric ulcer, duodenal ulcer, and others), vital symptoms (systolic blood pressure and pulse), blood test (hemoglobin, albumin, creatinine, blood urea nitrogen, international normalized ratio [INR]), drugs used (anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory drugs, steroids, and antisecretory agents), physical condition (Eastern Cooperative Oncology Group Performance Status [ECOG-PS]), comorbid conditions (Charlson Comorbidity Index [CCI]), and American Society of Anesthesiologists (ASA) score. Rebleeding was defined as vomiting of fresh blood at 7 days, bleeding with melena or hemodynamic instability, and was confirmed by endoscopy as recurrent episodes of bleeding from the same source. The primary outcome of this study was all-cause in-hospital mortality. The points of the predictive scores for each patient were calculated by two investigators blinded to the outcome.

CHAMPS score

The CHAMPS score is a simple equal-weight score, determined based on six variables (CCI ≥ 2 , in-hospital onset, albumin <2.5 g/dL, altered mental status, ECOG-PS ≥ 2 , steroid use); the maximum score is six points¹¹.

Statistical analyzes

Data were analyzed by using SPSS Statistics for Windows (version 23.0, SPSS Inc., Chicago, IL, USA) and MedCalc program (version 16.8.4; MedCalc Software, Mariakerke, Belgium). Whether the continuous variables were normally distributed or not was calculated by using the Kolmogorov-Smirnov test and histograms. Descriptive statistics were expressed as mean±standard deviation or median plus interquartile range (IQR), while categorical variables were expressed as numbers and percentages (%). Normally distributed data were compared with the Student's t-test, and non-normally distributed data were compared using the Mann-Whitney U test. The Pearson's chisquare test was used to compare categorical results (Table 1). The performance of the scoring systems for predicting outcomes was assessed by a receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was calculated, and the CHAMPS score was compared with those of four existing scores (GBS, CRS, AIMS65 score, and ABC score) using the DeLong test. According to the previous studies, the thresholds for low-risk patients were determined as $0, \leq 1, \leq 1$, ≤3, and 0 in the CHAMPS, GBS, AIMS65, ABC score, and CRS, and those for high-risk patients were determined as ≥ 3 , \geq 5, \geq 2, \geq 8, and \geq 5 in the five scores, respectively⁷⁻¹¹. The performance of the prediction scores was assessed to predict the low- and high-risk patients according to the specificities, sensitivities, negative predictive values (NPVs), positive predictive values (PPVs), and weighted accuracies (Table 2). p<0.05 was taken as the statistical significance level.

RESULTS

This study included 805 consecutive adult patients who met the eligibility criteria (Figure 1). The median age of the patients was 66 years (IQR: 51–80), and the female rate was 32.9% (n=265). The rebleeding rate was 9.1% (n=73), and the in-hospital mortality rate was 6.6% (n=53). The nonsurvivor group had a higher median age (76 years [IQR: 70–85] vs. 66 years [IQR: 50–80], p<0.001) and a higher rate of female patients (47.2 vs. 31.9%, p=0.022) than survivors. The characteristic features of the study population are shown in Table 1.

The CHAMPS, AIMS65, ABC score, GBS, and CRS classified patients as low risk at 26, 65.6, 59.3, 3.6, and 10.2%, respectively. In-hospital mortality rates in groups classified as low risk were calculated as 0, 20.8, 16.9, 0, and 0%, respectively. The CHAMPS, AIMS65, ABC, GBS, and CRS scores classified patients as high risk at 8.9, 34.4, 13.0, 89.1, and 49.2%, respectively. In-hospital mortality rates in groups classified as high risk were calculated as 30.6, 15.2, 22.9, 7.0, and 11.1%, respectively. The sensitivity, specificity, PPV, and NPV of the scoring system in predicting in-hospital mortality are shown in Table 2.

The CHAMPS score showed good performance in the prediction of in-hospital mortality in nonvariceal UGIB

patients with an AUC (95%CI) of 0.812 (0.783–0.839). The performance of the CHAMPS score was significantly superior to the GBS (AUC 0.683, 95%CI 0.650–0.713, p=0.008) and similar to the AIMS65 score (AUC 0.794, 95%CI 0.764–0.821, p=672), ABC score (AUC 0.829, 95%CI 0.801–0.854, p=0.563), and CRS (AUC 0.761, 95%CI 0.730–0.790, p=0.106).

DISCUSSION

The CHAMPS score has not been tested in UGIB patients except in Matsuhashi et al., and since our study is the first in this regard, it can be considered an external validation study in a sense¹¹. In our study, the CHAMPS score had a significantly better discriminating ability than GBS in predicting in-hospital mortality; however, there was no significant difference compared to the AIMS65 score, ABC score, and CRS. This new score, called CHAMPS, also outperformed other scores in identifying low-risk patients in the study population.

In our study, the percentage of patients in the low-risk group according to the CHAMPS score was lower than that in the study by Matsuhashi et al.¹¹. However, no mortality was observed in the patient group classified as low risk according to the CHAMPS score. The International Consensus Group suggests using a GBS of ≤ 1 to identify patients who are at very low risk of mortality and who can be considered for outpatient treatment⁶. In our study, no death was observed in patients classified as low risk according to GBS and CRS scores as well as CHAMPS score. However, a very small proportion of patients were classified as low risk by GBS and CRS. A higher proportion of patients were classified in the low-risk group of AIMS65 and ABC scores; however, the in-hospital mortality rate was higher in these groups when compared to other scores. For our study population, the low-risk classification of AIMS65 and ABC scores is not sufficient for safe discharge^{10,13}. Identifying low-risk patients with high accuracy is important for early discharge. This enables the physician to make a safe discharge decision, thereby reducing the burden on the emergency services and the health system¹⁴. For our study population, the CHAMPS score appears to be beneficial for safe discharge.

On the contrary, early recognition of high-risk patients requiring urgent hospitalization and intervention prevents delays in treatment, thus reducing morbidity and mortality¹⁵. In the high-risk patient group of the ABC score, which has the highest AUC value in this study, the in-hospital mortality rate was 22.9%, which is consistent with the literature^{10,16}. In our

Table 1. Descriptive statistics of study population in terms of in-hospital mortality.

| | All patients | Survivor | Nonsurvivor | p-value |
|-----------------------------------|----------------|----------------|----------------|---------|
| Demographic data | | | | |
| Age (years), median (IQR) | 66 (51-80) | 66 (50-80) | 76 (70-85) | < 0.001 |
| Sex: Female, n (%) | 265 (32.9) | 240 (31.9) | 25 (47.2) | 0.022 |
| Cause of nonvariceal UGIB, n (%) | l | | | |
| Gastric ulcer | 395 (49.1) | 367 (48.8) | 28 (52.8) | |
| Duodenal ulcer | 306 (38.0) | 293 (39.0) | 13 (24.5) | 0.031 |
| Others | 104 (12.9) | 92 (12.2) | 12 (22.6) | |
| Vital signs, mean±SD | | | | , |
| Systolic blood pressure (mmHg) | 121.6±18.0 | 122.7±17.1 | 104.6±22.0 | < 0.001 |
| Pulse (bpm) | 98.2±14.5 | 97.7±14.3 | 104.4±15.3 | 0.001 |
| Blood test, median (IQR) | | | | , |
| Hemoglobin (g/dL) | 9.0 (6.9–11.0) | 9.0 (7.0-11.0) | 8.4 (6.3-10.2) | < 0.001 |
| Albumin (g/dL) | 3.5 (3.0-3.9) | 3.5 (3.1-4.0) | 2.8 (2.3-3.4) | < 0.001 |
| Creatinine (mg/dL) | 0.9 (0.7-1.2) | 0.9 (0.7-1.2) | 1.2 (0.8-2.1) | < 0.001 |
| INR | 1.0 (0.9-1.2) | 1.0 (0.9-1.2) | 1.4 (1.2-1.8) | < 0.001 |
| Symptoms and signs | | | | |
| Melena | 686 (85.2) | 647 (86.0) | 39 (73.6) | 0.014 |
| Vomiting of fresh blood | 226 (28.1) | 202 (26.9) | 24 (45.3) | 0.004 |
| Syncope | 27 (3.4) | 21 (2.8) | 6 (11.3) | 0.001 |
| Altered mental status, n (%) | 30 (3.7) | 13 (1.7) | 17 (32.1) | <0.001 |
| Medication, n (%) | | | | |
| Anticoagulants | 121 (15.0) | 109 (14.5) | 12 (22.6) | 0.109 |
| Antiplatelet agents | 118 (14.7) | 107 (14.2) | 11 (20.8) | 0.194 |
| NSAIDs | 225 (28.0) | 210 (27.9) | 15 (28.3) | 0.953 |
| Steroids | 29 (3.6) | 24 (3.2) | 5 (9.4) | 0.018 |
| Antisecretory agents | 271 (33.7) | 214 (32.0) | 30 (56.6) | < 0.001 |
| Scoring system, median (IQR) | | | | |
| ASA, median (IQR) | 1 (0-3) | O (O-3) | 3 (2-4) | < 0.001 |
| ECOG-PS, median (IQR) | O (O-1) | O (O-1) | 2 (1-2) | <0.001 |
| CCI, median (IQR) | 4 (1-5) | 3 (1-5) | 6 (5-9) | <0.001 |
| CHAMPS score | 1 (0-2) | 1 (0-2) | 2 (2-3) | <0.001 |
| Glasgow-Blatchford score | 10 (7-12) | 10 (7-12) | 12 (9–15) | <0.001 |
| AIMS65 score | 1 (0-2) | 1 (0-2) | 2 (2-3) | <0.001 |
| ABC score | 3 (0-5) | 2 (0-5) | 7 (5-10) | < 0.001 |
| Complete Rockall score | 4 (3-6) | 4 (2-6) | 6 (5-8) | <0.001 |
| Rebleeding, n (%) | 73 (9.1) | 66 (8.8) | 7 (13.2) | 0.278 |
| Hospital stay (day), median (IQR) | 5 (5-6) | 5 (5-6) | 5 (5-7) | 0.116 |

ABC: age, blood tests, and comorbidities; AIMS65: albumin level <30 g/L (A), international normalized ratio >1.5 (I), altered mental status (M), systolic blood pressure ≤90 mmHg (S), and age >65 years (65); ASA: American Society of Anesthesiologists. CHAMPS: CCI ≥2, in-hospital onset, albumin <2.5 g/dL, altered mental status, ECOG-PS≥2, steroids; CCI: Charlson Comorbidity Index; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; INR: international normalized ratio; IQR: interquartile range; NSAIDs: nonsteroidal anti-inflammatory drugs, SD: standard deviation.

4

| | Cutoff value | Patients, n (%) | Mortality, n (%) | Sens. % | Spec. % | PPV, % | NPV, % | Weighted accuracy, % |
|-----------|-----------------|--------------------|---------------------|---------|---------|--------|--------|-------------------------|
| Low risk | | | | | | | | |
| CHAMPS | 0 | 209 (26.0) | 0 | 100 | 27.8 | 8.9 | 100.0 | 32.5 |
| AIMS65 | ≤1 | 528 (65.6) | 11 (2.1) | 79.3 | 68.8 | 15.2 | 97.9 | 69.4 |
| ABC score | ≤3 | 477 (59.3) | 9 (1.8) | 83.0 | 62.2 | 13.4 | 98.1 | 63.6 |
| GBS | ≤1 | 29 (3.6) | 0 | 100.0 | 5.7 | 7.0 | 100.0 | 11.9 |
| CRS | ≤1 | 82 (10.2) | 0 | 100.0 | 10.9 | 7.3 | 100.0 | 16.8 |
| High risk | | | | | | | | |
| CHAMPS | ≥3 | 72 (8.9) | 22 (30.6) | 41.5 | 93.4 | 30.6 | 95.8 | 89.9 |
| AIMS65 | ≥2 | 277 (34.4) | 42 (15.2) | 79.3 | 68.8 | 15.7 | 97.9 | 69.4 |
| ABC score | ≥8 | 105 (13.0) | 24 (22.9) | 45.3 | 89.2 | 22.9 | 95.9 | 86.3 |
| GBS | ≥5 | 717 (89.1) | 50 (7.0) | 94.3 | 11.3 | 6.9 | 96.6 | 16.8 |
| CRS | ≥5 | 396 (49.2) | 44 (11.1) | 83.0 | 53.2 | 11.1 | 97.8 | 55.2 |

Table 2. Predictive performance of scoring systems for in-hospital mortality.

ABC: age, blood tests, and comorbidities; CRS: Complete Rockall score; GBS: Glasgow-Blatchford score; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

study, GBS had the highest sensitivity in the high-risk group. Sensitivity for detecting high-risk patients is a critical outcome because it is important to avoid misclassifying high risk as low risk when making decisions about early discharge. However, it should be noted that a very high proportion of patients in this study were classified in the high-risk group of GBS. Another remarkable piece of data regarding the CHAMPS score in our study was the patients in the intermediate risk group with a rate of 65.1%. In this intermediate-risk group, which included the highest number of patients, the mortality rate was 0.6%. The article of Matsuhashi et al. does not offer any recommendations for the management of patients classified as intermediate risk based on the CHAMPS score. This uncertainty in the management of patients in the intermediate-risk group may be an important aspect that needs improvement for the CHAMPS score.

In our study, the CHAMPS score had a significantly better discriminating ability than GBS score, consistent with the study by Matsuhashi et al. GBS score showed lower performance in terms of AUC compared to all other scores. In a study by Ak and Hökenek, GBS showed poor performance in predicting mortality in patients with acute UGIB who visited the ED¹⁷. However, the GBS score is a score used to determine the need for treatment and was evaluated in our study in terms of mortality estimation due to its relatively poor performance. However, new scores are being developed to predict mortality in UGIB patients. Recently, Bai et al. in a study of patients with cirrhosis and acute gastrointestinal bleeding showed that the cirrhosis acute gastrointestinal bleeding score (CAGIB) outperformed the Child-Pugh, model for end-stage liver disease, and neutrophil-lymphocyte ratio¹⁸. The performance of the CAGIB score, which consists of comorbidity and laboratory data, can be tested or revised for patients with nonvariceal UGIB.

Our study has several limitations. It was a retrospective, single-center study, which may limit the generalizability of the results and lead to selection bias. We tried to minimize errors by collecting all medical records for nonvariceal UGIB patients. In the tertiary hospital where the study was conducted, although hospitalization and patient management are carried out according to the current American College of Gastroenterology Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding⁶, the patient management of clinicians may contain subjective decisions. Different treatment modalities may have affected the in-hospital mortality of the patients and thus the findings.

CONCLUSION

The CHAMPS score, which does not require endoscopy data, is a suitable classification score for use in the ED for risk stratification of nonvariceal UGIB patients. In our study population, it performed relatively well in identifying low-risk patients. It may facilitate the clinician in the management of low-risk patients in terms of early discharge. The performance of the CHAMPS score in predicting in-hospital mortality for our study population is better than GBS and similar to ABC, AIMS65, and CRS scores. There is a need to confirm the performance of the CHAMPS score in clinical practice with prospective studies in larger populations.

COMPLIANCE WITH ETHICAL STANDARDS

Health Sciences University Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee approved for the study (Date: 07.03.2022, protocol number: 2022/80). This article has not been previously presented at any event (congress, symposium, etc.).

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HUMAN RIGHTS

The principles set out in the Declaration of Helsinki were followed. The need for informed consent was waived due to the retrospective nature of the study.

AUTHORS' CONTRIBUTIONS

HA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Writing – review & editing. **GBB:** Conceptualization, Data curation, Supervision, Validation, Writing – review & editing. **MOE:** Methodology, Supervision, Validation, Writing – review & editing. **EG**: Data curation, Formal Analysis, Investigation, Writing – review & editing. **HD:** Investigation, Methodology, Supervision, Writing – review & editing.

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Factors affecting successful antituberculosis treatment: a single-center experience

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SUMMARY

OBJECTIVE: The identification of factors that influence a favorable antituberculosis treatment outcome could be of great use for the promotion of specific health actions to increase the success rate. Thus, the objective of this study was to investigate the factors affecting successful antituberculosis treatment in patients seen at a reference service in the Western region of São Paulo State/Brazil.

METHODS: A retrospective study was carried out from 2010 to 2016 based on the data obtained from the Notification Disease Information System of TB patients treated at a reference service in Brazil. The study included patients with treatment outcomes and excluded those from the penitentiary system or with resistant or multidrug-resistant TB. Patients were categorized as having a successful (cured) or unsuccessful (treatment default and death) treatment outcome. The association between TB treatment outcomes and social and clinical factors was analyzed.

RESULTS: A total of 356 cases of TB were treated between 2010 and 2016. Among the cases, the majority were cured and the overall treatment success rate was 85.96%, with a range between 80.33% (2010) and 97.65% (2016). After the exclusion of resistant/multidrug-resistant TB, 348 patients were analyzed. In the final logistic regression model analysis, education less than 8 years (OR 1.66; p<0.0001) and people living with human immunodeficiency virus/acquired immunodeficiency syndrome (OR 0.23; p<0.0046) were found to be significantly related to an unfavorable treatment outcome.

CONCLUSION: Low education and being a person living with human immunodeficiency virus/acquired immunodeficiency syndrome are vulnerability factors that can affect the successful outcome of antituberculosis treatment.

KEYWORDS: Tuberculosis. Antitubercular agents. Socioeconomic factors. HIV infections.

INTRODUCTION

Tuberculosis (TB) is still considered a major health problem worldwide. It is estimated that one-fourth of the global population is infected with the bacillus *Mycobacterium tuberculosis*, which is responsible for 1.3 million deaths¹. Brazil is considered one of the 22 countries, with the highest number of TB cases, an overall number of newly diagnosed patients of 95,000, and 4,800 estimated deaths, of which 1,900 were human immunodeficiency virus (HIV)-associated¹.

Besides the highest number of TB cases in Brazil, there was a considerable reduction in cases in the past years due to strategic programs to control TB. Among these, the National Tuberculosis Control Program established priority municipalities to implement actions to reduce TB incidence and mortality^{1,2}. The city of Presidente Prudente, which is located in the Western region of São Paulo State/Brazil, is considered one of the priority municipalities to control TB³. The average

TB incidence rate of this city was 41.05/100,000 inhabitants between 2007 and 2015⁴.

One of the strategic goals to eliminate TB is to increase the success rate of anti-TB treatment in the priority municipalities, which could be enhanced through the identification of factors that influence a favorable outcome, in order to guide the implantation of prevention health actions in the population. Thus, the objective of this study was to investigate the factors affecting successful anti-TB treatment outcomes in patients at a reference service in the Western region of São Paulo State/Brazil.

METHODS

Study design and setting

The city of Presidente Prudente, which is located about 560 km from the state capital São Paulo, is a mid-sized urban center.

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Conflict of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on January 17, 2023. Accepted on January 22, 2023.

According to the recent census, in 2019, the estimated population was 228,743 inhabitants, with a population density of 368.89 inhabitants/km^{2 5}.

A retrospective cross-sectional study was carried out based on the research of electronic data of patients with TB treated at the Tisiology Clinic of the Integrated Health Center of Presidente Prudente from 2010 to 2016. Patients with pulmonary and extrapulmonary TB were studied and divided according to the treatment outcomes.

The electronic data were obtained from the Notifiable Diseases Information System (SINAN), which is the Brazilian nationwide system responsible for notification, investigation, and, in the case of communicable diseases, follow-up and treatment⁶. Since we studied one single center, these specific data from SINAN were obtained with the staff of the Tisiology Outpatient Clinic of the Integrated Health Center of Presidente Prudente, which has exclusive access to the system and is responsible for uploading data from the patients attending the service.

Study groups

Patients were divided into two groups based on the treatment outcomes. The group with favorable treatment outcomes included patients defined as cured by the entry system. The unfavorable group brought together patients with an outcome of default, death from TB, and death from other causes.

In the SINAN, the TB outcomes are classified as follows: *Cure*: patients with two negative bacilloscopy, at any time of treatment and at the 5th or 6th month of treatment. For cases that need extension of the treatment time, the last 2 months will be considered. Discharge for cure will also be given to the patient who completed treatment without evidence of failure and was discharged based on the clinical and radiological criteria due to the impossibility of carrying out smear tests or culture; *Default*: patients who used the medication for 30 days or more and interrupted the treatment for more than 30 consecutive days; *Death by TB*; *Other causes of death* (died during TB treatment or another cause); and *MDR-TB/failure*⁶.

To understand the factors associated with the general population, patients belonging to the penitentiary system were excluded to obtain the data. Patients with resistant or multidrug-resistant TB (DR/MDR-TB), associated with the MDR-TB/failure outcome category, were also excluded after obtaining data because of the type of anti-TB treatment regimen.

Variables

The characteristics selected for the study were as follows: Sociodemographic: gender (male and female), age (\leq 19 years; 20–49 years; 50–69 years; \geq 70 years), skin color (white and non-white), education (<8 years and ≥8 years), and occupation (employed and unemployed); Clinics: bacteriological confirmation (no and yes) and bacilloscopy (negative and positive); Retreatment (no and yes); and Pulmonary form (no and yes). Patients diagnosed with both pulmonary and extrapulmonary TB were classified into the pulmonary TB group; Presence of cavitation (no and yes); Comorbidities: HIV/acquired immunodeficiency syndrome (AIDS) (no, yes, and unknown); Diabetes (no and yes); and Behavioral factors: Alcoholism (no and yes), Smoking (no and yes), and use of illegal substances (no and yes).

Data analysis

For data analysis, the multiple logistic regression model was used. For the selection of the explanatory variables used in the adjustment of the logistic regression model, it was considered an inclusion criterion that there was a relationship between the explanatory variable and the outcome variable based on the univariate analysis with a significance level of 25%⁷. Variables above this cutoff point were excluded from the final model. In this analysis, crude odds ratio values were also estimated with a 95% confidence interval. The entry order of the variables in the models was determined based on the value of the Wald chi-square test, followed by the odds ratio, found in the univariate analysis.

The R software was used to estimate the logistic model⁸. The stepwise procedure was used to adjust the models. The final model was defined according to the Akaike information criterion (AIC). For the purposes of the analysis, a significance level of p<0.05 was considered.

Ethical approval

The information was collected in the SINAN database of the Tisiology Clinic of the Integrated Health Center of Presidente Prudente. All variables that could identify the individuals were excluded, safeguarding the confidentiality of the identification data of each case. This work was approved by the Research Ethics Committee (protocol n° 48932315.6.0000.5515).

RESULTS

A total of 356 cases of TB were treated at the Tisiology Outpatient Clinic of the Integrated Health Center of Presidente Prudente between 2010 and 2016. Among the cases, the majority obtained cure, followed by treatment default, death by TB, death by other causes, and treatment failure. The overall treatment success rate was 85.96%, with a range between 80.33% (2010) and 97.65% (2016) (Table 1). Of these, eight were DR/MDR-TB, resulting in the inclusion of 348 patients to analyze the factors associated with the treatment outcomes (Table 1).

| Year | Total patients n | Cure n (%) | Default n (%) | Death by TB n (%) | Death by other causes n (%) | Failure n (%) |
|--|---------------------|---------------|------------------|----------------------|--|------------------|
| 2010 | 61 | 49 (80.33) | 5 (8.20) | 1 (1.64) | 6 (9.84) | 0 |
| 2011 | 49 | 43 (87.76) | 4 (8.16) | 0 | 2 (4.08) | 0 |
| 2012 | 69 | 60 (86.96) | 6 (8.70) | 3 (4.35) | 0 | 0 |
| 2013 | 51 | 43 (84.31) | 3 (5.88) | 2 (3.92) | 2 (3.92) 2 (3.92) 1 (3.92) 1 (2.27) 4 (9.09) 1 | 1 (1.96) |
| 2014 | 44 | 36 (81.82) | 3 (6.82) | 1 (2.27) | | 0 |
| 2015 | 41 | 35 (85.37) | 1 (2.44) | 2 (4.88) | 2 (4.88) | 1 (2.44) |
| 2016 | 41 | 40 (97.56) | 1 (2.44) | 0 | 0 | 0 |
| Total | 356 | 306 (85.96) | 23 (6.46) | 9 (2.53) | 16 (4.49) | 2 (0.56) |
| DR/MDR-TB patients excluded from the study | 8 | 6 (75) | 0 | 0 | 0 | 2 (25) |
| Total patients included in the study | 348 | 300 (86.21) | 23 (6.61) | 9 (2.59) | 16 (4.59) | 0 |

Table 1. Treatment outcomes and inclusion in the study of patients with tuberculosis followed at one reference service in Brazil, 2010–2016.

DR/MDR-TB: resistant or multidrug-resistant tuberculosis.

The distribution of the sociodemographic characteristics of the patients showed that most cases were male, aged 20–49 years, with white skin color and education less than 8 years, and employed. The evaluation of clinical characteristics showed that about half of the cases had bacteriological confirmation, with 137 cases of positive sputum smear microscopy. Among the patients with TB, only 25 cases were classified as retreatment, and there was a predominance of the pulmonary form of the disease, with 87 cases associated with cavitation. Regarding comorbidities, most patients were not associated with diabetes. Only 87.36% of the patients had a record for HIV/AIDS in their medical records, with the majority being negative for co-infection. Substance use evaluation demonstrated that most TB patients did not use alcohol, tobacco, or illicit substances (Table 2).

In the univariable analysis, education less than 8 years, people living with HIV/AIDS, and unknown HIV status were found to be significantly related to unfavorable treatment outcomes (Table 2). In the final logistic regression model analysis, education less than 8 years and people living with HIV/AIDS were found to be significantly related to unfavorable treatment outcomes (Table 3).

DISCUSSION

This study demonstrated that individuals with less than 8 years of schooling and living with HIV/AIDS are more likely to have an unfavorable outcome of anti-TB treatment.

The overall treatment success rate of this study was above the national rate of 72% in 2016⁹. Although there was an improvement in the service to achieve TB cure, the evaluation of factors associated with an unfavorable outcome of the anti-TB treatment could help build strategies to keep the high rate of cure.

Tuberculosis is a public health problem that is directly related to poverty and has been associated with low body mass index¹⁰. This could be due to more precarious living conditions, which include lower incomes and more limited access to health services, a common reality among the Brazilian black and "pardo" population¹¹. In Brazil, the "mixed" ethnic category is called "pardo", which means a mixture of European, black, and Amerindian¹². The Brazilian health indicators from 2014/2015 demonstrated that the black and "pardo" populations presented higher rates of TB incidence than those presented by the white population¹³. A Brazilian study demonstrated that the black population exceeded the average TB incidence rate in the general population more than three times¹².

The aforementioned precarious conditions could influence the level of education of TB patients. Low education can indicate a lower adherence to treatment, making it difficult to sterilize the bacilli, which facilitates their survival in a dormant form, suggesting that it would mask the effectiveness of the treatment¹⁴. Our results demonstrated an association between individuals who dropped out of the treatment and poor education, which agrees with other Brazilian studies¹⁴⁻¹⁶. A study with the Turkish population also demonstrated this association, highlighting the importance of educational actions for TB control¹⁷.

Other studies showed an association between other social characteristics and the unsuccessful anti-TB treatment outcome,

 Table 2. Univariate analysis of clinical and sociodemographic characteristics according to the treatment outcome of patients with tuberculosis followed at one reference service in Brazil, 2010–2016.

| Sociodemographic Gender (n=348) Male 188 (54.02) 35 (10.06) 1 Female 112 (32.18) 13 (3.74) 0.62 (0.31-1.21) | | |
|--|--------|--|
| Gender (n=348) Male 188 (54.02) 35 (10.06) 1 0.1721 Female 112 (32.18) 13 (3.74) 0.62 (0.31-1.21) 0.1721 | | |
| Male 188 (54.02) 35 (10.06) 1 0.1721 Female 112 (32.18) 13 (3.74) 0.62 (0.31-1.21) 0.1721 | | |
| Female 112 (32.18) 13 (3.74) 0.62 (0.31-1.21) 0.1721 | | |
| | | |
| Age (n=348) | | |
| ≤19 years 19 (5.46) 1 (0.29) 1 | | |
| 20-49 years 154 (44.25) 30 (8.62) 3.70 (0.72-67.75) 0.2105 | | |
| 50-69 years 101 (29.02) 8 (2.3) 1.50 (0.25-28.74) 0.7076 | | |
| ≥70 years 26 (7.47) 9 (2.59) 6.57 (1.09–126.57) 0.0858 | | |
| Skin color (n=332) | | |
| White 198 (59.64) 22 (6.63) 1 0.1 (20) | | |
| Non-white 95 (28.61) 17 (5.12) 1.611 (0.81-3.17) 0.1690 | | |
| Education (n=322) | | |
| <8 years 166 (51.55) 28 (8.70) 1 | | |
| ≥8 years 122 (37.89) 6 (1.86) 0.30 (0.11–0.68) 0.0081 | | |
| Occupation (n=341) | | |
| Unemployed 44 (12.91) 9 (2.64) 1 | | |
| Employed 253 (74.19) 35 (10.26) 0.68 (0.31–1.58) | | |
| Clinical | | |
| Bacteriological confirmation (n=348) | | |
| No 148 (42.53) 23 (6.61) 1 0 0 5 5 4 | | |
| Yes 152 (43.68) 25 (7.18) 1.06 (0.57–1.96) 0.8554 | | |
| Smear acid-fast bacilli (n=181) | | |
| Negative 38 (21.00) 6 (3.31) 1 | | |
| Positive 119 (65.75) 18 (9.94) 0.96 (0.37-2.79) 0.9325 | | |
| Retreatment (n=348) | | |
| No 278 (79.89) 45 (12.93) 1 | | |
| Yes 22 (6.32) 3 (0.86) 0.84 (0.19-2.56) 0.7875 | | |
| Pulmonary form (n=347) | | |
| No 71 (20.46) 11 (3.17) 1 | | |
| Yes 229 (66.00) 36 (10.37) 1.01 (0.50-2.18) | | |
| Cavitação (n=276) | | |
| No 165 (59.78) 24 (8.69) 1 | | |
| Yes 76 (27.54) 11 (3.99) 0.99 (0.45–2.09) 0.7877 | | |
| Comorbidities | | |
| HIV/AIDS(n-248) | | |
| No. 228 (69 20) 10 (5 46) 1 | | |
| $\frac{1}{10} \frac{1}{250(00.57)} \frac{17(3.40)}{17(3.45)} \frac{1}{120(1.88-9.54)} \frac{1}{10000}$ | | |
| Its 35 (10.00) 12 (3.45) 4.27 (1.00 7.54) 0.0003 Upknown 27 (7.76) 17 (4.88) 7.89 (3.66-17.08) <0.0001 | | |
| Diabetes (n=348) | - | |
| No 286(8218) 47(1351) 1 | | |
| $\frac{1}{100} \frac{1}{1000} \frac{1}{1000} \frac{1}{10000} \frac{1}{10000000000000000000000000000000000$ | | |
| Rebaviour factors If (F.02) I (0.27) 0.77 (0.02 2.24) | | |
| Alcoholism (n=348) | | |
| No 285 (81.9) 46 (13.22) 1 | | |
| Yes 15(431) 2(057) 0.83(013-306) 0.8039 | | |
| Smoking (n=348) | | |
| No 271 (77 87) 46 (13 22) 1 | | |
| Yes 29(8.33) 2(0.57) 0.41(0.06-1.41) 0.2290 | 0.2290 | |
| Illegal substance (n=348) | | |
| No 282 (81.03) 44 (12.64) 1 | | |
| Yes 18 (5.17) 4 (1.15) 1.42 (0.40-4.03) 0.5393 | | |

Bold indicates statistically significant p-values.

| Variables | OR _c | OR _a | 95%CI* | p† | p‡ | | | | |
|--------------------|------------------|-----------------|------------|---------|--------|--|--|--|--|
| HIV/AIDS (n=348) | HIV/AIDS (n=348) | | | | | | | | |
| No | 1 | 1 | | | | | | | |
| Yes | 4.29 | 1.66 | 0.53-4.73 | 0.3567 | 0.0001 | | | | |
| Unknown | 7.89 | 9.91 | 3.41-29.82 | <0.0001 | | | | | |
| Age (n=348) | | | | | | | | | |
| ≤19 years | 1 | 1 | | | | | | | |
| 20-49 years | 3.70 | 2.97 | 0.49-58.89 | 0.3296 | 0.1433 | | | | |
| 50–69 years | 1.50 | 0.88 | 0.12-18.47 | 0.9151 | | | | | |
| ≥70 years | 6.57 | 1.45 | 0.16-32.45 | 0.7669 | | | | | |
| Education (n=322) | | | | | | | | | |
| <8 years | 1 | 1 | | | | | | | |
| ≥8 years | 0.30 | 0.23 | 0.07-0.59 | 0.0046 | 0.0046 | | | | |
| Skin color (n=332) | | | | | | | | | |
| White | 1 | 1 | | | | | | | |
| Non-white | 1.611 | 1.57 | 0.69-3.58 | 0.2800 | 0.2800 | | | | |

Table 3. Final logistic regression model of clinical and sociodemographic characteristics according to the treatment outcome of patients with tuberculosis followed at one reference service in Brazil, 2010–2016.

OR_: crude odds ratio; OR_: adjusted odds ratio; 95%CI*: 95% confidence interval of adjusted odds ratio; p[†]: category p-value; p[†]: variable p-value.

such as male gender, age, and unemployment, as well as the influence of behavioral factors, such as the use of alcohol and illicit drugs, risks that did not show significance in our population^{15,16}. A study conducted in Finland demonstrated that death was the main reason for a non-successful outcome, justified by the advanced age of the study population¹⁸.

In our study, the only comorbidity that demonstrated the association with an unsuccessful anti-TB treatment outcome was HIV, a fact that has also been demonstrated by other authors, including the association with TB patients receiving antiretroviral drugs^{19,20}. A concerning fact was the lack of HIV status from some patients, evidencing that not all TB patients are being investigated for HIV coinfection. A study conducted in Nigeria demonstrated the association of not knowing HIV status with a higher chance of treatment failure¹⁹. It is recommended to conduct an anti-HIV test for all patients with TB because of its ability to change the clinical presentation of the disease, duration of treatment, tolerance to TB drugs, and resistance to available drugs²¹.

This study has the limitation of conducting a retrospective study of a single TB center which resulted in a reduced number of participants. The fact that we excluded patients belonging to the penitentiary system and that the treatment adherence was also not investigated could also be a bias to the distribution of the outcomes. Furthermore, the incompleteness of data available for each patient made other data analyses impossible.

CONCLUSION

Low education and being a person living with HIV/AIDS are vulnerability factors that can affect the successful outcome of anti-TB treatment. Health actions aimed at this group with social and medical support, focused on demystifying TB and better monitoring of patients, could contribute to the success of treatment.

AUTHORS' CONTRIBUTIONS

MCG: Data curation, Methodology, Writing – original draft. AASA: Data curation, Methodology. APB: Data curation, Methodology. PJMM: Data curation, Writing – review & editing. MVPR: Writing – review & editing. RLP: Formal Analysis, Writing – review & editing. EPL: Conceptualization, Data curation, Formal Analysis, Supervision, Writing – original draft, Writing – review & editing.

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The effect of psychological inflexibility on health-related quality of life, depression, and anxiety in patients with chronic tinnitus without hearing loss

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SUMMARY

OBJECTIVE: The purpose of this study was to investigate the relationship between psychological inflexibility, depression, anxiety, and quality of life in patients with chronic tinnitus without hearing loss.

METHODS: The study was carried out involving 85 patients with chronic tinnitus without hearing loss and a control group of 80 individuals. All participants completed the Acceptance and Action Questionnaire-II, the State-Trait Anxiety Inventory-Trait, the Beck Depression Inventory, and Short Form-36.

RESULTS: The patient group exhibited higher Acceptance and Action Questionnaire-II (t=5.418, p<0.001), State-Trait Anxiety Inventory-Trait (t=6.592, p<0.001), and Beck Depression Inventory (t=4.193, p<0.001) scores and lower physical component summary (t=4.648, p<0.001) and mental component summary (t=-5.492, p<0.001) scores than the control group. Psychological inflexibility predicted depression, anxiety, and impairment of quality of life. The effect of psychological inflexibility on physical component summary was mediated by depression (β =-0.15, [95%CI -0.299 to -0.017]), while its effect on mental component summary was mediated by anxiety and serial anxiety and depression (β =-0.17 [95%CI -0.344 to -0.055] and β =-0.06 [95%CI -0.116 to -0.100], respectively).

CONCLUSION: Psychological inflexibility plays an important role in patients with chronic tinnitus without hearing loss. It is associated with increased levels of anxiety and depression and decreased quality of life.

KEYWORDS: Tinnitus. Acceptance and commitment therapy. Depression. Anxiety. Quality of life.

INTRODUCTION

Tinnitus is defined as the perception of sound in the ear or head, with no identifiable external origin. The prevalence of tinnitus in the general adult population is between 11.9 and 30.3%¹. Tinnitus consists of not only a sensory component but also an emotional one reflecting discontent and associated distress². The presence of anxiety and depression in patients with tinnitus is associated with impairment of quality of life (QoL)³. While some studies have reported that tinnitus-related psychological stress is predominantly associated with anxiety, others have emphasized the role of depression, in particular, in triggering tinnitus-related psychological distress⁴. The audiological state most widely associated with tinnitus is subjective hearing loss, the presence of which contributes to impairment of QoL in patients with the condition⁵. Loss of hearing can significantly impact QoL and generally contributes to isolation, depression, and cognitive retardation⁶. This suggests that hearing problems affect the QoL in patients with tinnitus. Hearing difficulties appear to be a multilayered, confounding factor between tinnitus and QoL, as a result of both their frequent association with tinnitus and their effects at different stages. While there have been studies including psychometric assessments in patients with tinnitus, the number of studies of patients with tinnitus, but without hearing loss, is relatively low. Psychological inflexibility, a transdiagnostic concept, is defined as a pattern in which behavior is excessively controlled by the individual's thoughts, feelings, and other internal experiences or in which these are avoided at the expense of more effective and significant actions7. A few studies have shown a relationship between acceptance, one of the main components of psychological flexibility, and various QoL parameters in patients with tinnitus^{8,9}. However, hearing loss was not excluded in these studies. To the best of our knowledge, there has been no previous investigation of the effect of psychological inflexibility on QoL in patients with chronic tinnitus without hearing loss. The purpose of

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on November 06, 2022. Accepted on January 02, 2023.

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this study was to test the following hypotheses in patients with chronic tinnitus without hearing loss: that impaired QoL in patients is associated with anxiety (H1), depression (H2), and psychological inflexibility (H3), and that psychological inflexibility mediates the effect of anxiety (H4) and depression (H5) on QoL.

METHODS

Patients presenting with tinnitus symptoms to the Alanya Alaaddin Keykubat University Education and Research Hospital between June 01, 2018 and August 30, 2021 were included in the study. A control group was established consisting of volunteers similar to the patient group in terms of age and sex and not meeting any of the exclusion criteria. The study was approved by the Alanya Alaaddin Keykubat University clinical research ethical committee (decision no: 2018/26, dated April 13, 2018) and was conducted in accordance with the principles of the Declaration of Helsinki. Written consent was provided by all participants.

Participants

The study group consisted of individuals aged between 19 and 67 years with subjective idiopathic tinnitus and normal hearing. The control group consisted of volunteers with normal hearing and no tinnitus, matched to the study group in terms of age, sex, and mean hearing thresholds. The entire study group underwent detailed physical and ENT examinations, two-channel audiometry (Interacoustics AC40 Clinical Audiometer; Interacoustics AS, Assens, Denmark), standard with-head-phone conventional audiometry (TDH-39; Telephonics Co, Farmingdale, New York, USA), and impedance audiometry examinations. An A-type response was defined as normal at impedance audiometry¹⁰. The normal hearing sensitivity was defined as pure tone thresholds of 25 dB HL or better, at all frequencies studied in the 250 to 8,000 Hz range¹¹.

Exclusion criteria were abnormalities at ENT and/or audiometric examinations, drug use for tinnitus, recent ototoxic, diuretic, or chemotherapeutic agent use, acoustic trauma, vascular, metabolic, or ear diseases, vestibular diseases, hearing loss, or psychiatric diseases such as dementia and schizophrenia. Patients with organic tinnitus were also excluded from the study. Individuals with any psychiatric disease or hearing disorder were also excluded from the control group.

Instruments

Short Form-36 (SF-36): This 36-item test was developed for the measurement of QoL in clinical practice and research. Two summary scales, physical component and mental component, can be evaluated by calculating the scores obtained from the subdimensions. The scales are evaluated between 0 and 100, with higher scores indicating better QoL¹². Koçyiğit et al.¹³ performed the Turkish adaptation and validity and reliability study of SF-36.

Acceptance and Action Questionnaire-II (AAQ-II): This scale was developed by Bond et al⁷. The AAQ-II is a seven-point Likert-type scale with a single factor, consisting of seven items. High scores indicate high psychological inflexibility. The Turkish language version of the AAQ-II exhibits good internal consistency with a Cronbach's alpha of 0.84¹⁴. The internal consistency of the scale was calculated at 0.92 in this study.

Beck Depression Inventory (BDI): The BDI is a self-report scale consisting of 21 multiple-choice questions concerning the severity of depression¹⁵. Hisli¹⁶ carried out the Turkish validity and reliability study of the BDI. Higher scores indicate an increased depressive mood. The internal consistency of the scale was calculated at 0.89 in this study.

State-Trait Anxiety Inventory-Trait (STAI-T): Speilberg et al. developed this scale to measure state and trait anxiety¹⁷. Öner and Le Compte¹⁸ carried out the Turkish validity and reliability study of the scale. Higher scores obtained using the additional calculation method indicate high anxiety levels. The internal consistency of the scale was calculated at 0.79 in this study.

Statistical analysis

Statistical analyses were performed on the SPSS software (v. 22, SPSS, Chicago, IL, USA). The normality of distribution of variables was evaluated using skewness and kurtosis measurement, the values of which were regarded as normally distributed at a range of $\pm 2^{19}$. Multicollinearity was evaluated using variance inflation factor (VIF) values. Descriptive analyses were employed to assess the demographic variables and the mean scores for all variables. Differences between the tinnitus and control groups were compared using the t-test and χ^2 test. Pearson's correlation coefficients were calculated to investigate the relationships between AAQ-II, depression, anxiety, PCS, and MCS. The PROCESS macro (Model 6) on the SPSS software was used for mediation analysis. Two different models were established for the PCS and MCS outcome variables. Age, gender, and presence of chronic disease were controlled in both models. Significance tests for indirect effects were conducted using a 5,000-sample Bootstrap sampling and bias-corrected confidence levels set to 0.95. The effect was considered significant (p<0.05) if the upper and lower bounds of the 95% deviation-corrected confidence interval did not include zero²⁰.

RESULTS

The study was performed with 165 volunteers (85 patients and 80 controls). Seventy-eight (43.3%) participants were women. The mean age was 41.41(±11.41) years. No significant difference was observed between the patient and control groups in terms of sex (χ^2 =0.003, p=0.955) or age (t=1.396, p=0.165). Anxiety, depression, and psychological inflexibility scores were significantly higher in the patient group compared to the control group, whereas PCS and MCS scores were lower (Table 1). Cronbach's alpha values showed that the measurement tools were suitable for the study group. All psychological measurement parameters were significantly correlated with one another (Table 2). The VIF values were within an acceptable range (VIF=1.507-1.703).

In the model where PCS was the dependent variable, AAQ-II, BDI, and STAI-T explained approximately 39% of the variance in PCS (R²=0.394, F₍₆₋₇₈₎=8.441, p<0.001). The total AAQ-II effect (β =-0.32, p=0.002) and total indirect effect (β =-0.19, 95%CI -0.332 to -0.20) and its indirect effect via depression (β=-0.15, 95%CI -0.299 to -0.017) were found to be significant for the PCS variable. However, the indirect effect of the AAQ-II via STAI-T and STAI-T+BDI was not significant (β=-0.03 [95%CI -0.134 to 0.096] and β =-0.01 [95%CI -0.051 to 0.026], respectively). The effect

| Patient Control difference |
|----------------------------|
|----------------------------|

Table 1. Comparison between the patient and control groups.

| | /m_0E) /m_00) | | | | |
|--------|---------------|------------|--------|--------|------|
| | (0=05) | (11=60) | t | р | size |
| AAQ-II | 19.38±9.13 | 12.64±6.73 | 5.418 | <0.001 | 0.84 |
| STAI-T | 44.68±7.41 | 36.39±8.73 | 6.592 | <0.001 | 1.02 |
| BDE | 10.05±8.12 | 5.29±6.25 | 4.193 | <0.001 | 0.66 |
| PCS | 48.99±9.33 | 55.28±7.93 | -4.648 | <0.001 | 0.73 |
| MCS | 43.36±9.38 | 51.26±9.09 | -5.492 | <0.001 | 0.86 |

t-Test. "Cohen's d fo STAI-T: State-Trait PCS: physical com

0.52**

-0.31**

-0.52**

0.52**

-0.34**

-0.62**

| 6 | 5±9.38 | 51.26± | -9.09 | -5.492 | <0.001 | 0.86 | | | | | | | | |
|--------|--|--------|-------|--------|--------|------|-----|-----|-------|-------|--|--|--|--|
| p p | on MCS. However, depression alone does rt-tests.AAQ-II: Acceptance and Action Questionnaire-II, Anxiety Inventory-Trait, BDI: Beck Depression Inventory, ponent summary, MCS: mental component summary. | | | | | | | | | | | | | |
| | Tinni. | Dura. | AA | AQ-II | STAI- | т | BDI | PCS | Skew | Kurt | | | | |
| | | - | | | | | | | | | | | | |
| | 0. | 19 | | - | | | | | 0.42 | -0.62 | | | | |
| | 0. | 08 | 0. | .59** | - | | | | -0.35 | -0.45 | | | | |
| | 1 | | | | 1 | | | | | | | | | |

ect

Table 2. Correlat

0.12

0.09

-0.09

1. Tinni. Dura. 2. AAQ-II

3. STAI-S

4. BDE

5. PCS

6. MCS

of the AAQ-II on PCS lost its significance when STAI and BDI were included in the model (β =-0.13 p=0.31) (Table 3).

The variables included in the model in which MCS was the outcome variable explained approximately 45% of the variance in MCS (R²=0.453, F₍₅₋₇₉₎=13.118, p<0.001).

The analysis showed that AAQ-II had a significant negative effect on MCS (β =-0.46, p<0.001). In addition, the total indirect effect of the AAQ-II was also found to be significant (β=-0.30, 95%CI [-0.50 to -0.146]). While the indirect effect of AAQ-II via STAI-T and BDI+STA was significant (β =-0.17 [95%CI -0.344 to -0.055] and β=-0.06 [95%CI -0.116 to -0.100], respectively), its indirect effect via BDI was not significant (β=-0.07, [95%CI -0.186 to 0.024]). The effect of AAQ-II on MCS when all the variables were in the model was not significant (β =-0.16, p=0.11) (Table 3).

DISCUSSION

The most important finding of this study was the significant association between psychological inflexibility and health-related QoL, on both the MCS and PCS subscales, in patients with chronic tinnitus without hearing loss (H3). Impairment in both the physical and mental components of QoL increased in line with psychological inflexibility in the tinnitus patient group. Another important finding of this study is that depression (H5) and anxiety (H4) play a mediating role in the effect of psychological inflexibility on health-related QoL. The results of the study show that depression plays a mediating role in the effect of psychological inflexibility on PCS. Interestingly, anxiety did not mediate this effect. The presence of somatic depressive symptoms, such as sleep disorder, appetite changes, and loss of energy, may be associated with the mediatory effect on the physical component of QoL. Anxiety and anxietv-depression mediate the effect of psychological inflexibility not mediate this cal patient groups ession on PCS and

1.41

-0.88

-0.27

1.98

0.21

-0.15

0.92

0.79

0.89

0.74

0.72

Pearson's correlation test. **p<0.01. AAQ-II: Acceptance and Action Questionnaire-II; STAI-T: State-Trait Anxiety Inventory-Trait; BDI: Beck Depression Inventory; PCS: physical component summary; MCS: mental component summary; Skew: skewness; Kurt: Kurtosis; Tinni Dura: Tinnitus duration; α: Cronbach's alpha.

-0.48**

-0.46**

_

0.28**

3

| | ~~ | β | SE | р | 95%CI | |
|--------------------------|-----------------------|---------|------|--------|--------|--------|
| Mediation analysis for P | | | | | LLCI | ULCI |
| Total effect | AAQ-II→PCS | -0.32 | 0.10 | 0.002 | -0.515 | -0.118 |
| | Total (AAQ-II →PCS) | -0.19** | 0.08 | - | -0.332 | -0.020 |
| Indirect offects | AAQ-II→BDI →PCS | -0.15** | 0.07 | - | -0.299 | -0.017 |
| mairecteriects | AAQ-II →STAI-T→PCS | -0.03 | 0.06 | - | -0.134 | 0.096 |
| | AAQ-II→BDI→STAI-T→PCS | -0.01 | 0.02 | - | -0.051 | 0.026 |
| Direct effect | AAQ-II→PCS | -0.13 | 0.12 | 0.31 | -0.367 | 0.117 |
| Mediation analysis for M | ICS | | | | | |
| Total effect | AAQ-II→MCS | -0.46 | 0.10 | <0.001 | -0.664 | -0.264 |
| | Total (AAQ-II →MCS) | -0.30** | 0.09 | - | -0.503 | -0.146 |
| Indiract officiate | AAQ-II→BDI →MCS | -0.07 | 0.05 | - | -0.186 | 0.024 |
| indirect effects | AAQ-II→STAI-T→MCS | -0.17** | 0.07 | - | -0.344 | -0.055 |
| | AAQ-II→BDI→STAI-T→MCS | -0.06** | 0.03 | - | -0.116 | -0.010 |
| Direct effect | AAQ-II→MCS | -0.16 | 0.11 | 0.16 | -0.389 | 0.067 |

Table 3. Mediation analysis for physical component summary and mental component summary result variables.

**p<0.05 for 95%CI does not include zero. CI: confidence interval; AAQ-II: Acceptance and Action Questionnaire-II; STAI-T: State-Trait Anxiety Inventory-Trait; BDI: Beck Depression Inventory; PCS: physical component summary; MCS: mental component summary. Statistically significant results are shown in bold.

MCS varied depending on the diseases involved. The authors reported that anxiety and depression generally contributed to MCS more than PCS, whereas depression was predominantly effective on the PCS subscale of QoL²¹. Considering the results of previous studies, together with those of the present research, these suggest that anxiety and depression may represent a separate sphere of interest for different dimensions of QoL. In our study group, psychological inflexibility, anxiety, and depression explained 39% of the variance in PCS and 45% of that in MCS. Psychological symptoms, rather than audiological components, are reported to affect QoL in patients with tinnitus, with psychological parameters explaining 61% of the variance in QoL and audiological parameters explaining only 4%²². Consistent with previous research, this study shows the importance of psychological factors in the impairment of QoL in patients with tinnitus. In agreement with previous research, in this study, scale scores for depression and anxiety were significantly higher in patients with chronic tinnitus without hearing loss^{23,24}. A growing number of studies show the efficacy of acceptance and commitment therapy (ACT) aimed at reducing psychological inflexibility, by including patients with tinnitus²⁵. This study suggests that in addition to reducing symptoms in patients with tinnitus, ACT can also improve their QoL. Transdiagnostic processes may be defined as common processes underlying different disorders. Psychological inflexibility is a transdiagnostic concept explaining numerous psychopathological processes²⁶. The

comorbidity of depression and anxiety is not unusual. Anxiety and depression are also co-present in 39.2% of patients with tinnitus, and this comorbidity appears to make a negative contribution to adverse outcomes in QoL²⁷. The tendency for comorbid presentations to be associated with greater impairment of QoL increases the importance of targeting transdiagnostic structures, such as psychological inflexibility for individuals experiencing comorbid problems.

There are several limitations to this study. The first is that the severity of the patients' tinnitus was not measured. The type of tinnitus (such as pulsatile or constant) was also not recorded. The cross-sectional nature of the study also necessitates a cautious approach to inferring causality amid our results. Our method of including the participants in the study (consecutive patients diagnosed with tinnitus presenting to the ENT clinic) may also have led to selection bias. The possibility must be considered of greater admission to the hospital in the group with more severe tinnitus complaints, or suffering from this condition, or whose functionality is also affected. Our study group may therefore represent a more severe part of the tinnitus group seen in the general population.

CONCLUSION

This study shows the importance of depression and anxiety in the diminution of QoL in patients with chronic tinnitus without
hearing loss and also reveals the contribution of psychological inflexibility as a single factor affecting all these structures. When considering the high comorbidity rates among depression, anxiety, and tinnitus and the negative impact these comorbid conditions have on treatment, transdiagnostic processes remain an important area of a treatment goal.

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AUTHORS' CONTRIBUTIONS

TK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **CŞ:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – review & editing.

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Evaluation of descriptive performances of platelet indices, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio in aortic dissections

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SUMMARY

OBJECTIVE: Mechanical damage resulting from aortic dissection creates a thrombus in the false lumen, in which platelets are involved. Platelet index is useful for the function and activation of platelets. The aim of this study was to show the clinical relevance of the platelet index of aortic dissection. METHODS: A total of 88 patients diagnosed with aortic dissection were included in this retrospective study. Demographic data and hemogram and biochemistry results of the patients were determined. Patients were divided into two groups: deceased and surviving patients. The data obtained were compared with 30-day mortality. The primary outcome was the relationship of platelet index with mortality.

RESULTS: A total of 88 patients, 22 of whom were female (25.0%), diagnosed with aortic dissection, were included in the study. It was determined that 27 (30.7%) of the patients were mortal. The mean age of the entire patient group was 58±13 years. According to the DeBakey classification of aortic dissection of the patients, the percentages of the 1-2-3 type were determined as 61.4, 8.0, and 30.7%, respectively. Platelet index was not found to be directly related to mortality. Increase in age, decrease in bicarbonate value, and presence of diabetes mellitus were associated with mortality. **CONCLUSION:** Although there were no significant changes in platelet index in aortic dissection, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were found to be high in line with the literature. In particular, the presence of advanced age diabetes mellitus and decrease in bicarbonate are associated with mortality.

KEYWORDS: Aortic dissection. Lymphocytes. Neutrophils. Platelet activation.

INTRODUCTION

Aortic dissection (AD) is a highly mortal clinical condition that is most commonly seen in the seventh decade^{1,2}. According to the DeBakey classification, 75% of them are types 1 and 2³. Partial thrombosis in the false lumen is an independent predictor of mortality in patients³. Platelets are also blood components that play an active role in the thrombosis process, and it has been observed that platelets are activated in dissection patients^{4,5}. The association of PLT decrease and D-dimer elevation with in-hospital mortality in AD has been reported⁵⁻⁷. Tests evaluating platelet function and activation are both difficult and expensive. Values such as mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio, and platelet crit also provide information about platelet functions and are useful markers that can be accessed quickly and easily^{5,8}.

Budak et al. stated that C-reactive protein, known as an inflammatory marker, is parallel and related to dissection⁹.

In addition, leukocytes (WBC) in the blood are above normal values in AD and correlate with mortality, and the neutrophil/ lymphocyte ratio (NLR) has been reported to be significantly higher in AD¹⁰. In the active disease phase of ulcerative colitis, in the impaired glucose metabolism of diabetic patients, and in autoimmune inflammatory diseases such as Hashimoto's thyroiditis and euthyroid chronic autoimmune thyroiditis, the NLR value is high and correlated with the severity of the disease¹¹⁻¹⁴. The platelet/lymphocyte ratio (PLR) is an inflammatory index associated with poor outcomes and integrates risk estimation of PLTs and lymphocytes, reflecting the activation of both hemostatic and inflammatory pathways^{15,16}. The PLR value is higher in patients with hepatitis B-associated liver fibrosis and type 2 diabetes compared to healthy individuals^{17,18}. PLR and NLR values are increased in SARS-CoV-2-positive patients, patients with irritable bowel syndrome, and patients with malignant thyroid nodules compared to those with benign thyroid nodules¹⁹⁻²².

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

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Received on December 15, 2022. Accepted on December 27, 2022.

In line with the current information, the aim of this study was to evaluate the relationship between PI, NLR, and PLR values, which are available in the routine complete blood count, with mortality and morbidity in AD.

METHODS

This observational study was initiated after approval by the ethics committee of Ankara City Hospital No. 2 (E2-22-1693-13.04.2022). The study was carried out with the patients diagnosed for AD who were admitted to the emergency department between May 2019 and December 2021.

A form was prepared to collect the data from the patients. Data such as age, gender, comorbidities (diabetes mellitus [DM], hypertension [HT], and coronary artery disease [CAD]), and smoking history of the patients were recorded. Patients were divided into two groups: deceased and survivors.

Hemogram, biochemistry, and blood gas values were determined from intravenous blood samples taken from the patients. Hemogram results were studied on the Advia 2120 (Simens/Germany) device. Blood analyses were performed with Siemens atellica solution device (Simens/Germany). The blood gas parameters of the patients were analyzed using RAPIDLAB 1200 Series (Simens/Germany). Coagulation parameters were analyzed using the Sysmex cs-5100 (Simens/Germany) instrument. AD diagnoses of the patients were made with a contrast-enhanced thoracoabdominal computed angiography 64-slide spiral GE/Revolution CT (General Electric/USA) tomography device in the aortic phase. DeBakey criteria were used for AD classification.

The data of the patients were compared with their 30-day mortality. All parameters were compared in two groups: mortal (group 1) and nonmortal (group 2). Hospital automation system (HiCamp) and examination forms were used for the data acquisition.

The primary outcome of the study was the association of PI values with mortality. Another outcome was the association of NLR and PLR values with mortality.

Statistical analysis

Analysis was carried out with IBM SPSS Statistics 20.0 for Windows. The Shapiro-Wilk test was used for normality analysis. The non-normally distributed data were expressed with median and 25–75% quartiles, and normally distributed data were expressed as mean and standard deviation. The comparisons between the two groups were made using the independent samples t-test and the Mann-Whitney U test. Ratio comparisons in categorical data were performed using chi-square tests. Logistic regression analysis was used to determine mortality predictors. The p<0.200 level was used for the parameters to be included in the multiple logistic regression analysis. In the final step, age, DM, and HCO3 parameters were included in the analysis with the backward elimination method. A ROC analysis was then performed for age and HCO3. A p-value of <0.05 was accepted as statistically significant.

RESULTS

Out of 113 patients, 25 were excluded from the study due to a lack of data. A total of 88 patients diagnosed with AD, of whom 22 (25.0%) were female, were included. It was determined that 27 (30.7%) of the patients were mortal. Demographic characteristics, laboratory parameters, and the AD classification of the patients were compared between the two groups formed according to the 30-day mortality data (Table 1). Age, diabetes, creatinine, INR, HCO3, and the DeBakey class were found to be associated with mortality in terms of the p<0.05 level. No difference was observed in other parameters in the mortal group (Table 1).

In univariate analysis, parameters with p-values <0.200 were determined as age, gender, presence of diabetes, GFR, potassium, AST, ALT, amylase, lipase, pH, HCO3, troponin, fibrinogen, and DeBakey type. Troponin and fibrinogen parameters were not included in the continuation of the analysis, as there were intolerably missing data. In summary, it was determined that parameters of age, presence of diabetes, and HCO3 were found to be independent predictors for mortality (Table 2).

In ROC analysis, the area under the curve was found to be 0.726 (0.572–0.841; p=0.001) for age and 0.707 (0.621–0.830; p=0.003) for HCO3. For individuals aged 52 years, sensitivity and specificity were 92.59 and 44.26%, respectively. For individuals aged 57 years, sensitivity and specificity were 81.48 and 54.10%, respectively. At the level of 21.4 in the HCO3 parameter, sensitivity and specificity were detected as 64.00 and 79.31%, respectively. ROC curves for "age" and "HCO3" are shown in Figure 1.

DISCUSSION

It has been reported that predictors such as advanced age, female gender, smoking, renal dysfunction, and hypotension are associated with increased mortality and morbidity in terms of poor clinical outcomes in AD patients³. In this study, we concluded that advanced age, low HCO3,

Table 1. All parameters in two groups.

| | Groups (30-day mortality) | | | | |
|-------------|-------------------------------|-----------|-------------------------------|-----------|--------------------|
| Darameters | Survival | | Mortal | | n-value |
| | Mean±SD or Median (25–75%) | n (%) | Mean±SD or Median (25–75%) | n (%) | p-value |
| Age (years) | 55±12 | | 65±10 | | <0.001* |
| Gender | | | | | |
| Male | | 49 (74.2) | | 17 (25.8) | 0.000 |
| Female | | 12 (54.5) | | 10 (45.5) | 0.083† |
| DM | | 5 (35.7) | | 9 (64.3) | 0.009‡ |
| HT | | 44 (69.8) | | 19 (30.2) | 0.866† |
| CAD | | 24 (64.9) | | 13 (35.1) | 0.440† |
| Smoker | | 24 (70.6) | | 10 (29.4) | 0.838† |
| WBC | 12.47 (9.43-14.85) | | 11.65 (8.96-15.92) | | 0.762 [§] |
| Hb | 13.4 (12.1-15.1) | | 14.3 (11.9-15.5) | | 0.450§ |
| Hct | 40.8±6.1 | | 41.8±6.5 | | 0.478* |
| Neu | 8.75 (6.92-10.82) | | 8.92 (5.55-13.41) | | 0.978§ |
| Lymphocyte | 1.7 (1.19-2.53) | | 1.82 (0.98-2.38) | | 0.697§ |
| PLT | 234 (188-304) | | 252 (153-317) | | 0.717§ |
| NLR | 4.83 (3.24-8.05) | | 6.03 (2.15-10.46) | | 0.776§ |
| PLR | 136.9 (91.4-205.1) | | 143.4 (75.4-182.1) | | 0.741 [§] |
| MPV | 8.1 (7.4-8.9) | | 8.1 (7.5-8.5) | | 0.807§ |
| Urea | 35 (30-45) | | 41 (34-57) | | 0.185§ |
| Creatinine | 0.92 (0.8-1.12) | | 1.11 (0.9-1.43) | | 0.016§ |
| GFR | 90 (67-99) | | 64 (40-80) | | <0.001§ |
| Na | 139.4±3.4 | | 139±2.9 | | 0.603* |
| К | 3.9 (3.7-4.5) | | 4.2 (3.8-4.9) | | 0.128§ |
| CI | 106 (102-108) | | 106 (104-109) | | 0.438§ |
| AST | 26 (19-40) | | 28 (19-58) | | 0.180§ |
| ALT | 27 (17-35) | | 22 (17-48) | | 0.835 [§] |
| LDH | 292 (233-345) | | 308 (245-427) | | 0.375 [§] |
| Amylase | 56 (46-69) | | 65 (47-80) | | 0.172§ |
| Lipase | 31 (25-39) | | 32.5 (27-45) | | 0.278§ |
| pН | 7.401 (7.36-7.458) | | 7.37 (7.334-7.42) | | 0.090§ |
| HCO3 | 24.12±3.86 | | 20.46±5.28 | | 0.001* |
| Lactate | 2.36 (1.4-3.79) | | 2.76 (1.86-4.68) | | 0.274§ |
| Blood group | | | | | |
| А | | 26 (68.4) | | 12 (31.6) | |
| В | | 9 (69.2) | | 4 (30.8) | 0.004 |
| 0 | | 17 (65.4) | | 9 (34.6) | 0.834+ |
| AB | | 9 (81.8) | | 2 (18.2) | |
| Rh | | | | | |
| + | | 54 (69.2) | | 24 (30.8) | 1.000+ |
| - | | 6 (66.7) | | 3 (33.3) | 1.000+ |
| INR | 1.1 (1.1-1.2) | | 1.2 (1.1-1.4) | | 0.039§ |
| aPTT | 26.4 (23.9-30.2) | | 28.5 (24.5-31.4) | | 0.338§ |
| D-dimer | 5.56 (2.11-23.54) | | 11.03 (7.26-23.06) | | 0.296⁵ |
| Troponin | 18.03 (6-37) | | 10 (5-115) | | 0.772⁵ |
| Fibrinogen | 3.75±1.75 | | 2.68±1.72 | | 0.063* |
| CRP | 0.037 (0.010-0.114) | | 0.020 (0.006-0.069) | | 0.450§ |
| DeBakey | | | | | |
| 1 | | 36 (66.7) | | 18 (33.3) | |
| 2 | | 2 (28.6) | | 5 (71.4) | 0.012‡ |
| 3 | | 23 (85.2) | | 4 (14.8) | |

*Independent samples t-test; mean±standard deviation. †Pearson chi-square test; n (%). ‡Fisher's exact test; n (%). §Mann-Whitney U test; median (25–75% quartiles).

3

and the presence of diabetes are independent predictors of mortality.

It has been previously reported that platelets are activated as a result of thrombosis occurring in the false lumen in dissections^{5,6}. MPV and PDW are also platelet activation markers²³. In our study, we could not detect a statistically significant relationship on mortality in AD. However, it was drawing an upward graph in both values close to the reference upper limits. The reason for this is that platelet agglutination is caused by waiting for blood in hemogram tubes with EDTA. Since this is a retrospective study and the study period of blood may be long, our PI may have been affected. This may have caused the PIs to be monitored within normal reference ranges. In addition, we may not have seen dramatic increases in PDW and MPV values because AD is an acute and rapidly developing clinical condition and there is no enough time for new platelet production.

In AD patients, CRP increases with inflammation and correlates with Ischemia markers. In addition, WBC values in AD patients are higher than normal, and this has been reported to be associated with increased mortality²⁴. Our CRP and WBC

| | | В | Sig. | Exp(B) |
|----------|-------------|--------|-------|----------------------|
| Step 10ª | Age | 0.099 | 0.006 | 1.104 (1.029–1.184) |
| | DM (if yes) | 2.118 | 0.010 | 8.316 (1.646-42.016) |
| | HCO3 | -0.260 | 0.001 | 0.771 (0.659-0.902) |
| | Constant | -0.327 | 0.898 | 0.721 |

Table 2. Multiple logistic regression analysis for 30-day mortality.

^aVariable(s) entered on step 1: Age, gender, DM, GFR, K, AST, ALT, amylase, lipase, pH, HCO3, DeBakey. values were similarly high, but were relatively lower in the mortal group, although not statistically significant.

In a study by Bedel et al., including 96 patients with type A AD, NLR and PLR values were significantly increased in patients with type A AAD, and the best NLR threshold value to predict in-hospital mortality was 9.74 with 70.6% sensitivity and 76.8% specificity. They reported that the PLR threshold value was 195.8 with a sensitivity of 76.5% and a specificity of 78.1%²⁵. As it is known, WBC subtypes and NLR are frequently compared and evaluated in many clinical situations. It has been previously reported that the NLR value is significantly higher in AD patients. In our study, the rate of NLR increased in mortality and surviving groups, but this difference was not statistically significant and was incompatible with the literature²⁶.

Sbarouni et al., like Bedel et al., have reported that the PLR rate is significantly higher in ADs. It has a significantly specific and low sensitivity in estimating AD and can be used in the exclusion of AD¹¹. The fact that PLR is both inexpensive and easily available makes it more useful. In our study, PLR values did not show a statistically significant relationship between the mortal and nonmortal groups. It was also found in other studies that the PLR value increased with adverse events associated with negative outcomes in the hospital^{11,23}. In our study, it was observed that the PLR values were increasing, but we concluded that there was no statistically significant difference between the mortal and the nonmortal groups.

The most important limitations are that it is a retrospective study, and the conditions under which the blood was taken



Figure 1. ROC curves for age and HCO3.

from the patients and the laboratory admission and procedure times are not standard.

CONCLUSION

No statistically significant changes were observed in PI, NLR, and PLR values in the mortal group of AD patients, which is not compatible with the literature. However, age, presence of diabetes, and HCO3 were determined as independent mortality

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predictors for AD. More robust results can be obtained with prospective studies with a larger sample.

AUTHORS' CONTRIBUTIONS

SD: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **ABE:** Formal Analysis. **AŞ:** Formal Analysis. **GKÇ:** Formal Analysis. **SÖ:** Formal Analysis. **ST:** Formal Analysis.

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Evaluation of the relationship between monocyte to high-density lipoprotein cholesterol ratio and thrombus burden in patients with deep vein thrombosis

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SUMMARY

OBJECTIVE: The purpose of this study was to evaluate monocyte count and high-density lipoprotein cholesterol levels and their ratio (monocyte/ high-density lipoprotein ratio) in patients with deep venous thrombosis as well as to determine whether this ratio at the time of diagnosis can be an indicator of thrombus burden in terms of thrombus location in deep venous thrombosis.

METHODS: We retrospectively analyzed the patient's diagnosis of deep venous thrombosis confirmed with venous Doppler ultrasound, using a database query for outpatients between 2018 and 2022. Of 378 patients included, blood count results at the time of diagnosis were available for 356. We recruited 300 age- and sex-matched patients with appropriate blood counts, without a diagnosis of deep venous thrombosis, as the control group, by querying the outpatient clinic database. The monocyte/high-density lipoprotein ratio was computed from the ratio of monocyte count to high-density lipoprotein-C. Patients were categorized based on the level of thrombus and the number of vein segments involved as evidenced by Doppler ultrasound findings.

RESULTS: The serum level of monocyte/high-density lipoprotein ratio was significantly higher in the patient group compared to the control group (p<0.01). Patients with proximal deep venous thrombosis had a higher mean monocyte/high-density lipoprotein ratio (19.6±5.1 vs. 17.1±5.5; p<0.01) than patients with distal deep venous thrombosis. Monocyte/high-density lipoprotein ratio increased with the number of vein segments involved (p<0.01). **CONCLUSION:** Monocyte/high-density lipoprotein ratio is significantly elevated in patients with deep venous thrombosis when compared to the control group. Monocyte/high-density lipoprotein ratio levels were correlated with disease burden reflected by thrombus location and the number of vein segments involved in deep venous thrombosis patients.

KEYWORDS: Venous thrombosis. Cholesterol, HDL. Monocytes.

INTRODUCTION

Deep venous thrombosis (DVT) is the third leading vascular problem globally¹, and evidence of its association with inflammation is increasing²⁻⁶. In patients with acute DVT, several inflammatory markers were shown to be at increased levels⁶⁻⁸. Whether the relationship with increased inflammation is causal to or a result of DVT is under dispute, but it is apparent that a state of increased inflammation is present in patients with DVT at the time of diagnosis.

In current clinical practice, high-sensitivity C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most widely used inflammatory markers^{9,10}. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are calculated from the white blood cell count, are reported to be novel inflammatory biomarkers in patients with venous thrombosis¹¹. Decreased high-density lipoprotein cholesterol (HDL-C) levels and increased monocyte counts were also found to be associated with inflammation, and the monocyte to HDL-C ratio (MHR) was suggested to be used as a novel inflammatory biomarker^{12,13}. HDL-C has a protective effect against low-density lipoprotein (LDL) oxidation and monocyte activation¹⁴⁻¹⁶. MHR was reported to be a new cardiovascular prognostic marker in chronic kidney disease¹³. The MHR is also associated with coronary artery disease (CAD) severity and complexity in stable CAD¹⁷.

To the best of our knowledge, no study has evaluated the association of MHR with venous thrombotic events. Therefore, the objective of this study was to determine whether MHR, calculated at the time of diagnosis, can be an indicator of thrombus burden in terms of thrombus location and the number of vein segments involved in DVT patients.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none. Received on December 30, 2022. Accepted on January 08, 2023.

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METHODS

We retrospectively analyzed patients with a diagnosis of DVT, using a database query for outpatients at our referral center between 2018 and 2022. This study was approved by the hospital's review board, and the study was carried out in accordance with the Declaration of Helsinki. Patients whose diagnosis of acute DVT was confirmed with venous Doppler ultrasound in the records were included. Patients with known prior DVT or signs of chronic thrombus on Doppler ultrasound screening were excluded. Of 378 patients included, blood count results at the time of diagnosis were available for 356. We recruited 300 age- and sex-matched patients with appropriate blood counts, without a diagnosis of DVT, as the control group, by querying the outpatient clinic database (Figure 1). The basic demographic and clinical characteristics (i.e., age, sex, hypertension, diabetes mellitus, smoking, and heart diseases) were recorded. Evaluation of the association of MHR with DVT at the time of diagnosis was performed for patients with blood counts at the index visit.

The standard ultrasound screening protocol included all deep and superficial lower extremity veins, including the external iliac veins, with compression, followed by a color and spectral Doppler ultrasound evaluation of filling and flow patterns. Higher portions of the external iliac vein and the common iliac vein were evaluated as much as permitted by the patient's anatomy.



Figure 1. Receiver operating characteristic curve of the monocyte to high-density lipoprotein ratio for predicting thrombus localization in patients with deep venous thrombosis. AUC: area under the curve; CI: confidence interval.

MHR at the time of diagnosis was calculated for each patient from standard blood cell counts. Patients were grouped based on the location of venous thrombus visualized by Doppler ultrasound as iliac, femoral, popliteal, or crural. When thrombus was located in more than one segment, categorization followed the highest of the segments. Crural veins included anterior tibial, posterior tibial, and peroneal veins along with gastrocnemius and soleal veins. Groups were compared for MHR of corresponding patients. Thromboses were categorized as distal DVT in the crural or popliteal veins and as proximal DVT in femoral or iliac veins to facilitate receiver operating characteristic (ROC) curve analysis used to determine the discriminatory ability of MHR for thrombus location. The extent of thrombus was evaluated with the number of vein segments with thrombus detected by Doppler ultrasound in an additive fashion.

Statistical methods

The SPSS 21.0 for Windows was used for statistical analyses (SPSS, Chicago, IL). Besides descriptive statistics, Student's t-test and one-way analysis of variance (ANOVA) were used to compare groups for quantitative data. The Tukey test was used for post hoc analysis of ANOVA results. ROC curves were used to determine a cutoff value for variables. Significance was set at p<0.05.

RESULTS

As a result of our database query, 378 patients were identified with a diagnosis of DVT between 2018 and 2022 confirmed with venous Doppler ultrasound. Of 378 patients included, blood count results at the time of diagnosis were available for 356. We recruited 300 age- and sex-matched patients with appropriate blood counts, without a diagnosis of DVT, as the control group, by querying the outpatient clinic database. The baseline demographic and laboratory features of both two groups are given in Table 1. Both study groups were similar with regard to age, sex, BMI, diabetes mellitus, hypertension, previous history of CAD, and smoking habits. Serum levels of MHR were significantly higher in the patient group when compared to the control group (p<0.01).

Patients were separated into four groups (i.e., iliac, femoral, popliteal, and crural) based on the anatomic location of venous thrombus. MHRs of 356 patients with blood count results were calculated and compared across groups. The results of group comparisons are given in Table 2A. For MHR, there was a statistically significant difference between groups as determined by one-way ANOVA (p<0.010). To evaluate the discriminatory value of MHR for thrombus location, the four anatomic

locations were classified as proximal (iliac and femoral) or distal (popliteal or crural). MHR was then compared between proximal and distal DVT classifications. Proximal DVT was found to have higher means of MHR than that of distal DVT (p<0.010) (Table 2A). MHR was compared in terms of the number of segments involved in DVT. MHR in those with three and four segments involved was observed to be higher than those with one and two segments involved (Table 2B). We used ROC curves to investigate whether MHR (Figure 1) could be used to predict thrombus localization. The area under the curve is 0.688 (95% confidence interval, 0.641–0.733; p<0.001). The

cutoff value of MHR for the diagnosis of proximal DVT was 16.8 with a sensitivity of 60.5% and a specificity of 69.6%.

DISCUSSION

Our study showed that MHR is significantly elevated in patients with DVT when compared to the control group. Therefore, elevated MHR levels may be a useful marker for the assessment of DVT development.

There is growing evidence that inflammation plays a role in the pathophysiology of DVT¹⁸. Elevated levels of CRP and

| Table 1. Baseline demographic and | laboratory characteristics of both | n patient and control groups. |
|-----------------------------------|------------------------------------|-------------------------------|
|-----------------------------------|------------------------------------|-------------------------------|

| Parameters | Patient group (n=356) | Control group (n=300) | p-value | |
|---------------------------|-----------------------|-----------------------|---------|--|
| Demographic parameters | | | | |
| Age, years | 55.14±9.4 | 54.71±9.5 | 0.52 | |
| Gender (male/female) | 207/149 | 168/132 | 0.62 | |
| Hypertension, n (%) | 78 (21.9%) | 70 (23.3%) | 0.73 | |
| Diabetes mellitus, n (%) | 32 (8.9%) | 33 (11.0%) | 0.41 | |
| Smoker, n (%) | 155 (43.5%) | 126 (42.0%) | 0.80 | |
| History of CAD, n (%) | 49 (13.7%) | 45 (15.0%) | 0.69 | |
| Laboratory parameters | | | | |
| Monocyte (×10º/L) | 604±198.6 | 420.4±120.1 | <0.01 | |
| HDL (mg/dL) | 33.9±8.2 | 43.3±11.9 | <0.01 | |
| LDL (mg/dL) | 116±31.6 | 123.1±37.2 | 0.34 | |
| TG (mg/dL) | 140±75.1 | 131±47.5 | 0.21 | |
| Total cholesterol (mg/dL) | 195.2±42.4 | 191.3±41.0 | 0.28 | |
| MHR | 18.3±4.6 | 10.4±5.2 | <0.01 | |

Bold indicates statistically significant p-values.

Table 2A. Monocyte to high-density lipoprotein-C ratio based on the thrombus location.

| Ratio | lliac (n: 56) | Femoral (n: 185) | Popliteal (n: 92) | Crural (n: 23) | p-value |
|-------|-------------------|------------------|-------------------|----------------|---------|
| MHR | 19.8±5.4* | 19.2±4.9** | 17.6±4.4*** | 17.3±5.8 | <0.010 |
| | Proximal (n: 241) | | Distal (n: 115) | | |
| MHR | 19.6 | ±5.1 | 17.1±5.5 | | <0.010 |

*Iliac vs. Femoral p<0.05; and vs. Popliteal and vs. Crural p<0.010; **Femoral vs. Popliteal and vs. Crural p<0.010; ***Popliteal vs. Crural p>0.05.

Table 2B. Monocyte to high-density lipoprotein-C ratio based on the number of affected venous segments.

| | Number of segments with thrombus | | | | |
|-----|----------------------------------|----------|----------|----------|--------|
| | 1 | 2* | 3** | 4*** | p p |
| MHR | 17.8±4.3 | 17.7±4.7 | 19.4±5.8 | 20.1±5.2 | <0.010 |

***4 vs. 3 p<0.05 and vs. 2 and vs. 1 p<0.010; **3 vs. 2 and vs. 1 p<0.05; *2 vs. 1 p>0.05.

interleukin (IL)-6 at the time of diagnosis have been linked to increased inflammation, DVT severity, and thrombus location at the femoral and iliac sites⁶. Low levels of CRP were also found to be useful as a negative predictor in DVT¹⁹, and plasma levels of IL-6, IL-8, and CRP were higher in patients with newly diagnosed DVT²⁰. The release of tissue factors caused by inflammatory cytokines has been linked to the thrombosis cascade's initial event, which is vein wall inflammation². Increased levels of inflammatory mediators following surgery can also be blamed for the higher frequency of VTE during the immediate postoperative period. This could also be the reason why DVT is linked to conditions including sepsis, CMV, influenza, chlamydia, and other infections, as well as inflammatory bowel disease, obesity, rheumatological disorders, and cystic fibrosis^{2,21}. All these pathological processes and other well-known risk factors of DVT are associated with an inflammatory state³. As inflammation is involved in both thrombus formation and its clearance, it is still unclear whether this link is causal or a consequence².

Moreover, MHR was investigated as a new inflammation biomarker and considered superior to subtypes of white blood cells (WBCs) in patients with cardiovascular and cerebrovascular diseases^{12,13,22-26}. Monocytes are the indicators of inflammatory reactions because they are responsible for the secretion of proinflammatory and prooxidant cytokines²⁷. On the contrary, HDL cholesterol has antioxidant and anti-inflammatory effects such as reducing macrophage accumulation, inhibiting the transmigration of monocytes, increasing the expression of nitric oxide synthase in endothelial tissues, and protecting the endothelial cells²⁸.

Based on our findings, MHR increased in DVT patients with a higher location of thrombus. Patients with iliac or femoral vein thromboses had statistically higher MHR compared with patients with distal DVT. Differentiation cannot be made as to whether the environment of increased inflammation was present before the onset of the disease and caused the thrombus or whether it was a response to the thrombus forming within the vein. Regardless of the direction of the relationship, the findings point to an elevated level of inflammation with a higher thrombus location in DVT. Similarly, our results showed an increase in MHR, albeit partially proportional to the number of vein segments with thrombus, signifying an increased inflammation associated with the extent of thrombus. Other inflammatory markers including D-dimer, soluble P-selectin, and CRP were investigated by Vandy et al.²⁹, who demonstrated an increase in these biomarkers with the extent of thrombus in the vein segments of the lower extremity. These findings together suggest an elevated state of inflammation with increased thrombus severity.

MHR is a marker of inflammation that is inexpensive, ubiquitous, and easy to interpret. We performed an ROC curve analysis to assess whether the increased MHR value at the time of diagnosis can provide predictive information for the thrombus location. The area under the curve for MHR was 0.688, and the sensitivity and specificity of the calculated cutoff scores were not sufficiently high (60.5 and 69.6%) for these values to be confidently used alone to ascertain a proximally located DVT. Further research can be conducted by combining these ratios with clinical findings or other laboratory markers to aid in patient evaluation or to guide treatment. Another direction for further clinical studies may also be to look into the relationship between these markers in the follow-up or recurrence of DVT to assess the value of MHR in directing an anticoagulation regimen and its duration.

Limitations

We did not analyze other inflammatory parameters such as ILs, CRP, and other subtypes of WBC. Our study had a retrospective single-center study design. A similar study with a prospective design can be carried out, potentially including clinical variables at the time of diagnosis, to assess the relationship of MHR with disease severity and their predictive ability.

CONCLUSION

MHR is significantly elevated in patients with DVT when compared to the control group. We found that MHR levels were correlated with disease burden reflected by thrombus location and the number of vein segments involved in DVT patients, a finding that supports the relationship between the extent of venous thrombus and increased inflammation. MHR may have diagnostic use at the bedside. Further studies are required to confirm their value.

AUTHORS' CONTRIBUTIONS

ZD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing - original draft. GB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing - review & editing. **SD:** Investigation, Methodology, Visualization. HU: Investigation, Methodology, Visualization. IE: Methodology, Project administration, Supervision, Visualization, Writing review & editing. MY: Methodology, Supervision, Visualization, Writing - review & editing.

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Right ventricular myocardial performance index (Tei) in premature infants

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SUMMARY

OBJECTIVE: The objective of this study was to evaluate the right ventricular myocardial performance index) based on echocardiography in very low birth weight premature neonates, close to hospital discharge.

METHODS: This was a prospective cross-sectional study that included premature neonates with birth weight < 1,500 g and gestational age <37 weeks at the Intermediate Neonatal Unit of Bonsucesso Federal Hospital from July 2005 to July 2006. The infants underwent two-dimensional color Doppler echocardiography, being the right ventricular myocardial performance index evaluated close to hospital discharge. We compared the neonatal and echocardiographic variables in neonates with and without bronchopulmonary dysplasia.

RESULTS: A total of 81 exams were analyzed. The mean birth (standard deviation) weight and gestational age were 1,140 (235) g and 30 (2.2) weeks, respectively. The incidence of bronchopulmonary dysplasia was 32%. The mean right ventricle myocardial performance index (standard deviation) of the sample was 0.13 (0.06). We found a significant difference in aortic diameter [non-bronchopulmonary dysplasia 0.79 (0.07) vs. bronchopulmonary dysplasia 0.87 (0.11) cm, p=0.003], left ventricle in diastole [non-bronchopulmonary dysplasia 1.4 (0.19) vs. bronchopulmonary dysplasia 1.59 (0.21) cm, p=0.0006], ventricular septal thickness [non-bronchopulmonary dysplasia 0.23 (0.03) vs. bronchopulmonary dysplasia 0.26 (0.05) cm, p=0.032], and "a" measurement [(= sum of the isovolumetric contraction time, ejection time, and isovolumetric relaxation time) when calculating the myocardial performance index (p=0.01)].

CONCLUSION: Higher "a" interval in neonates with bronchopulmonary dysplasia suggests right ventricle diastolic dysfunction. We conclude that the right ventricle myocardial performance index is an important indicator both of ventricular function and for serial follow-up testing of very low birth weight premature neonates, especially those with bronchopulmonary dysplasia.

KEYWORDS: Bronchopulmonary dysplasia. Infant, low birth weight. Ventricular dysfunction, right. Echocardiography, doppler, color.

INTRODUCTION

Despite tremendous technological progress and new practices in handling very low birth weight (VLBW) neonates, bronchopulmonary dysplasia (BPD) is still a major complication, due to its high morbidity and mortality, principally in the first 2 years of life¹. In 1995, Fanaroff et al.² reported BPD in 51% of neonates weighing from 501 to 750 g and 35% of those from 751 to 1,000 g. BPD, especially in the severe form, can evolve with cardiovascular complications such as right ventricular dysfunction associated with pulmonary hypertension (PH). Right ventricle (RV) dysfunction can increase the mortality rate to 39% in these patients³. It is thus recommended to perform cardiologic evaluation and routine echocardiography to estimate the presence of PH, thereby aiding the proper management of these infants⁴.

In the past 20 years, echocardiography has proven to be an important tool for anatomical diagnosis of congenital and acquired cardiopathies, in addition to allowing systolic and diastolic functional evaluation of both ventricles. In special situations such as the absence of tricuspid valve regurgitation on color Doppler mapping, as well as alterations in heart rate and RV geometry, it is sometimes difficult to achieve morphofunctional assessment of the RV in PH when using traditional parameters to perform echocardiographic measurements⁵.

In 1995, a new echocardiographic measurement, known as the myocardial performance index (MPI or Tei index), was

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

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Received on December 23, 2022. Accepted on January 10, 2023.

developed, which measures time intervals using Doppler and allows for estimating global ventricular performance⁶. Several studieson children have shown its value as a sensitive indicator of the presence of left and right ventricular dysfunction⁷⁻⁹. This measurement has been considered operator-friendly and reproducible and has advantages over traditional measurements since it is not altered by variations in heart rate or ventricular geometry.

Therefore, the objective of this study was to assess the RV function in VLBW newborns with and without BPD using the RV MPI, close to hospital discharge.

METHODS

This study protocol was approved by the Research Ethics Committee of Bonsucesso Federal Hospital (n° 23/05) and the National Institute of Women, Children and Adolescents Health Fernandes Figueira/Oswaldo Cruz Foundation (IFF/ FIOCRUZ) (n° 045/065). This was a prospective cross-sectional study carried out at an Intermediate Neonatal Unit (INU) of Bonsucesso Federal Hospital from July 2005 to July 2006. The inclusion criteria were prematurity (gestational age (GA) <37 weeks), birth weight <1,500 g, and patients whose at least one of the parents or legal guardians has provided written informed consent. Neonates admitted to the INU from other units and more than 3 days old were excluded, as were those with thoracic or diaphragmatic malformations or congenital cardiopathies. The study sample was divided into two groups, namely, newborns with and without BPD.

Gestational age was calculated based on the last menstrual period (LMP), and when this date was unknown, it was calculated based on the early obstetric ultrasound, which was performed up to 18 weeks of gestation. When neither of the above was available, GA was estimated by the new Ballard method¹⁰. Adequacy of birth weight for GA was classified as adequate for GA (AGA), small for GA (SGA), and large for GA (LGA) based on the Lubchenco classification¹¹. BPD was defined as the use of oxygen therapy for 28 days or longer¹².

The echocardiogram was performed using two-dimensional color Doppler (Philips EnVisor C HD model, sector transducer 21350A, 5 MHz, 400 filter, with speeds of 50 and 100 ms). Images were stored in digital format in HD and CD for subsequent analysis. Echocardiography was performed once by the same examiner (EL) when the patient was clinically and hemodynamically stable, without the need for oxygen, close to hospital discharge. The mean of three measurements was taken for each echocardiographic parameter. A single pediatric cardiologist (EL), blinded to the newborns' clinical data, used a high-resolution echocardiography machine. Patients underwent echocardiography without sedation and with continuous electrocardiographic monitoring.

The echocardiographic parameters by the M mode included the left ventricular systolic and diastolic diameters (LVs and LVd), RV, left atrium (LA), aorta (AO), ventricular septal thickness (VST), and posterior wall of the left ventricle (PW). The Doppler method was used to acquire the following measurements: calculation of systolic pressure (SAP) estimated by tricuspid regurgitation, analysis of the pulmonary systolic flow curve, and RV MPI. We estimated pressure gradient values using the Bernoulli equation ($\Delta P=4 V^2$, where P=pressure gradient and V=maximum velocity of the flow curve).

To calculate the RV MPI, we obtained the RV inlet tract (tricuspid valve) and outlet tract curves. Measurement "a" corresponds to the time interval between the end and beginning of RV flow, which equals the sum of the isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT). Measurement "b" corresponds to the ejection time (ET) of the RV outlet tract. As the Tei index is calculated according to the formula ICT + IRT/ET, one must subtract "b" from "a" and divide by "b" (= a-b/b). The size of the Doppler sample volume was standardized at 2 mm to obtain the time intervals, and the means were calculated for at least five consecutive cardiac cycles.

To calculate the sample size, considering an altered RV MPI rate of 3% for the age bracket, 95% confidence interval, and 3% precision, the necessary sample size was 56 infants.

The maternal and neonatal variables were described through frequency measurements and means, medians, and respective standard deviations (SDs). We used statistical tests for differences between means and proportions, Student's t-test/F-statistic, and Fisher's exact test, respectively. The statistical significance level for comparisons was set at 5%.

RESULTS

A total of 84 preterm newborns with GA <37 weeks and birth weight <1,500 g were admitted to the INU. We excluded two neonates with congenital pulmonary malformations and one newborn aged more than 3 days and was transferred from another hospital unit. Therefore, the final sample size was 81 newborns.

Regarding gender, 34 newborns (42%) were male and 47 (58%) were female. Of the entire sample, 49 (60.5%) were AGA and 32 (39.5%) were SGA, with no LGA preterm newborn. Birth weight was distributed as follows: <750 g: 2 (2.5%), 750–999 g: 22 (27.5%), 1,000–1,249 g: 24 (29.6%),

and 1,250–1,499 g: 33 (40.7%). Birth weight ranged from 575 to 1,495 g, with a mean of 1,140 \pm 235 g (median: 1,142 g). The mean GA was 30 \pm 2.2 weeks (median: 30 weeks). For 31 cases (40%), it was not possible to estimate GA according to the LMP.

Regarding postnatal complications, 47 newborns (58%) had hyaline membrane disease, and surfactant was used in 46, corresponding to 56.8% of the total sample. Mechanical ventilation was required in 53 newborns (65.4%), and the mean time (SD) and the median were 14.9 (18.9) days and 5.5 days, respectively. Nasal continuous airway positive pressure (CPAP) was required in 69 (85.1%), for a mean time (SD) of 5.9 (6.8) days and a median of 3.0 days. Oxyhood was used for a mean (SD) of 3.1 (3.9) days and a median of 2.0 days, and oxygen catheter was used for a mean (SD) of 7.1 (11.7) days and a median of 1.5 days. The total oxygen time ranged from 4 to 120 days, with a mean (SD) of 24.7 (28.6) days and a median of 9.0 days.

Of note, 26 infants (32%) met the diagnostic criteria for BPD, 19 of which were classified as moderate. No neonate was classified as severe. The infants were distributed with and without BPD, based on birth weight brackets, and 18 (69%) of the neonates with BPD were born weighing <1,000 g. Time on mechanical ventilation and total O_2 demand in the BPD group were higher compared to the group without BPD (SD) [23.6 (20.9) vs. 4.1 (4.7) days and 59.0 (23.4) vs. 7.2 (1.1) days, respectively].

Newborns with BPD showed statistically significant differences in weight and GA on the exam date compared to those without BPD (SD) [1,643 (113) vs. 1,991 (352) g (p= 0.001) and 34.5 (2.2) vs. 38.2 (3.3) weeks (p=0.001), respectively].

| Table 1. Echocardiographic measurements of neonates (n=81) admitter | d |
|---|---|
| to the Intermediate Neonatal Unit. | |

| Echocardiographic parameter | Mean | SD |
|-----------------------------|------|------|
| LA (cm) | 0.82 | 0.09 |
| AO (cm) | 0.86 | 0.15 |
| LVd (cm) | 1.46 | 0.21 |
| LVs (cm) | 0.86 | 0.15 |
| RV (cm) | 0.66 | 0.14 |
| VST (cm) | 0.24 | 0.04 |
| PWT (cm) | 0.23 | 0.03 |
| "a" measurement (ms) | 215 | 15 |
| "b" measurement (ms) | 189 | 14 |
| RV MPI | 0.13 | 0.06 |

LA: left atrium; AO: aorta; SD: standard deviation; LVd left ventricle in diastole; LVs: left ventricle in systole; RV: right ventricle; VST: ventricular septal thickness; PWT: posterior wall thickness.

Patent ductus arteriosus was found in 18 newborns (22.2%), and surgical closure was indicated in 9. Septicemia confirmed by positive blood culture occurred in 15 cases (18.5%).

Table 1 shows the analysis of the echocardiographic values of the 81 children in the sample. Table 2 shows that the diameters of the aorta, left ventricle in diastole, ventricular septum, and posterior wall in diastole were also significantly higher in the BPD group. There was no significant difference between the two groups in terms of RV and LA diameters.

Evaluating the ventricular septal excentricity index, no alteration was observed in the study sample. Doppler mapping analysis of the right atrioventricular valve identified only 9 (11%) newborns with mild tricuspid regurgitation. The mean RV MPI (SD) was 0.13 (0.06), and no statistically significant difference was observed in this value when comparing neonates with and without BPD (Table 2).

Considering the measures comprising the MPI separately, at the time of the echocardiograph exam (Table 3), we observed that there were no differences in the "b" measurement but a statistically significant difference in the "a" measurement between the two groups (BPD vs. non-BPD).

DISCUSSION

BPD is a complex disease and extensively studied in the literature^{13,14}. However, with technological advances and improved perinatal care, the incidence of severe BPD has decreased, and "new BPD" is now the most common presentation¹⁵. Some authors have shown that 20–25% of newborns with BPD can

Table 2. Echocardiographic measurements of neonates without andwith bronchopulmonary dysplasia admitted to the IntermediateNeonatal Unit.

| Echocardiographic parameter | Non-BPD (n=55) Mean (SD) | BPD (n=26) Mean (SD) | p-value |
|--------------------------------|--------------------------------|----------------------------|---------|
| LA (cm) | 0.85 (0.14) | 0.90 (0.17) | 0.23 |
| AO (cm) | 0.79 (0.07) | 0.87 (0.11) | 0.003 |
| LVd (cm) | 1.40 (0.19) | 1.59 (0.21) | 0.0006 |
| LVs (cm) | 0.84 (0.15) | 0.91 (0.13) | 0.053 |
| RV (cm) | 0.65 (0.13) | 0.68 (0.16) | 0.392 |
| VST (cm) | 0.23 (0.03) | 0.26 (0.05) | 0.032 |
| PWT (cm) | 0.22 (0.03) | 0.25 (0.04) | 0.01 |
| "a" measurement (ms) | 213 (14) | 221 (17) | 0.03 |
| "b" measurement (ms) | 189 (13) | 191 (15) | 0.41 |
| RVMPI | 0.12 (0.05) | 0.14 (0.06) | 0.23 |

LA: left atrium; AO: aorta; BPD: bronchopulmonary dysplasia; SD: standard deviation; LVd: left ventricle in diastole; LVs: left ventricle in systole; RV: right ventricle; VST: ventricular septal thickness; PWT: posterior wall thickness.

present cardiac involvement, and a significant portion can evolve to PH^{16,17}. During the clinical follow-up of these infants, cardiac assessment is of the most importance, orienting adequate treatment with diuretics and vasodilators, the prolonged use of which can have adverse effects on these VLBW infants⁵. In our study, we observed that 11% of newborns with BPD evolved to PH with a higher prevalence of cardiac involvement related to RV diastolic dysfunction.

The prevalence of BPD in our study was 32%. Of these, 76% were O₂-dependent with 36 weeks of GA corrected at the moment of evaluation and classified as moderately severe. The morphometric data of the newborns in this study were within the normal range for GA¹⁸. Comparing the groups with and without BPD, there was a statistically significant difference in the aorta, left ventricle in diastole, ventricular septal thickness, and posterior wall. This finding can be attributed to the fact that newborns with BPD require more time on oxygen therapy, presenting higher corrected GA and weight compared to those without BPD, reflected in the measurements of the cardiac cavities. There was no statistically significant difference between the two groups in the RV and LA measurements.

Color Doppler mapping of the study sample identified only three cases of mild tricuspid regurgitation, absence of RV hypertrophy, and no case of alteration in the ventricular septal excentricity index, showing that in these 81 neonates, there were no signs of PH as evaluated by the traditional echocardiographic methods.

MPI has been used for predicting perinatal morbidity and mortality in fetuses of pregnant women with diabetes mellitus, fetal growth restriction, and twin-to-twin transfusion syndrome¹⁹. This study satisfactorily measured the RV MPI in newborns, confirming the reports in the literature that this is a simple and user-friendly method^{20,21}. In this study, the mean value of this

Table 3. Characteristics of the study sample based on the right ventricle myocardial performance index (RV MPI) values.

| Variable | MPI≤0.24 n=76 Mean (SD) | MPI>0.24 n=5 Mean (SD) | p-value |
|----------------------------------|-------------------------------|------------------------------|---------|
| Birth weight (g) | 1,149 (237) | 1,103 (278) | >0.05 |
| Gestational age (days) | 209 (17.1) | 208 (15.8) | >0.05 |
| Weight at exam (g) | 1,739 (245) | 1,941 (498) | >0.05 |
| Corrected GA (weeks) | 35.5 (2.6) | 38.1 (6.0) | >0.05 |
| Total O ₂ time (days) | 23.2 (26.4) | 45.2 (49.2) | >0.05 |
| Ventilation time (days) | 14.6 (18.4) | 19.7 (28.0) | >0.05 |
| "a" measurement (ms) | 215 (15) | 229 (12) | 0.04 |
| "b" measurement (ms) | 191 (14) | 179 (8) | >0.05 |

SD: standard deviation; GA: gestational age.

index (SD) was 0.13 (0.06), which is within the range reported in the literature for infants born at term²². Ishii et al.²³ reported mean RV MPI (SD) values of 0.24 (0.04), but their findings are difficult to compare with our results because the authors studied normal children with ages ranging from 30 days to 18 years, which were different from those of our sample. Malakan-Rad and Momtazmanesh²⁴ studied neonates at term between 48 and 72 h after birth and found a mean RV MPI (SD) of 0.23 (0.14), but again a comparison is difficult because the authors studied neonates at term in an initial phase of life in which the RV MPI presents higher values (as days pass, the pulmonary vascular resistance decreases and these values tend to drop). Our study evaluated MPI in premature infants close to hospital discharge that were clinically stable at the time of examination, with a mean GA of 36 weeks corrected for prematurity.

Schmitz et al.²⁵ studied LV diastolic function in healthy neonates and infants through mitral valve flow parameters. They demonstrated that the isovolumetric relaxation time in neonates is significantly prolonged compared to infants older than 2 months. This may indicate that immature LV diastolic function plays an important role in the severity of cardiopulmonary complications in this age group. In our study, although the values found in the "a" measurement (which includes the isovolumetric relaxation and contraction times) showed a statistically significant difference between neonates with and without BPD, we cannot compare our results with the abovementioned study because we evaluated not only the diastolic ventricular function but also the global RV function.

The limitations of this study were the lack of long-term postnatal follow-up about the applicability of MPI and the absence of interobserver variability analysis.

In summary, from our data, we conclude that RV MPI is an important indicator of combined ventricular function and important for serial follow-up testing of VLBW neonates, especially those with BPD.

AUTHORS' CONTRIBUTIONS

EL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. CLR: Conceptualization, Formal Analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EAJ: Formal Analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. RRM: Formal Analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. NJBV: Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Serum chromogranin A levels are associated with the SYNTAX score in coronary artery disease

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SUMMARY

OBJECTIVE: In this article, we investigated the association of chromogranin A with coronary artery disease.

METHODS: Biochemical parameters and chromogranin A levels obtained from peripheral blood samples during coronary angiography were analyzed in 90 patients. Patients were classified into two groups, namely, SYNergy between PCI with TAXUS and Cardiac Surgery score \geq 1 (n=45) and SYNergy between PCI with TAXUS and Cardiac Surgery score=0 (n=45). This is a cross-sectional, prospective study.

RESULTS: Serum chromogranin A levels were significantly higher in the group with SYNergy between PCI with TAXUS and Cardiac Surgery score ≥ 1 compared to the group with SYNergy between PCI with TAXUS and Cardiac Surgery score=0 (1381.5±418.9 ng/mL and 1121.2±290.7 ng/mL, respectively; p=0.002). Serum chromogranin A levels were correlated with SYNergy between PCI with TAXUS and Cardiac Surgery score (r=0.556, p<0.04). ROC analysis showed that the area under the curve for serum chromogranin A levels was 0.687 (p=0.007), and the best cutoff value of 1,131 ng/mL had a sensitivity of 67% and a specificity of 65% for the prediction of coronary artery disease.

CONCLUSION: Serum chromogranin A levels were increased in coronary artery disease patients with SYNergy between PCI with TAXUS and Cardiac Surgery score ≥1. Increasing serum chromogranin A levels are proportional to the SYNergy between PCI with TAXUS and Cardiac Surgery score. KEYWORDS: Chromogranin A. Coronary artery disease. Hypertension.

INTRODUCTION

Granins contain three types of proteins with acidic structure, namely, chromogranin A (CgA), chromogranin B, and secretogranin II. CgA is the major protein found in the nuclei of catecholamine storage vesicles of chromaffin cells and postganglionic sympathetic axons. CgA is stored and released together with catecholamines in chromaffin granules of neuroendocrine cells of the adrenal medulla^{1,2}. It is an acidic protein of 439 amino acids with a molecular weight of 48 kDa. The prohormone CgA is metabolized by extracellular proteases (cathepsin, plasmin, and kallikrein) both in the cardiomyocyte cell membrane and in the extracellular matrix and cleaved into biologically active peptides^{3,4}:

- 1. Catestatin (Cts),
- 2. pancreastatin, a dysglycemic peptide,
- 3. vasostatin-1, a vasodilator, antiadrenergic and antiangiogenic peptide,
- 4. serpinin, a proadrenergic peptide.

Plasma Cts concentration is a predictor of hypertension. Previous studies have observed elevated serum CgA levels and reduced Cts processing in hypertension. Cts levels have been shown to decrease, while plasma CgA level increases. Metabolic and vascular effects of CgA have been investigated and their role in hypertension and coronary artery disease has been studied. CgA levels have also been found to increase in heart failure, acute myocardial infarction, old age, pulmonary hypertension, and inflammatory disease⁵⁻⁸.

We investigated the relationship between serum CgA levels and SYNTAX scores in patients with coronary artery disease.

METHODS

Study population and study design

Patients who underwent coronary angiography from March 2020 to March 2021 for the diagnosis and treatment of coronary

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on December 15, 2022. Accepted on January 09, 2023.

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artery disease were included in the study. This is a cross-sectional, prospective study.

A SYNTAX score of all patients was calculated⁹. Patients were classified into two groups, namely, SYNTAX score=0 and SYNTAX score ≥ 1 . Patients with more than 50% narrowing of the lumen diameter in at least one coronary artery were defined as the SYNTAX score ≥ 1 group. Patients with normal coronary arteries or non-significant coronary artery disease (less than 50% coronary stenosis) were defined as the SYNTAX score=0.

Baseline clinical and biochemical characteristics and blood pressure measurements were recorded during physical examination. The diagnoses of type 2 diabetes mellitus, hypertension, and hyperlipidemia were defined according to published guidelines. To avoid confounding effects, patients with acute coronary syndrome, a history of myocardial infarction and heart disease, heart failure, valvular heart disease, congenital heart disease, cardiomyopathy, stroke, chronic viral or bacterial infection, asthma, tumors, or immune system disorders were excluded. In addition, due to the possibility of elevated CgA levels, patients taking proton-pump inhibitors, H2 receptor antagonists, and somatostatin analogs, with renal failure, cirrhosis, chronic atrophic gastritis, irritable bowel disease, rheumatoid arthritis, hyperthyroidism, hyperparathyroidism, and breast, prostate, and colon cancers were also excluded from the study.

The study protocol was approved by the Ethics Committee of non-interventional clinical research and written informed consent was obtained from all subjects.

Qualitative evaluation of angiograms

All diagnostic coronary angiograms were scored according to the SYNTAX score (SYNergy between PCI with TAXUSTM and Cardiac Surgery) algorithm. The images were jointly reviewed by two cardiologists with more than 10 years of clinical experience. Coronary angiograms (visual assessment) were quantitatively evaluated for the presence of \geq 50% stenosis in major epicardial coronary arteries and >1.5 mm branches. Patients who met the 50% diameter stenosis threshold by quantitative coronary angiographic information (QCA) were defined as SYNTAX score \geq 1.

Biochemical analysis

Blood samples were collected from all participants after an overnight fast. Serum glucose, liver function, blood urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured by standard laboratory techniques on a Cobas c8000 c502 Analyzer (Roche Diagnostics, Geneva, Switzerland). Serum levels of high-sensitivity C-reactive protein (hs-CRP) (Biocheck Laboratories, Toledo, OH, USA) were determined by ELISA.

Peripheral venous blood samples were collected from the antecubital vein after centrifugation at 3,000 rpm for 15 min. All serum samples were stored at -0°C until analysis. Serum CgA level was measured with a commercially available ELISA assay (human chromogranin-A catalog number E1730Hu). The standard curve range of the assay was 300–9,000 ng/L, and the intra-assay and inter-assay coefficients of variance were <8 and <10%, respectively. The sensitivity of the test is 15.21 ng/L.

Statistics

G * A total of 90 patients, 45 patients with SYNTAX score \geq 1 and 45 patients with SYNTAX score=0, were included in the study by performing power analysis with an effect size of 0.5, a first-type error of 0.05, and a power of 0.95 using the Power 3.1 manual 2021 program. SPSS statistical package program was used for computerization and analysis of the data. Variables were expressed as mean (median), standard deviation (minumum-maximum), frequency, and percentage. The Shapiro-Wilk test was used to check whether the variables were normally distributed. The independent sample t-test (or Mann-Whitney U test) was used for measurement and independent two-group comparisons. A value of p<0.05 was considered statistically significant.

RESULTS

The baseline demographic, clinical, and biochemical characteristics of all participants are listed in Table 1. Compared with the SYNTAX score=0 group, patients in the SYNTAX score \geq 1 group were older (51±7 years vs. 58±8 years; p=0.047) and had a higher number of male patients, [23(51%) vs. 29(64%); p=0.002] and a higher prevalence of smoking, [8 (17%) vs. 15(33%); p<0.001]; systolic blood pressure was higher (124 ± 12 mmHg vs. 134±15 mmHg; p=0.042), type 2 diabetes was more frequent [16 (35%) vs. 22 (48%); p=0.001], and HDL cholesterol levels were lower (51±11 mg/dl vs. 36±15 mg/dL; p=0.034). Serum CgA levels were significantly higher in the SYNTAX score ≥1 group compared to the SYNTAX score=0 group (1381.5±418.9 ng/mL and 1121.2±290.7 ng/mL, respectively; p=0.002). There was a moderate to good significant and positive correlation between serum CgA levels and SYNTAX scores (r=0.556, p<0.04).

Multivariate logistic regression analysis

Multivariate logistic regression analysis was performed to determine the risk of more than 50% luminal stenosis of the

| Variable | SYNTAX score=0 n=45 | SYNTAX score ≥1 n=45 | p-value |
|---|------------------------|-------------------------|---------|
| Plasma CgA level, ng/mL | 1121.2±290.7 | 1381.5±418.9 | 0.002 |
| Age, years | 51±7 | 58±8 | 0.047 |
| Male, n (%) | 23 (51) | 29 (64) | 0.002 |
| Systolic blood pressure, mmHg | 124±12 | 134±15 | 0.042 |
| Diastolic blood pressure, mmHg | 75±8 | 76±9 | 0.876 |
| Type II diabetes mellitus, n (%) | 16 (35) | 22 (48) | 0.001 |
| Smoking, n (%) | 8 (17) | 15 (33) | <0.001 |
| Hypertension, n (%) | 25 (55) | 32 (71) | <0.001 |
| Hyperlipidemia, n (%) | 18 (40) | 19 (42) | 0.828 |
| Glucose, mg/dL | 106±16 | 141±66 | 0.012 |
| Creatinine, mg/dL | 0.8±0.1 | 0.8±0.2 | 0.354 |
| Urea, mg/dL | 26±6 | 29±9 | 0.079 |
| Total cholesterol, mg/dL | 191±32 | 193±36 | 0.850 |
| HDL cholesterol, mg/dL | 51±11 | 36±15 | 0.034 |
| LDL cholesterol, mg/dL | 117±27 | 114±39 | 0.727 |
| Triglycerides, mg/dL | 162 ± 75 | 194±90 | 0.284 |
| CRP, mg/dL | 1.6±1 | 3.2±1 | 0.101 |
| Leukocytes, 10 ⁶ /mm ³ | 6.7±2.6 | 7.3±1.6 | 0.193 |
| Neutrophils, 10 ⁶ /mm ³ | 3.7±1.2 | 4.6±1.4 | 0.009 |
| Lymphocytes, 10 ⁶ /mm ³ | 2.0±0.5 | 2.1±0.6 | 0.403 |
| Monocytes,10 ⁶ /mm ³ | 0.4±0.1 | 0.5±0.1 | 0.602 |
| Hemoglobin, g/dL | 14.2±1.6 | 13.7±1.5 | 0.246 |
| Platelets, 10 ³ /mm ³ | 214±62 | 253±60 | 0.013 |

Table 1. Baseline clinical and biochemical characteristics of the study population.

Data were expressed as number (%) and mean (SD). HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; CgA, chromagranin A.

coronary arteries as a function of traditional risk factors and biochemical variables (Table 2). Adjusted for traditional cardiovascular risk factor, male sex, age, smoking, hypertension, and hs-C-reactive protein were independent risk factors for coronary artery disease. When CgA was included in the multivariate regression analysis (Model 2), all remained significantly associated with a SYNTAX score ≥ 1 (Table 2). ROC analysis showed that the area under the curve for serum CgA levels was 0.687 (p=0.007), and the best cutoff value of 1131 ng/mL had a sensitivity of 67% and a specificity of 65% for the prediction of a SYNTAX score ≥ 1 (Figure 1).

Our study revealed that elevated serum CgA levels were moderately but significantly associated with the presence of coronary artery disease as determined by the SYNTAX score. These results, therefore, suggest a possible causal link between elevated CgA level and atherosclerosis. Cardiac CgA, in particular, is found to be stored in atrial granules together with natriuretic peptides involved in water and blood pressure regulation.

Plasma levels of natriuretic peptides have been observed to decrease in parallel with natriuretic peptides with treatment in patients with heart failure who were implanted with a left ventricular assist device. Corti et al. found that increased CgA levels were closely associated with mortality in patients with heart failure¹⁰. In patients with dilated and hypertrophic cardiomyopathy, circulating plasma CgA levels and B-type natriuretic peptide (BNP) levels were found to be high in correlation with each other. In another study of CgA, in heart failure, it has been shown to be a prognostic marker of the disease such as N-terminal proBNP¹¹. In GISSI trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico), CgA was related to all-cause mortality or cardiovascular morbidity¹².

In GISSI trial, it was found that plasma CgA concentrations increased in proportion to disease severity¹².

| Variable | OR (95%CI) | p-value |
|-------------------------|---------------|---------|
| Model 1 | | |
| Age, years | 1.9 (1.7-2.9) | <0.001 |
| Gender, male | 2.0 (1.5-2.7) | <0.001 |
| Diagnosis of diabetes | 1.3 (0.9–1.9) | 0.082 |
| Hyperlipidemia | 1.4 (1.1-2.0) | 0.071 |
| Smoking | 3.2 (2.3-6.5) | <0.001 |
| hs-C-reactive protein | 1.7 (1.2–2.5) | 0.003 |
| Model 2 | | |
| Age, years | 2.0 (1.8-3.1) | <0.001 |
| Gender, male | 2.0 (1.4-2.7) | <0.001 |
| Diagnosis of diabetes | 1.1 (0.7–1.7) | 0.212 |
| Hyperlipidemia | 1.2 (1.0-1.8) | 0.121 |
| Smoking | 2.2 (1.3-4.5) | <0.001 |
| hs-C-reactive protein | 1.6 (1.1-2.3) | 0.006 |
| Plasma CgA level, ng/mL | 1.6 (1.1–1.9) | 0.036 |

 Table 2. Multivariate stepwise logistic regression analysis for coronary artery disease risk.

OR indicates the odds ratio for significant coronary artery disease (CAD). Cl, confidence interval.



Figure 1. ROC curve testing the accuracy of serum CgA levels in predicting coronary artery disease (SYNTAX score \geq 1). A optimal serum CgA cutoff value of 1,131 ng/mL provided the highest sensitivity (67%) and specificity (65%) for the prediction of coronary artery disease. The area under the curve for serum CgA levels was 0.687 (p=0.007). ROC: receiver operator characteristics; Syntax: SYNergy between PCI with TAXUS and Cardiac Surgery.

The effects of CgA at the vascular level are largely unknown. The 439 amino acid CgA (hCgA1-439) and its N-terminal fragments hCgA1-76 (vasostatin-1) and hCgA1-113 (vasostatin-2) have important roles in the regulation of the cardiovascular system¹³. These fragments can suppress vasoconstriction in isolated human conduit vessels. In another study, vasostatin-2 improved cardiac function and reduced remodeling, fibrosis, and inflammation in the heart in mice with myocardial infarction¹⁴. CgA and vasostatin-1 have been shown to have cardioprotective effects against Ischemia/reperfusion (I/R) injury.

Chromogranin A is physiologically degraded by tissue-specific proteases such as plasmin. Levels and activities of tissue plasminogen activator are reduced in inflammatory, diabetic vascular tissues and in smoking; therefore, this reduction may contribute to impaired CgA turnover. Vasostatin-1, produced by proteolytic cleavage of CgA, inhibits endothelin-1-induced vasoconstriction. This information is consistent with our idea that CgA is closely involved in the development of significant coronary artery disease. It also suggests that impaired processing of CgA occurs in the setting of atherosclerosis. In rodents, administration of Cts, a breakdown product of CgA, reduced hypertension, cardiac contractility, obesity, atherosclerosis and inflammation, and increased insulin sensitivity were observed. In contrast, pancreastatin, another breakdown product of CgA, has increased levels in diabetic patients. When given exogenously to rodents, obese mice have reduced insulin sensitivity and increased inflammation¹⁵⁻¹⁸.

In the largest study on CgA levels in acute coronary syndromes, in which 1268 patients participated and followed up for 7.5 years, baseline CgA levels were associated with increased long-term mortality [OR 1.27 (95%CI 1.10–1.47)] and repeat myocardial infarction [OR 1.57 (95%CI 1.44–1.70), respectively¹⁹. In another study, a two-fold increase in plasma CgA levels was found 24 h after myocardial infarction.

Previous studies have suggested that the vascular protective activities of vasostatin-2, a CgA degradation product, are reduced in atherosclerosis or in the presence of diabetes due to low levels of proteolysis²⁰.

Another product produced by proteolytic cleavage of CgA is Cts. Although initially described as a physiological brake mechanism on catecholamine secretion, it reduces blood pressure, positively regulates baroreflex sensitivity and heart rate variability, and has cardioprotective effects. Cts induces nitric oxide synthesis from endothelial cells and cardiomyocytes. Based on *in vitro* and *in vivo* animal models, Cts has been shown to exhibit a potential cardioprotective effect by acting as a cardiodepressive peptide directly through multiple signaling pathways and may also reduce the apoptosis of

cardiomyocytes induced by oxidative stress. Chen et al. showed that serum Cts levels were lower in patients with stable angina pectoris (SAP) compared to healthy controls. Furthermore, a gradual decrease in serum Cts was found when stratifying CAD patients according to the number of diseased vessels. However, Liu et al. showed that SAP patients had significantly higher Cts levels compared to controls. The different findings are difficult to explain, Cts may increase as CgAs are released when pain occurs, and also the small patient sample size in Liu et al.'s study may have biased their results. Furthermore, Xu et al. showed that mean plasma Cts in patients with chronic total occlusion of the coronary arteries undergoing first-time coronary angiography or percutaneous coronary intervention was significantly higher than in patients with chest pain but normal coronary arteries²¹⁻²⁶.

In our study, elevated serum CgA level was an independent risk factor for coronary artery disease with severe luminal stenosis in multivariate regression analysis. Therefore, such data suggest the possible use of this molecule as a marker of atherosclerosis risk. Such studies will need to be validated using prospective cohort data.

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This is a cross-sectional study, so while it allows for the identification of relationships, it does not allow for the inference of causality. Furthermore, several exclusion criteria and the selection of the study population may reduce the prognostic significance we found for CgA and introduce several selection biases. Large-scale, long-term prospective studies are needed to confirm our results and assess the prognostic significance of possible drugs that alter CgA levels.

The demonstration that elevated serum CgA levels are positively associated with the presence and severity of coronary artery disease provides a rationale for further research. More data are also needed to investigate the mechanisms underlying this relationship.

AUTHORS' CONTRIBUTIONS

AÇ: Conceptualization, Funding acquisition. AD: Data curation, Investigation, Project administration, Supervision, Writing – original draft. MK: Data curation. SG: Formal analysis, Visualization. CA: Methodology, Software. MME: Resources.
AY: Validation. AA: Writing – review & editing.

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Clinical profile and severity predictors of coronavirus disease 19 infection in a reference center from southern Brazil: a cross-sectional study

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SUMMARY

OBJECTIVES: The coronavirus disease pandemic has become a major global health crisis since 2019. Recent data show the association of diabetes, hypertension, and obesity with poor related outcomes in coronavirus disease infection. This descriptive study aimed to identify the clinical and laboratory parameters in patients with acute respiratory syndrome and confirmed severe acute respiratory syndrome coronavirus 2 infection. **METHODS:** In this cross-sectional study, we analyzed data of 409 patients admitted to a referral hospital in Rio Grande do Sul, Brazil, with coronavirus

disease infection confirmed by reverse transcription polymerase chain reaction. Clinical, laboratory, and imaging data were collected retrospectively from electronic medical records using a template with the variables of interest.

RESULTS: The average age was 64 years (52–73), and the body mass index was 27 kg/m² (22.1–31.2). Hypertension, diabetes, and obesity were observed in 58, 33, and 32% of the patients, respectively. Patients admitted to an intensive care unit were older [66 years (53–74) vs. 59 years (42.2–71.7)], with significantly higher impairment on chest computed tomography [75% (50–75) vs. 50% (25–60)] and received higher doses of corticosteroid therapy [39.4 mg (14.3–70.3) vs. 6 mg (6–14.7)]. Hematological parameters were lower in critically ill patients, with greater differences observed on the fifth day of hospitalization [hemoglobin 11.5 g/dL (9.5–13.1) vs. 12.8 g/dL (11.5–14.2), platelets 235,000 μ L (143,000–357,000) vs. 270,000 μ L (192,000–377,000), and lymphocytes 900 μ L (555–1,500) vs. 1,629 μ L (1,141–2,329)]. C-reactive protein levels and kidney function were also worse in intensive care unit patients. The mortality rate was significantly higher in the intensive care unit compared to the basic care unit (62.8 vs. 12.2%). **CONCLUSION:** Our findings suggest that metabolic and cardiovascular comorbidities, as well as abnormal hematological parameters, are common findings among patients with severe respiratory syndrome related to coronavirus disease.

KEYWORDS: COVID-19. Severe acute respiratory syndrome. Hemoglobins. Blood platelets. Lymphocytes.

INTRODUCTION

Coronavirus disease 19 (COVID-19) first emerged as an unknown pneumonia in December 2019 in the city of Wuhan, China, quickly spreading to other regions of the world^{1,2}. Coronaviruses are single-stranded RNA viruses that belong to the *Coronaviridae* family and are widely distributed in mammals and humans³. Although infections in humans are usually mild, there have been two epidemics in the past associated with respiratory syndrome, including SARS-CoV1 and MERS-CoV^{4,5}.

The World Health Organization (WHO) declared the disease COVID-19 as a pandemic in March 2020⁶—a pandemic unprecedented in scale and speed, reaching more than 188 countries, affecting countless individuals, and causing thousands of deaths. COVID-19 infection can lead to severe pneumonia, acute respiratory distress syndrome, acute kidney injury, and acute heart failure³. According to the COVID-19 panel of the Center for System Science and Engineering at Johns Hopkins University, until September 2021, almost 221 million cases were registered and 20 million cases were present only in Brazil.

As a rapidly spreading disease, SARS-CoV-2 infection transmits mainly by droplets and direct contact between people and is highly contagious. Although the incubation period averages 5.5 days, it is known to last up to 14 days⁷. The clinical manifestations of this disease vary; however, the typical symptoms

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on December 29, 2022. Accepted on January 10, 2023.

of COVID-19 are fever, sore throat, fatigue, cough, and shortness of breath. Self-reported olfactory and taste disorders have also been reported⁸. In the acute phase, COVID-19 infection leads to a pronounced systemic increase in inflammatory mediators and cytokines, with high levels of pro-inflammatory interleukins (IL1B, IL6, IFN γ , IP10, and MCP1) and tumor necrosis factor-alpha (TNF- α). This cytokine storm leads to lymphocyte apoptosis, inflammation, and excessive lung damage, although the pathophysiology of the disease has not been fully elucidated⁴. Besides reduced lymphocyte counts, leukocytes, neutrophils, and platelets can also be affected and can be used as markers of systemic inflammation and possibly as prognostic indicators^{5,9}.

Considering the significant morbidity and mortality associated with COVID-19 infection, as well as the existence of viral variants and the unpredictability of the course of the SARS-CoV-2 pandemic, studies in different populations are needed to understand the behavior of the infection and identify markers capable of predicting patients at risk for a more severe course. This study aimed to describe and evaluate useful clinical (i.e., comorbidities, length of hospitalization, admission to intensive care, mechanical ventilation support, use of glucocorticoids and insulin therapy after hospital admission, and mortality rate), laboratory (i.e., glucose, renal function, and hematological and inflammatory parameters), and imaging predictors in patients with an unfavorable outcome in a population in southern Brazil.

METHODS

This is a cross-sectional and retrospective study based on electronic medical records. Hospitalized patients were analyzed at a reference hospital for COVID-19 from the metropolitan region of Porto Alegre, state of Rio Grande do Sul, from the period between September 2020 and July 2021. Data were collected from the medical records, using a template with the variables of interest previously established based on the available literature. All the medical records of patients with severe acute respiratory syndrome and suspected COVID-19 infection needing hospital admission were evaluated, using the hospital database for COVID-19 screening tests. All the patients were tested with reverse transcription polymerase chain reaction (RT-PCR) collected from upper airway samples through nasal swabs, and patients with negative RT-PCR tests for COVID-19 or aged less than 18 years were excluded. The study was approved by the Research Ethics Committee under protocol number 38815320.0.0000.5349 on October 14, 2020. All the participants signed the informed consent form.

Medical records were collected including clinical and anthropometric data, such as age, sex, ethnicity, body mass index (BMI), initial symptoms, vital signs (i.e., blood pressure, heart rate, and respiratory frequency), laboratory tests (i.e., creatinine, blood counts, electrolytes, C-reactive protein (CRP), and fasting glucose), ICU admission, oxygen supplementation, use of glucocorticoids and insulin therapy after hospital admission, and mortality rate. The presence of comorbidities such as diabetes mellitus, systemic arterial hypertension, cardiovascular disease (CVD), cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and history of malignancy and tobacco consumption were also evaluated. Biochemical tests including blood count, platelets, kidney function, electrolytes, and CRP were evaluated on the arrival and the fifth day of hospitalization. In addition, imaging studies such as chest X-ray, chest computed tomography (CT), and echocardiogram when needed were also included in the evaluation of these patients. Only CT exams performed in our hospital and analyzed by the same specialist (RGT) were considered in this study, assessing the findings of typical pulmonary involvement of COVID-19 infection and the extent of lung injury.

Statistical analysis

The results were presented as means±standard deviation or medians and interquartile range. The normality tests of each variable were performed using the Shapiro-Wilk test. Variables with non-Gaussian distribution underwent a logarithmic transformation for statistical analysis, being transformed back into their original units for data presentation. Differences between groups were analyzed using the t-test for independent samples, and the chi-square test was used to assess the association between categorical variables. Correlation analysis was performed using Pearson's test for variables with normal distribution and Spearman's test for variables with abnormal distribution. Values of p<0.05 will be considered significant. The IBM Statistical Package for Social Sciences 26.0 (SPSS, Chicago, IL, USA) software was used to analyze the present data.

RESULTS

We evaluated a total of 700 medical records, with 409 patients admitted to a referral hospital for acute respiratory syndrome related to COVID-19 infection (Figure 1). Regarding skin color, 75% of individuals were white and the remaining subjects were of mixed ancestry. More than half were men (51%), the average age was 64 years (52–73), and the BMI was 27 kg/m² (22.1–31.2). Previous or current use of tobacco was recorded in 25.9% of patients. Regarding medical conditions, about a



Figure 1. Patient selection flowchart. RT-PCR: reverse transcription polymerase chain reaction.

third presented previous diabetes (33%) and obesity (32%) and almost two-thirds (58%) had a diagnosis of arterial hypertension. Cardiovascular and cerebrovascular diseases were reported in 18 and 14% of the patients, respectively. Other conditions reported in less than 5% of the patients were COPD (8%), malignancies (4.6%), chronic kidney disease (CKD) (3.4%), and HIV infection (1%). The average length of stay in the hospital was 12 days (8–24).

The main presenting clinical findings were desaturation (64.6%), dyspnea (63.2%), cough (51.7%), and fever (47.8%). Other symptoms included myalgia (22%), headache (15.1%), fatigue (12.9%), vomiting (12.7%), anosmia (7.3%), and nasal congestion (7.1%). The average time from the onset of symptoms leading to hospital admission was 6 days (3–10). The laboratory and tomographic findings of all patients are detailed in Tables 1 and 2. The mortality rate was 29%.

A negative correlation was observed between lymphocytes on the fifth day of hospitalization and impairment on CT chest (p=0.037 r=-0.174), CRP (p=0.001 r=-0.210), and hospitalization time (p<0.001 r=-0.338).

DISCUSSION

In this study, approximately 30–60% of the patients admitted for COVID-19 infection presented with hypertension, diabetes, and obesity. In addition, we observed that patients admitted to ICU had lower hematological parameters and higher glucose levels and received corticosteroids in larger doses and for a longer period when compared to BCU patients. These results suggest that the clinical parameters can be used to predict unfavorable outcomes in patients with COVID-19 infection, in accordance with previously published data^{10,11}.

| Measures (unit) | All patients |
|---|------------------------------|
| Hemoglobin (g/dL) | 12.8 (10.3-14.9) |
| Hematocrit (%) | 38.8 (31.5-44.6) |
| Lymphocytes (µL) | 1,410 (675-1,609) |
| Platelets (µL) | 183,000 (131,500-244,000) |
| Urea (mg/dL) | 36 (21.5-97.5) |
| Sodium (mEq/L) | 138 (135.5-140.5) |
| Potassium (mEq/L) | 4.6 (4.1-5.2) |
| Creatinine (mg/dL) | 1.19 (0.70-2.05) |
| CRP (mg/L) | 69.2 (17.3-175.8) |
| Supplemental oxygen therapy (%) | 88.1 |
| Oxygen therapy length in days | 17 (9–25) |
| ICU admission (%) | 34.2 |
| ICU length of stay in days | 12 (6–20) |
| Tracheal intubation (%) | 29.2 |
| Days to orotraqueal intubation | 11 (6-17.5) |
| Systemic glucocorticoids use (%) | 85.4 |
| Systemic glucocorticoids therapy length in days | 11 (6-17.5) |
| Daily dose of systemic glucocorticoid (mg) | 39.4 (13.1-71.2) |
| Insulin therapy (%) | 47.7 |
| Left ventricle ejection fraction on echocardiogram (n=65) (%) | 66.3 (53.7-69.2) |
| Impairment on chest CT (n=194) (%) | 75 (37.5-82.5) |
| Pleural effusion on chest CT (%) | 14.6 |

| Table 1. Baseline characteristics of patients admitted to the referra |
|---|
| hospital with coronavirus disease 19 (n=409). |

CRP: C-reactive protein; ICU: intensive care unit; CT: computed tomography. Median (interquartile range).

Both obesity and diabetes have been shown deleterious effects on host immunity, increasing the risk for infectious susceptibility and severity. These comorbidities are generally associated with low-grade chronic inflammation, which might intensify the cytokine storms, contributing to the severe outcomes of COVID-19¹². The results of this study agree with this hypothesis, with approximately 30% of the subjects fulfilling diabetes and obesity criteria. In addition, more than half of the patients hospitalized for COVID-19 infection presented previous hypertension and 18% had established CVD. According to other published studies, the prevalence of hypertension and CVD is clinically relevant in patients with COVID-19, particularly the elderly, although the impact of these conditions on the outcome is still uncertain¹³.

| | ICU (n=140) | BCU (n=269) | р | | |
|---|--|---------------------------|--------|--|--|
| Variables | | | | | |
| Age (years) | 66 (53-74) | 59 (42.2-71.7) | <0.001 | | |
| Hospitalization length in days | 19 (11-28) | 8 (5.2–12) | <0.001 | | |
| Days from symptoms to admission | 7 (3-11) | 7 (3-10) | 0.608 | | |
| BMI (kg/m²) | 26.5 (23.7–31.0) | 28.0 (23.6-32.4) | 0.524 | | |
| Glucose (mg/dL) | 184 (133–241) | 140 (118-200) | <0.001 | | |
| Impairment on chest CT (%) | 75 (50–75) | 50 (25–60) | <0.001 | | |
| Daily dose of systemic glucocorticoid (mg) | 39.4 (14.3-70.3) | 6 (6-14.7) | <0.001 | | |
| Systemic glucocorticoids therapy length in days | ticoids therapy length in days 11 (6–17) 6 (4–8) | | <0.001 | | |
| Laboratory findings on hospital admission | | | | | |
| Hemoglobin (g/dL) | 13.0 (11.3-14.0) | 13.1 (11.8–14.4) | 0.056 | | |
| Hematocrit (%) | 38.6 (34.0-41.9) | 39.2 (34.9-42.8) | 0.141 | | |
| Lymphocytes (µL) | 983 (744-1,434) | 1,313 (982-1,796) | <0.001 | | |
| Platelets (µL) | 217,000 (155,000-287,000) | 238,000 (184,000-303,000) | 0.021 | | |
| Urea (mg/dL) | 56 (37-104) | 36 (25–54) | <0.001 | | |
| Creatinine (mg/dL) | 1.13 (0.88-1.70) | 0.90 (0.70-1.17) | <0.001 | | |
| CRP (mg/L) | 234 (104-9,347) | 172 (58-7,750) | 0.183 | | |
| Laboratory findings on the fifth day of hospitalization | | | | | |
| Hemoglobin (g/dL) | 11.5 (9.5-13.1) | 12.8 (11.5-14.2) | <0.001 | | |
| Hematocrit (%) | 35.3 (29.3–39.5) | 37.5 (33.8-42.3) | <0.001 | | |
| Lymphocytes (µL) | 900 (555–1,500) | 1,629 (1,141-2,329) | <0.001 | | |
| Platelets (µL) | 235,000 (143,000-357,000) | 270,000 (192,000-377,000) | 0.005 | | |
| Urea (mg/dL) | 90 (50-149) | 45 (32-64) | <0.001 | | |
| Creatinine (mg/dL) | 1.16 (0.88-2.03) | 0.95 (0.76-1.11) | <0.001 | | |
| CRP (mg/L) | 51.8 (22.6-133) | 30.9 (10.3-88.4) | 0.001 | | |
| Death (%) | 62.8 | 12.2 | <0.001 | | |

Table 2. Comparison of patients admitted to the intensive care unit and the basic care unit.

BMI: body mass index; CRP: C-reactive protein; ICU: intensive care unit; BCU: basic care unit; CT: computed tomography. Median (interquartile range). Bold values indicate statistical significance at the p<0.05 level.

The difference found in this study between the hematological parameters of ICU and BCU patients was confirmed in other studies. A meta-analysis, including 21 studies, found significantly lower lymphocytes, platelets, and hemoglobin in patients with severe disease¹¹. Several factors may be involved in the pathogenesis of these findings, including the presence of hypoxia in critically ill patients, which may have contributed to dysfunctional hematopoiesis. Despite the medulla being a naturally hypoxic tissue, hematopoietic cells require high levels of oxygen. Another factor that may have contributed to these results is the activation of the immune system, which may contribute to the senescence of hematopoietic stem cells. In this study, the CRP values did not show a significant difference

between the groups, demonstrating that perhaps inflammation does not play a central role in bone marrow suppression and a direct effect of viral on hematopoiesis should be considered^{11,14}. Our results suggest that hematological parameters could be used for monitoring prognosis in COVID-19 patients over the course of hospitalization.

In this study, 85% of the patients were submitted to systemic therapy with corticosteroids and 34% of them were admitted to the ICU. In this group, the mean dose and duration of the therapy were higher compared to BCU patients, although ICU patients had higher CRP levels and greater lung involvement in thorax CT. Importantly, almost half of the patients evaluated required insulin therapy during hospitalization. However, only 33% of all patients had a previous history of diabetes mellitus. Corticosteroids are a class of anti-inflammatory and immunosuppressive drugs, with a high risk of adverse effects, which are time- and dose-dependent. These drugs increase hepatic gluconeogenesis and reduce peripheral glucose use, which have direct effects on glycemic control and hyperglycemia. This explains the higher use of insulin therapy in critically ill patients receiving systemic glucocorticoid^{15,16}, as recommended by the American Diabetes Association (ADA) in order to achieve better glycemic control. Huang et al., describe the importance of using corticosteroids in the treatment of critically ill patients with COVID-19, based on the justification that the damage caused by the disease is related to the intense inflammatory response that is triggered⁴. However, previous studies demonstrate that hyperglycemia and insulin resistance should be considered in the decision of dose and duration of corticosteroid therapy, especially in the setting of uncontrolled or drug-induced diabetes (depending on the dose and time of use)17. The available literature recommends attention to blood glucose monitoring in patients with a previous diagnosis of diabetes who will be undergoing corticosteroid therapy or in patients with iatrogenic hyperglycemia, considering early intervention (insulin therapy) to avoid the complications of poorly controlled blood glucose¹⁶.

This study had some limitations. We can highlight the temporality of the condition studied, the retrospective collection of data from electronic medical records, and missing data, common within this design of the study. As the strengths of the study,

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all included patients had COVID-19 infection confirmed by RT-PCR and a significant number of patients performed thorax CT, all of them evaluated by a single medical professional.

In conclusion, this study showed that patients with acute respiratory syndrome related to COVID-19 infection presented an elevated prevalence of comorbidities such as obesity, diabetes, hypertension, and CVD. In addition, critically ill patients who needed intensive care presented a significant decrease in hemoglobin, lymphocytes, and platelet parameters compared to BCU patients. Taking together, our findings suggest that patients with metabolic and cardiovascular diseases are at higher risk of worse outcomes in COVID-19 infection and that simple and accessible hematological parameters may be helpful in identifying the severity of the disease.

AUTHORS' CONTRIBUTIONS

RGT: Conceptualization, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. TMF: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. GCB: Data curation, Investigation, Writing – original draft. GLF: Data curation, Investigation, Writing – original draft. ISR: Data curation, Investigation, Writing – original draft. TBSC: Data curation, Investigation, Writing – original draft. LKML: Data curation, Investigation, Writing – original draft.

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The effect of the tumor-to-skin distance on axillary lymph node metastasis in breast cancer

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SUMMARY

OBJECTIVE: Tumor-to-skin distance is known to have an effect on axillary lymph node metastasis but has no clinical use with nomograms. This study aimed to investigate the effect of tumor-to-skin distance on axillary lymph node metastasis alone and in combination with nomogram for clinical use. **METHODS:** A total of 145 patients who underwent surgery for breast cancer (T1–T2 stage) and whose axillary lymph nodes were evaluated (axillary dissection or sentinel lymph node biopsy) between January 2010 and December 2020 were included in the study. Tumor-to-skin distance and other pathological data of the patients were evaluated.

RESULTS: Of the 145 patients, 83 (57.2%) had metastatic lymph nodes in the axilla. Tumor-to-skin distance was different in terms of lymph node metastasis (p=0.045). In the receiver operating characteristic curve for tumor-to-skin distance, area under curve was 0.597 (95%CI 0.513–0.678, p=0.046), area under curve of the nomogram was 0.740 (95%CI 0.660–0.809), p<0.001) and nomogram+tumor-to-skin distance was 0.753 (95%CI 0.674–0.820), p<0.001). No statistical difference was found for axillary lymph node metastasis between the nomogram+tumor-to-skin distance and the nomogram alone (p=0.433).

CONCLUSION: Although tumor-to-skin distance demonstrated a significant difference in axillary lymph node metastasis, it had a poor association with an area under curve value of 0.597 and did not produce a significant improvement in predicting lymph node metastasis when combined with the nomogram. The tumor-to-skin distance may be unlikely to enter clinical practice.

KEYWORDS: Axilla. Breast. Lymph nodes. Lymphatic metastasis. Neoplasms.

INTRODUCTION

Breast cancer is the most common type of cancer among women worldwide. According to the World Health Organization, there were 2.3 million new diagnoses and 685,000 deaths in 2020¹. Regional metastases to lymph nodes and surrounding tissues and distant metastases to organs such as bone, liver, and brain are considered to be among the factors that adversely affect the prognosis in breast cancer^{2,3}. Evaluation of axillary lymph node metastases in breast cancer is important in planning the patient's treatment⁴.

The most commonly used methods to evaluate axillary lymph nodes are preoperative Tru-Cut biopsy or intraoperative sentinel lymph node biopsy (SLNB)⁵. Both of these techniques are invasive and require a pathologist. Therefore, noninvasive efforts have been tried to be developed to detect metastatic lymph nodes. As part of these efforts, studies have been conducted to examine the relationship between tumorto-skin distance (TSD) and metastatic axillary lymph nodes in breast cancer. The rate of lymph node metastasis was found to be high in tumors close to skin^{4,6-10}. Although the results of these studies presented similar characteristics, there has been no use of TSD in clinics or nomograms^{11,12}. This has led us also to investigate the diagnostic value of TSD.

The present study aimed to examine the area under curve value of TSD alone and in combination with nomogram and evaluate their potential use in clinical practice for axillary lymph node metastasis in breast cancer.

METHODS

Ethical approval

This study was conducted with the approval of Ethics Committee for Non-Interventional Research (No. 2021/02-18, Date: 04.02.2021) of the Firat University.

Patient selection

Between January 2010 and December 2020, 177 female patients who underwent surgery for T1–T2 stage breast cancer were selected using the hospital data system. The exclusion criteria were as follows:

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on January 12, 2023. Accepted on January 20, 2023.

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- Having neoadjuvant chemoradiotherapy,
- T3–T4 stage tumor,
- Paget's disease,
- Recurrence of disease,
- Skin invasion,
- Multicentric cancer,
- Previous breast surgery in the studied breast,
- Skin-sparing mastectomy or excisions,
- Failure to investigate axillary lymph node status,
- Diseases that may cause alterations in the breast tissue (chronic heart/kidney disease).

This study included 145 female patients aged between 18 and 90 years who did not meet any of the exclusion criteria. The patients were classified into two groups based on having axillary lymph node metastasis. Group 1 comprised axillary nonmetastatic (N0) patients, and group 2 comprised metastatic (N+) patients. Memorial Sloan Kettering Cancer Center nomogram was used for prediction of axillary lymph node metastasis¹². Demographic and histopathological data were recorded for evaluation.

Pathological and immunohistochemical examination

All resection samples were examined by the pathology department of our institution based on standard clinical protocols. Immunohistochemistry was performed using 4-µm-thick histological tissue slides obtained from the paraffin blocks. The Olympus Microscope Digital Camera model DP71 (Olympus Co., Shinjuku, Tokyo, Japan) software imaging system was used for histological analysis of estrogen, and progesterone status was defined as positive when 10% or more of nuclei showed positive staining. For HER2 status, tumors with IHC staining of 3+ (uniform, intense membrane staining of 30% of invasive tumor cells) were considered HER2-positive. Cases with an IHC staining of 2+ were considered positive if they turned out to be positive in subsequent HER2/neu gene amplification (fluorescence in situ hybridization). HER2 1+ status and the absence of staining were considered negative. Breast cancer is divided into five molecular subtypes¹³. Histological grades were determined using the Modified Bloom-Richardson Nottingham Score index. TSD was measured macroscopically or under a light microscope.

Statistical analyses

Data analysis was performed using the SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov/ Shapiro-Wilk test was applied to assess the distribution normality of the data. Nonparametric data were presented as median (minimum-maximum) and parametric data as mean±standard deviation. The independent sample t-test was applied for normally distributed data, the Mann-Whitney U test was used for non-normally distributed data, and the chi-square or Fisher's exact test was used for nominal/ordinal data. Logistic regression analysis was performed to determine significant predictors of the axillary lymph node metastasis with univariate and multivariate analyses. Odds ratios (OR) with 95% confidence intervals were used. The optimal cutoff point of the TSD was evaluated by receiver operating characteristic (ROC) curve analysis. The comparison of nomogram with TSD+nomogram area under curves (AUCs) and the examination of the statistical significance of the AUCs were performed via the DeLong method¹⁴. An AUC-ROC >0.7 indicates a good discrimination model¹⁵. Binary logistic regression formula for TSD+nomogram was "Y=[(100-Nomogram)*(-0.04539)]+[TSD*(-0.03779)]+3.12636." The statistical level of significance for all tests was considered to be <0.05.

RESULTS

A total of 145 female patients [62 (42.8%) in group 1 and 83 (57.2%) in group 2] were included in the study. The demographic characteristics of the patients are presented in Table 1. There was a significant difference between the groups for TSD [20 mm in group 1 (1–55) and 15 mm in group 2 (2–45), p=0.045). A significant difference was observed between the groups for LVI and tumor grade (p<0.001 and p=0.008, respectively). No significant difference was observed between groups in terms of other data (p>0.05).

Univariate analysis showed that the TSD, LVI, nomogram, and grade were significantly associated with a higher risk of metastasis (p<0.05). In multivariate analysis, TSD (p=0.015) and LVI (p<0.001) were the independent risk factors of axillary lymph node metastasis. Nomogram was not entered into multivariate analysis owing to multicollinearity.

In the ROC curve analysis, the cutoff value of TSD for lymph node metastasis was calculated to be 21 mm (sensitivity 77.1%, specificity 38.7%, p=0.046). The cutoff value of the nomogram for lymph node metastasis was calculated to be 52.5 (sensitivity 69.9%, specificity 72.6%, p<0.001), and nomogram+TSD was 0.404 (sensitivity 89.1%, specificity 48.4%, p<0.001) (Figure 1). The comparison of the nomogram and TSD+nomogram curves indicated that the difference was not significant (p=0.433) (Table 2).

| Variables | | Group 1 (n=62) mean±std/median (min–max) | Group 2 (n=83) mean±std/median (min–max) | Total (n=145) | OR | p-value | |
|--------------------------------|----------------------|--|--|---------------|-------|----------|--|
| Age | | 60.29±1.586 | 60.78±1.257 | 60.57±0.986 | | 0.806ª | |
| Tumor-to-skin distar | nce (mm) | 20 (1-55) | 15 (2-45) | 17 (1-55) | | 0.045* | |
| Tumor diameter (mn | n) | 26 (7-50) | 27 (9-47) | 26 (7-50) | | 0.307* | |
| Tumor site | Right | 32 | 45 | 77 | 1.05 | 0.754** | |
| | Left | 30 | 38 | 68 | 0.95 | 0.750 | |
| | UOQ | 27 | 39 | 66 | | | |
| | LOQ | 8 | 11 | 19 | | | |
| Quadrant | LIQ | 8 | 12 | 20 | | 0.970*** | |
| | UIQ | 17 | 19 | 36 | | | |
| | Central | 2 | 2 | 4 | | | |
| ED | Negative | 10 | 14 | 24 | 0.95 | 0.906** | |
| | Positive | 52 | 69 | 121 | 1 | | |
| DP | Negative | 9 | 18 | 27 | 0.67 | 0.272** | |
| | Positive | 53 | 65 | 118 | 1.09 | | |
| | Negative | 39 | 48 | 87 | 1.09 | 0.5.27** | |
| | Positive | 23 | 35 | 58 | 0.88 | 0.537 | |
| | Type A | 5 | 11 | 16 | | | |
| | Type B HER2-negative | 29 | 30 | 59 | | | |
| Luminal types | Type B HER2-positive | 19 | 30 | 49 | | 0.698*** | |
| | HER2-positive | 4 | 5 | 9 | | | |
| | Triple negative | 5 | 7 | 12 | | | |
| Menopausal status | Premenopausal | 17 | 18 | 35 | 1.26 | 0.405** | |
| | Postmenopausal | 45 | 65 | 110 | 0.927 | 0.420 | |
| Grade | 1 | 27 | 19 | 46 | 1.90 | 0.009** | |
| | 2/3 | 35 | 64 | 99 | 2.598 | 0.008 | |
| Lymphovascular invasion | Negative | 43 | 11 | 54 | 0.36 | <0.001** | |
| | Positive | 19 | 72 | 91 | 4.43 | 0.001 | |
| | IDC | 47 | 65 | 112 | | | |
| Histological type of cancer | ILC | 6 | 10 | 16 | | 0.646*** | |
| | Mix type and others | 9 | 8 | 17 | | | |

Table 1. Distribution of data within groups.

^aIndependent sample t-test; *Mann-Whitney U test; **Chi-square test; ***Fisher's exact test. UOQ: upper outer quadrant; LOQ: lower outer quadrant; LIQ: lower inner quadrant; UIQ: upper inner quadrant; IDC: invasive ductal cancer; ILC: invasive lobular cancer. Bold values indicate statistical significance at the p<0.05 level.

DISCUSSION

This study aimed to examine the effect of TSD on axillary lymph node metastasis in breast cancer and its feasibility in clinical practice. According to the results of the study, although the TSD differed significantly between the groups, it was not superior to the nomogram, and it was not effective when used together with the nomogram. Low AUC-ROC curve value of TSD and lack of a significant difference for its combined use with nomogram compared to nomogram alone indicated that it was an inefficient parameter for clinical use in breast cancer.

Axillary lymph node metastasis plays an important role in the prognosis of breast cancer, such as the surgical margin^{16,17}. Therefore, the most reliable method for axillary lymph node involvement today is the SLNB examination¹⁸. There have been



Figure 1. Areas under the receiver operating characteristic curve for comparisons of tumor-to-skin distance, nomogram, and tumor-to-skin distance+nomogram. The area under curve of the tumor-to-skin distance, nomogram, and nomogram+tumor-to-skin distance were 0.597 (95%CI 0.513–0.678), 0.740 (95%CI 0.660–0.809), and 0.753 (95%CI 0.674–0.820), respectively.

 Table 2. Comparison of groups' discriminative abilities for axillary lymph node metastasis.

| Comparison of groups | Difference between AUCs | Significance level (p) |
|------------------------------|----------------------------|---------------------------|
| Nomogram vs. TSD | 0.143 | 0.024 |
| Nomogram vs. nomogram+TSD | 0.0128 | 0.433 |
| TSD vs. nomogram+TSD | 0.155 | 0.003 |

TSD: tumor-to-skin distance; AUC: area under curve. Bold values indicate statistical significance at the p<0.05 level.

efforts to predict the status of breast regional lymph nodes using other methods without resorting to SLNB^{11,12,19-22}. TSD is one of them. This method was reported to be associated with the tumor's proximity to dermal lymphatics²³.

Studies reported a significant relationship between TSD and axillary lymph node metastasis^{4,6-10}. Only a study by Lee et al., reported no significant difference for TSD²⁰. The studies indicated different cutoff values in the range of $3-14 \text{ mm}^{4,6-10}$. The lack of a clear cutoff value complicates the clinical use of TSD. In the present study, cutoff value was found at 21 mm. In tumors close to the skin, the rate of lymph node metastasis was higher than that in tumors far from the skin.

In the present study, the AUC-ROC value of TSD was <0.7. Therefore, the discrimination ability was categorized as weak¹⁵. In addition, the low sensitivity and specificity of the cutoff value is a reflection of this weak effect. In our

study, although there was a small increase in AUCs in nomogram+TSD compared to nomogram, no significant difference was observed between the groups in the DeLong method. Nomogram alone indicated a significant statistical superiority to the TSD. Therefore, TSD may only be a statistical parameter for predicting axillary lymph node metastasis and it may not be clinically useful. Torstenson et al., reported that TSD measurement increased the AUC-ROC from 0.71 to 0.75 on the nomogram¹⁰. However, this study made no mentioning of the pairwise comparison of ROC curves analysis that was performed for the AUC-ROC values. Therefore, it may not be possible to make a statistical comment about the AUC-ROC values. The present study is the first to compare the AUC-ROC values of nomogram with nomogram+TSD combination in the literature.

Different measurement methods can affect the results of studies. While USG was used in many studies, Ojha et al., used pathology specimens^{4,6-10}. The inability of radiologists to stabilize probe pressure while measuring with USG may have led to varying results. In our study, pathological specimens were used for the measurement.

Hormonal status and T stage are important factors that affect the treatment of breast cancer. In the present study, hormonal status of the tumor did not indicate any difference in groups. There are opposing views on hormonal status and tumor diameter^{4,6-10}. Song et al., reported no difference between groups for the luminal types, while a study reported difference between luminal A and triple negative^{13,24}. In our study, no difference was observed among the luminal types for groups. Eom et al.,¹⁰ did not report any difference among patient groups with different tumor sizes for lymph node metastases, while other studies found varying rates of difference^{4,6-8}. In the present study, no relationship was found between lymph node metastasis and tumor diameter.

Lymphovascular invasion affects tumor aggressiveness and lymph node metastasis. Eom et al., found no association between lymph node metastasis and LVI⁸. However, several other studies and the present study found a significant correlation between LVI and axillary lymph node metastasis^{4,7,10}. In the present study, LVI was the independent risk factor for axillary lymph node metastasis. Moreover, there was a significant difference in grade between groups. The grade was high in the axillary metastatic group. Similar to our findings, Cunningham et al.⁷ reported higher lymph node metastasis in higher grades while other studies reported no difference^{10,24,25}.

Among the study limitations are the retrospective and single-center nature of the study. Besides, the TSD measurements were conducted by multiple pathologists, and on a limited number of patients, which may have affected the study results.

CONCLUSION

The effect of TSD in predicting axillary lymph node metastasis is poor due to the low AUC value. Moreover, TSD was not superior to the nomogram. Due to the low AUC value of TSD and lack of a significant difference between nomogram+TSD and nomogram AUC-ROC curves, the TSD may not constitute a useful parameter for clinical use in breast cancer.

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AUTHORS' CONTRIBUTIONS

MY: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. EA: Conceptualization, Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. YSI: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Validation, Visualization. AL: Data curation, Investigation, Visualization. MFE: Data curation, Methodology, Software, Supervision, Visualization.

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Trait creativity among midwifery students: a cross-sectional study

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SUMMARY

OBJECTIVE: Midwifery services are a cornerstone of maternal care but the trait creativity of midwifery students is unclear. The aim of this study was to assess trait creativity among midwives in Taizhou, China.

METHODS: A cross-sectional online survey among midwives was conducted from July 20 to August 10, 2022. Trait creativity was assessed using the Williams Creativity Assessment Packet.

RESULTS: A total of 300 survey respondents were studied. The mean scores for the imagination dimension (p=0.032) and the risk-taking dimension (p=0.049) differed across major groups. We further compared the scores of trait creativity dimensions after excluding male participants. Midwifery students only scored lower on the specific imagination dimension (p=0.024).

CONCLUSION: The imagination level of midwifery students certainly deserves further attention. Education workers should pay more attention to the imagination of midwifery students.

KEYWORDS: Creativity. China. Imagination. Midwifery.

INTRODUCTION

Globally, maternal mortality has declined by 47% (from 400 to 210 maternal deaths per 100,000 live births) over the last two decades (1990–2010), but considerably greater progress will be needed to reach Millennium Development Goal 5¹. The availability of midwifery services has been identified as a cornerstone of quality maternal care. The provision of midwifery services was shown to have a positive effect on several outcomes of maternal care, including reductions in maternal and neonatal mortality, improved psychosocial outcomes, reductions in infections, and a shorter hospital stay for newborns². Standardized and high-quality midwifery services³.

A widely accepted definition for creativity is a person's ability to generate an idea or a product that is deemed as both novel and appropriate by experts in a field of human activities⁴. Trait creativity has a positive impact on creative thinking and creative problem-solving⁵. As we know, numerous outstanding creators like Albert Einstein always possess a great creative potential that makes them unique and acquires more creative achievements. One study demonstrated that having some college research experience (such as taking research method courses) could positively influence the creativity and critical thinking skills of both the United States and Chinese students⁶. To the best of our knowledge, this is the first study to report trait creativity for midwifery students in China.

The aims of this study were (1) to assess the score of trait creativity (i.e., imagination, challenging, risk-taking, and curiosity) among midwives based on an online survey at Taizhou University, China and (2) to compare the scores of trait creativity (i.e., imagination, challenging, risk-taking, and curiosity) among different majors.

METHODS

Study design and data collection

A cross-sectional online survey was conducted among midwifery students from July 20 to August 10, 2022. The survey collected data on the subjects' major, age, gender, grade, and parents' education level. To assess creativity, the Williams Creativity Assessment Packet scale was included in the online survey. Participation was voluntary, anonymous, and possible from July 20 to August 10, 2022⁷.

Trait creativity

The Williams Creativity Assessment Packet (Chinese version⁸) consists of four dimensions: curiosity consists of items 2, 8, 11,

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: The research was supported by 2022 Taizhou University Higher Education Teaching Reform Project (No.105 and No.114) and the Taizhou University Cultivation Project (Grant No. 2019py045). Received on October 10, 2022. Accepted on January 21, 2023.
12R, 19, 27, 33, 34, 37, 38, 39, 47, 48R, and 49 (inclination to explore or play with an idea); challenging consists of items 3, 4R, 7, 9R, 10, 15, 17R, 18, 26, 41, 42, and 50 (tend to look for new alternatives and ways to solve problems, restoring order from chaos); risk-taking consists of items 1, 5, 21, 24, 25, 28, 29R, 35R, 36, 43, and 44 (the tendency to act and defend one's ideas in disorganized conditions); and imagination consists of items 6, 13, 14, 16, 20, 22, 23, 30, 31, 32, 40, 45R, and 46 (tend to imagine and construct mental images or feel intuitively)^{9,10} "R" denotes reverse-scored items, and reverse questions were used for reverse scoring. Questions are answered on a three-point Likert scale. Participants indicated their choices on this scale, ranging from 1 (strongly disagree) to 3 (strongly agree). In this study, Cronbach's α value was 0.88, KMO value was 0.85, and Bartlett's test p=0.000 value was evident.

Data analysis

The analyzed study sample was generated by excluding surveys with missing values for the study variables. For each creativity dimension, a creativity score was derived from the individual creativity questions. The internal reliability of the creativity scores was assessed using Cronbach's alpha. The characteristics of midwives were analyzed by descriptive statistical analysis. Pearson's chi-square tests were used to assess the differences in categorical variables. One-way analysis of variance was used to assess the differences in imagination, challenging, risk-taking, and curiosity between males and females and among different majors. LSD (least significant difference) post-hoc tests were performed to evaluate post-hoc pairwise comparisons. The statistical significance level was p<0.05. All analyses were conducted using SPSSAU (Version 22.0) [Online Application Software] (https://www.spssau.com).

RESULTS

Of the 300 surveys submitted, 108 were conducted on midwives who practiced midwifery in the year before the study. The age ranged from 18 to 22 years. More than half of the subjects in the study sample were female (82.67%) and in sophomore year (43.33). Most of the subjects (36%) majored in midwifery. Over half (70.33%) of the mother's education of the subjects was junior high school and below. Over half (61%) of the father's education of the subjects was junior high school and below. The family's year income per capita (CNY) varied from >1,000,001 RMB (1%) to 80,001–150,000 CNY (32%) (see Table 1).

The scores of trait creativity dimensions

The mean scores for imagination dimension (p=0.032) and risk-taking dimension (p=0.049) differed across major groups

| Table 1. Characteristics of subjects participating in a survey | of trait |
|--|----------|
| creativity in Taizhou, China, 2022 (n=300). | |

| Items | Categories | n | Percent (%) |
|-----------------------|------------------------------------|-----|----------------|
| Condor | Male | 52 | 17.33 |
| Gender | Female | 248 | 82.67 |
| | Freshman year | 82 | 27.33 |
| Crada | Sophomore year | 130 | 43.33 |
| Grade | Sophomore year | 65 | 21.67 |
| | Senior year | 23 | 7.67 |
| | Clinical medicine | 87 | 29 |
| Major | Nursing | 105 | 35 |
| | Midwifery | 108 | 36 |
| | 0-30,000 | 46 | 15.33 |
| | 30,001-80,000 | 75 | 25 |
| Family's year | 80,001-150,000 | 96 | 32 |
| capita (CNY) | 150,001-300,000 | 63 | 21 |
| | 300,001-1,000,000 | 17 | 5.67 |
| | 1,000,001 | 3 | 1 |
| | Junior high school and below | 211 | 70.33 |
| Mother's education | High school or secondary school | 66 | 22 |
| | College degree or above | 23 | 7.67 |
| | Junior high school and below | 183 | 61 |
| Father's education | High school or secondary school | 87 | 29 |
| | College degree or above | 30 | 10 |

(Figure 1A). However, the mean score for challenging dimension (p=0.58) and curiosity dimension (p=0.17) was not statistically significant among the three major groups (Figure 1B).

To rule out a direct effect of gender on creativity, we compared gender differences in trait creativity (i.e., imagination, risk-taking, challenging, and curiosity) among major groups. The results revealed that there are statistically significant differences between groups in risk-taking dimension (Table 2), except for the following three dimensions: imagination, challenging, and curiosity. We further compared the scores of trait creativity dimensions after excluding male participants. Midwifery students only scored lower on the specific imagination dimension (p=0.024).

DISCUSSION

Based on the data from a cross-sectional online survey, we studied the level of trait creativity among midwifery



Figure 1. Comparison of the scores of imagination, challenging, risk-taking, and curiosity. (A) Including the male students. (B) Excluding the male students.

Table 2. Comparison of the scores of imagination, challenging, risktaking, and curiosity between males and females.

| | Gender (r devia | nean±std. ation) | - | - |
|-------------|--------------------|---------------------|-------|---------|
| | Male (n=52) | Female (n=248) | F | p |
| Imagination | 26.68±3.73 | 25.57±3.91 | 3.562 | 0.06 |
| Challenging | 28.16±3.56 | 27.51±3.07 | 1.867 | 0.173 |
| Risk-taking | 24.86±3.00 | 23.59±2.62 | 9.477 | 0.002** |
| Curiosity | 33.27±5.40 | 32.21±4.48 | 2.249 | 0.135 |

**p<0.01.

students in China. Our study found that the mean scores for imagination and risk-taking dimensions differed across major groups.

The imagination and risk-taking dimensions of trait creativity were lower in the major of midwifery than in the major of clinical medicine and nursing. At present, there is little literature on the creativity of midwifery students. Future studies should further expand the sample size to confirm our findings and explore the influencing factors of the low creative ability of midwifery students. This is helpful to education-related workers to further improve the cultivation of students' creative abilities.

Since gender is one of the most important factors affecting the research conclusion, the proportion of male midwifery students was small in this study. To exclude the influence of gender on the experimental results, we further analyzed the data after excluding all male students. The results revealed that midwifery students only scored lower on the specific imagination dimension. In conclusion, the creativity of midwifery students, especially the imagination dimension, deserves attention in future research.

Limitations

This study is subject to limitations. First, the survey was promoted through an online questionnaire survey (https:// www.wjx.cn). Participating students may have considered that this study can be used to underscore midwifery, which could have biased the given answers. Second, all students in our sample studied in Taizhou of Zhejiang Province (China). This might limit the validity of our findings to other provinces in China. Third, we collected data from a convenience sample of subjects, which may have introduced a selection bias to our study. Finally, we used a cross-sectional study design, which does not allow the inference of causal relationships.

CONCLUSION

This cross-sectional study assessed trait creativity among midwifery students in China. Using the Williams Creativity Assessment Packet, we found that the mean scores for imagination and risk-taking dimensions differed across major groups and the mean score for challenging and curiosity dimensions was not statistically significant among the three major groups. The imagination level of midwifery students certainly deserves further attention. Education workers should pay more attention on the imagination of midwifery students.

AUTHORS' CONTRIBUTIONS

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

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Evaluation of microRNA let-7b-3p expression levels in methamphetamine abuse

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SUMMARY

OBJECTIVE: In this study, we aimed to identify a microRNA expression signature that could be used to distinguish methamphetamine from control samples. We also utilized the existing bioinformatics tools in order to predict the candidate microRNAs that could play potential key roles in regulating drug addiction-related genes.

METHODS: Methamphetamine samples from 21 ventral tegmental area and 21 nucleus accumbens samples and their control regions were obtained from the Council of Forensic Medicine (Istanbul). Quantitative analysis of let-7b-3p was studied using quantitative reverse transcription PCR. Statistical analysis was carried out using Student's t-test. The receiver operating characteristic curves were plotted with Statistical Package for the Social Sciences (SPSS 20.0).

RESULTS: Our quantitative reverse transcription PCR results revealed that let-7b-3p was significantly overexpressed in brain tissues of the methamphetamine-user group. Let-7b-3p had significant power to discriminate methamphetamine from control samples in the ventral tegmental area (AUC; 0.922) and nucleus accumbens (AUC; 0.899) regions.

CONCLUSION: We have shown for the first time in the literature the differential expression of let-7b-3p in samples from methamphetamineaddicted individuals. We suggest that let-7b-3p could be a powerful marker for the diagnosis of methamphetamine addiction. Our results showed that differentially expressed let-7b-3p in methamphetamine users could be used as a diagnostic and therapeutic marker.

KEYWORDS: Methamphetamine. MicroRNAs. Autopsy. Biomarkers. Brain.

INTRODUCTION

Methamphetamine, usually known as "crystal meth", is the most widely used psychoactive component of illicit drugs¹. Similar to other amphetamines, methamphetamine increases the levels of neurotransmitters such as dopamine and norepinephrine and shows a notably strong serotonergic effect². Methamphetamine is one of the most widely used illegal synthetic drugs, especially in Europe (nearly 15 million users), Oceania, and North America³. The European Drug Report has estimated that the availability and use of methamphetamine have increased and the trend will continue to rise. The report also highlighted that the number of methamphetamine deaths has dramatically increased among adolescents and young adults in recent years⁴.

Drug addiction is a serious psychiatric disorder that is characterized by loss of control over drug consumption⁵. Addictive drugs converge on the mesocorticolimbic dopaminergic [DA] circuitry, which contains the nucleus accumbens (NAc) and ventral tegmental area (VTA) in the brain's limbic system⁶. Therefore, VTA and NAc regions are the major components of the brain reward system and also play a highly important role in response to drug addiction⁷. Drug addiction induces adjustment in neuroplasticity, which is regulated by permanent alterations in gene expression and protein function in the VTA and NAc8. As potent regulators of post-transcriptional gene expression, microRNAs (miRNAs) are poised to play key roles in the addiction-relevant reprogramming of neuronal gene expression in the corticostriatal system⁹⁻¹¹. miRNAs are a class of non-coding 18-25 bp long nucleotide RNAs that can regulate the expression of hundreds of genes, either by translational suppression or by degrading mRNAs to bind their complementary sequences in the 3' UTR^{12,13}. Recent studies demonstrated that miRNA expression plays a key role in drug addiction in the NAc and VTA

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on October 20, 2022. Accepted on January 09, 2023.

as well as in other regions of the mesocorticolimbic DA system^{14,15}. Furthermore, the impact of drugs such as heroin, morphine, and alcohol on differentially expressed miRNAs has been shown both *in vivo* and *in vitro*. However, the role of miRNAs in methamphetamine-seeking behaviors and the specific targets of key regulatory miRNAs need to be identified. In our previous study, we have worked on unraveling the molecular mechanisms underlying 3,4-methylenedioxymethamphetamine (MDMA)-seeking behavior to develop specific biomarkers of therapeutic approaches in postmortem human brain tissues of MDMA users¹⁶.

In this study, we have utilized diverse bioinformatics resources to predict potential miRNA regulators of drug addiction. Based on our literature search and bioinformatics analysis, we selected let-7b-3p as a top candidate biomarker for methamphetamine-seeking behavior. The family members of let-7 are extremely evolutionarily conserved across various animal species, including flies and mammals. Some known biological roles for let-7b, which was the first defined human miRNA, include the regulation of stem-cell differentiation, cell differentiation, and neuromuscular development. Many studies have shown that let-7b has putative target sites on several addiction-related genes and causes neurodegeneration diseases¹⁷. The findings of our study highlight a new role of let-7b-3p in methamphetamine-seeking behavior.

METHODS

Postmortem human brain tissue acquisition

The NAc and VTA regions of postmortem human brain tissues were collected from the Morgue Department, Council of Forensic Medicine, Istanbul, Turkey, and local ethical approval was obtained (approval number: 2020/38). The study consisted of 21 subjects (13 males and 8 females) whose deaths were ruled methamphetamine intoxication based on toxicology findings and 21 drug-free control subjects (13 males and 8 females) matched pairwise with methamphetamine users for age and gender. Post-hoc analysis elicited no meaningful differentiation between the study of methamphetamine users and the control subjects for any demographic parameter. The brain samples were collected under full ethical clearance. Cases with a history of poly-drug abuse or other complicating conditions such as HIV/AIDS were excluded. Brain specimens of VTA and NAc were collected as part of the routine autopsy process, and the tissues were flash-frozen in isopentane in liquid nitrogen. The frozen samples were stored at -80°C until further use.

Total RNA extraction

An amount of 50–100 mg of NAc and VTA brain tissues were homogenized in 1 mL TRIzol reagent (Invitrogen, USA). Total RNA was extracted following the manufacturer's instructions. Total RNA concentrations and purities of the samples were determined by spectrophotometry using a NanoDrop ND-2000 system (Thermo Fisher Scientific Inc., Wilmington, DE).

Validation by real-time RT-PCR analysis

Validation of let-7b-3p was studied from the VTA and NAc regions of 21 methamphetamine users and 21 matched controls. Let-7b-3p and RNU43 assays were purchased from Applied Biosystems, Foster City, CA. Single-stranded complementary DNA (cDNA) was synthesized from total RNA using the TaqMan[®] MicroRNA Reverse Transcription Kit according to the manufacturer's protocol (Applied Biosystems, Foster City, CA, USA). Following reverse transcription, quantitative reverse transcription PCR (qRT-PCR) reactions were carried out in duplicate using TaqMan[®] MicroRNA Assays (Applied Biosystems) in a Light Cycler 480-II real-time thermal cycler (Roche, Switzerland, Basel). RNU43 was used for the normalization of miRNA expression analyses. Relative quantification analysis was performed by delta-delta-Ct (2^{-ΔΔCT}) calculation as described previously¹⁸.

Statistical analysis

Data presented as means±standard error and Student's t-test (unpaired, two-tailed) were used for statistical analysis of the qRT-PCR. A two-tailed p-value of 0.05 or below was considered statistically significant. The receiver operating characteristic (ROC) curves were plotted using SPSS 21.0 (Statistical Package for the Social Sciences) to determine the power of control and validated let-7b-3p to differentiate between the samples.

Target analysis and miRNA target prediction

We used miRDB (http://www.mirdb.org/), TargetScan 6.0 (www. targetscan.org), and mirTarBase (http://mirtarbase.mbc.nctu. edu.tw/) to identify the predicted let-7b-3p targeting mRNAs with p-value smaller than 0.01 involved in addiction. Using STRING (http://string-db.org/) to demonstrate the interrelationships between genes and their interactive functional networks, we demonstrated the common let-7b-3p targets in protein-protein interaction (PPI) networks.

RESULTS

A total of 21 methamphetamine tissues (21 VTA and 21 NAc) and 21 normal tissues (21 VTA and 21 NAc) were obtained

from the Council of Forensic Medicine, Istanbul, Turkey. We performed qRT-PCR to investigate the expression levels of let-7b-3p in order to determine the differences between methamphetamine and control subjects in VTA and NAc parts of human postmortem brain tissues. The mean age of methamphetamine subjects was 27.61±9.08, whereas controls had an average age of 30.09±10.43 years (Table 1). The methamphetamine group was found to have methamphetamine in the blood ranging from 569.3 to 1025.6 ng/mL with a median of 798 ng/mL (Table 1).

 Table 1. Age, brain pH, postmortem interval, and methamphetamine in the blood level of methamphetamine and control postmortem samples that were involved in the study.

| | Methamphetamine (n=21) | Control (n=21) | p-value |
|--------------------------------|---|-------------------|---------|
| Age | 27.61±9.08 | 30.09±10.43 | 0.42 |
| Brain pH | 6.61±0.25 | 6.48±0.23 | 0.09 |
| PMI | 17.38±4.55 | 16.9±4.47 | 0.74 |
| Blood level of methamphetamine | 798 ng/mL (569.3-1025.6 ng/ mL min-max) | _ | - |

PMI: postmortem interval.

When the two groups were compared in terms of the postmortem interval (PMI) samples, the difference between the mean PMI levels of the two groups was not significant. We investigated the expression profiles of let-7b-3p in methamphetamine samples and controls in VTA and NAc parts of brain tissues using qRT-PCR analysis. The results showed that the expression levels of let-7b-3p in VTA samples and NAc samples in Figure 1A (p<0.002 and p<0.004, respectively) were significantly upregulated in methamphetamine-addicted brain tissue samples compared to normal tissues.

To test the power of let-7b-3p for distinguishing the methamphetamine group from controls, we plotted ROC curves and the results showed that let-7b-3p had a higher area under the curve for NAc (AUC; 0.899) and VTA regions (AUC; 0.922) (Figure 1B).

The biological process, molecular function, cellular component, and KEGG pathways analysis of the potential targets of let-7b-3p with functional enrichments in the PPI network showed that the genes shown in Table 2 play an important role in the mechanisms of neurexins and neuroligins and in the neuronal system (Figure 1C).



Figure 1. (A) Relative expression levels of let-7b-3p in control versus methamphetamine-addicted brain tissues. (B) ROC analysis of let-7b-3p in methamphetamine versus control samples (NAc and VTA regions). Let-7b-3p cooperative power to discriminate two sets of samples composed of 21 methamphetamine and 21 control samples. (C) PPI network of commonly deregulated let-7b-3p targets. Pink: experimentally determined (known interactions); blue: from curated databases (known interactions); yellow: text mining; green: gene neighborhood (predicted interactions); black: co-expression. The interaction score was set to high confidence of 0.49. ***p<0.01.

| DethursulD | Biological process (GO) | | Falsa diagona manta | |
|------------|--|------------------|----------------------|--|
| Pathway ID | Pathway description | Count in network | Faise discovery rate | |
| GO:0048699 | Generation of neurons | 11 | 8.43e-06 | |
| GO:0031175 | Neuron projection development | 8 | 1.54e-05 | |
| GO:0030182 | Neuron differentiation | 9 | 1.60e-05 | |
| GO:0010976 | Positive regulation of neuron projection development | 6 | 2.16e-05 | |
| GO:0051962 | Positive regulation of nervous system development | 7 | 3.63e-05 | |
| | Molecular function (GO) | | | |
| | Pathway description | | | |
| GO:0099106 | lon channel regulator activity | 3 | 0.0177 | |
| GO:0005184 | Neuropeptide hormone activity | 2 | 0.022 | |
| GO:0098772 | Molecular function regulator | 7 | 0.0248 | |
| GO:0005246 | Calcium channel regulator activity | 2 | 0.0248 | |
| | Cellular component (GO) | | | |
| | Pathway description | | | |
| GO:0150034 | Distalaxon | 6 | 1.43e-05 | |
| GO:0098793 | Presynapse | 6 | 2.28e-05 | |
| GO:0043005 | Neuron projection | 9 | 2.28e-05 | |
| GO:0030426 | Growth cone | 5 | 2.28e-05 | |
| GO:0030424 | Axon | 7 | 2.28e-05 | |
| | KEGG pathways | | | |
| | Pathway description | | | |
| GO:6794361 | Neurexins and neuroligins | 3 | 0.0016 | |
| GO:112316 | Neuronal system | 4 | 0.0078 | |

Table 2. Biological, molecular, cellular functions gene ontology, and Kyoto Encyclopedia of Genes and Genomes pathway analysis of let-7p-3p potential targets for functional enhancements in the protein-protein interaction network.

GO: gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes.

DISCUSSION

Drug addiction is believed to be a neurological dysfunction because altered gene expression affects neuronal function and eventually behavior. Early detection and correct diagnosis are especially important for methamphetamine addiction in the therapy decision-making process. miRNAs have become a popular research subject among scientists in recent years. It has been shown that miRNAs can be used to explain several addiction processes, and determining the levels of miRNAs is proposed as an important approach to overcome therapeutic resistance in drug addiction. They are potential diagnostic and therapeutic biomarkers that have been shown to be present in the use of various types of drugs in recent years¹⁹.

MicroRNAs, which are among the non-coding RNAs, have a critical role in gene expression. The first known human miRNA, let-7, is expressed in both embryonic and adult mammalian brains. Let-7b serves as a key regulator of neural stem cell proliferation and differentiation. Overexpression of let-7 elicits neuronal cell proliferation and accelerated neural differentiation²⁰.

The let-7 miRNA family was identified as a top candidate based on the number of assumed target sites. This study experimentally validated the *in silico* prediction that *let-7b-3p*, which is a member of the let-7 miRNA family, can interact with methamphetamine addiction.

Downregulation of let-7 was found to increase morphine and related μ -opioid receptor (MOR) expression in a human neuroblastoma cell line. This suggests that MOR is a target of let-7 because the expression of MOR is under constitutive suppression by let-7. Accordingly, morphine treatment causes an increase in let-7. Chronic morphine treatment notably upregulated let-7 expression in sensory neurons and brain stem nuclei²¹. The brain expression of the level of let-7 increases after morphine treatment, temporally correlating with the development of tolerance to morphine. Treatment with a let-7 inhibitor decreases brain let-7 levels and opioid tolerance. Let-7b has been previously proposed as an important factor for distinguishing morphine exposed from non-morphine-exposed brain tissues²². In parallel with this finding, our results showed that let-7b-3p is significantly overexpressed in brain tissues.

Recent studies have identified the role of several miRNAs in mammalian midbrain dopaminergic neurons and that they are related to addictive behaviors. Deregulation of let-7 seems to play a key role in neurological disorders²³. Also, cocaine addiction affects the expression of let-7d, highlighting the possibility that some miRNAs are important regulators of the brain reward pathway and likely implicated in addiction²¹. Toll-like receptor (TLR) signaling is known to be a key component of neurodegeneration, and TLR7 responds to miRNAs in promoting immune responses leading to neurodegeneration²². Moreover, an alcoholic individual's brain contains more ATP (adenosine triphosphate) than a non-alcoholic individual's brain, and alcohol dependence is associated with hippocampal degeneration. Studies of postmortem human alcoholic brain hippocampal tissues have shown that increased expression of TLR7 and let-7b causes neurodegeneration²⁴.

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CONCLUSION

Our findings show that let-7b-3p is differentially expressed in methamphetamine users and let-7b-3p could serve as a potential biomarker for predicting methamphetamine abuse and treatment response. Let-7b-3p has been linked to mechanisms of drug abuse, and further studies would be very important in developing preventive strategies and new therapeutic interventions for methamphetamine abuse.

ACKNOWLEDGMENTS

We gratefully acknowledge the directors of the Council of Forensic Medicine for tissue acquisition.

AUTHORS' CONTRIBUTIONS

EGT: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation. Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **GD:** Conceptualization, Data curation, Funding acquisition, Investigation. Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. **HA:** Conceptualization, Formal Analysis, Project administration, Resources, Software, Supervision, Validation, Writing – original draft.

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An online platform for COVID-19 diagnostic screening using a machine learning algorithm

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SUMMARY

OBJECTIVE: COVID-19 has brought emerging public health emergency and new challenges. It configures a complex panorama that has been requiring a set of coordinated actions and has innovation as one of its pillars. In particular, the use of digital tools plays an important role. In this context, this study presents a screening algorithm that uses a machine learning model to assess the probability of a diagnosis of COVID-19 based on clinical data. METHODS: This algorithm was made available for free on an online platform. The project was developed in three phases. First, an machine learning risk model was developed. Second, a system was developed that would allow the user to enter patient data. Finally, this platform was used in teleconsultations carried out during the pandemic period.

RESULTS: The number of accesses during the period was 4,722. A total of 126 assistances were carried out from March 23, 2020, to June 16, 2020, and 107 satisfaction survey returns were received. The response rate to the questionnaires was 84.92%, and the ratings obtained regarding the satisfaction level were higher than 4.8 (on a 0–5 scale). The Net Promoter Score was 94.4.

CONCLUSION: To the best of our knowledge, this is the first online application of its kind that presents a probabilistic assessment of COVID-19 using machine learning models exclusively based on the symptoms and clinical characteristics of users. The level of satisfaction was high. The integration of machine learning tools in telemedicine practice has great potential.

KEYWORDS: COVID-19. Machine learning. Diagnosis. Telemedicine.

INTRODUCTION

The emerging public health emergency and the new challenges imposed by COVID-19 have configured a complex panorama¹ that has been requiring a set of coordinated actions and has innovation as one of its pillars. In particular, the use of digital tools plays an important role. The use of telemedicine was encouraged as an alternative form of care². On the contrary, artificial intelligence (AI) tools can be of fundamental value. This encompasses a complex framework of sophisticated mathematical-computational models that allow the construction of algorithms to be used to emulate the realization of various human tasks, such as pattern recognition, problem-solving, and language processing³. There is an AI subarea called machine learning (ML), which offers the possibility of learning from experience gained with large databases collected and properly processed³. Several applications using ML have been proposed with very promising results^{4,5}. In this context, in this study, we developed an application software that uses an ML risk model to estimate the probability of a diagnosis of COVID-19 based on clinical data. This application was made available for free on an online platform.

Application software

In this section, a summary of the system—registered with the Brazilian Institute of Intellectual Property—is presented. It consists of four steps: (1) symptoms, in which a user inputs the patient's clinical data regarding symptoms; (2) radiography, an optional step, such that the user submits a frontal radiograph of the patient's chest; (3) general information, such that this information is related to the patient's demographic; and (4) an estimate, which presents a probability of a patient having COVID-19.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on October 24, 2022. Accepted on January 20, 2023.

Before entering the phases described previously, a screen with general information about the system is first presented. Upon entering the platform link (Figure 1), the user accesses a home screen, which has an option to click to find out more information about the system ("Learn More" button), which brings information about what the project is, its motivations, and specifics about the programming part or start entering your clinical information ("Start" button).

Symptoms

By clicking on "Start," the patient has access to a screen, in which he must select the symptoms he has had in the past 15 days.

Radiography

At this stage, the user sends a photo of the patient's radiograph. This should be a frontal chest X-ray. The image can be taken from a smartphone or in its original format. Some procedures are informed so that more than one image is not placed in the photo and that it is taken close and vertically.

General information

On the subsequent screen, users must inform about gender, age (if over 60 years), and the presence of comorbidities and must also accept the terms and conditions and the privacy policy. If you click on "Previous," the user is taken to the screen before the one he is browsing.

By clicking on "Analyze," the system outputs the probability that the patient in those conditions has the disease. Figure 2 shows an example of a user aged 60 years, without comorbidities who presented symptoms of arthralgia, hyposmia, cough, fever, and chills. The tool indicated an 80% probability that a user with these clinical characteristics had the disease.

METHODS

The project was developed in three phases. First, a risk model was developed. Second, a system was developed which would allow the user to enter patient data. Finally, this platform was used in teleconsultations carried out during the pandemic period.

Phase 1: machine learning risk predictor

The ML risk predictor works from the patient's symptom characteristics and, optionally, with imaging characteristics of their lung radiograph. The risk model constructed is based on a Bayesian model. In the case of radiography data entry, ML is used to predict pulmonary anomalies. The information used for building a risk predictor was obtained from scientific articles, such as the selection of the most common symptoms and the presence of other important clinical characteristics. Regarding radiography, a convolutional neural network is trained for learning anomaly lung features from images of a public radiography database⁶. Submitting the chest X-ray, however, is optional and was not considered in phase 3. The evaluation of the model's performance was performed using a set of traditional metrics that include sensitivity, specificity, accuracy, and the area under the receiver operating characteristic curve (AUC).



Figure 1. Machine learning tool presentation screen.

Phase 2: online platform development

In this phase, we develop an online platform freely available at https://tools.atislabs.com.br/covid. This platform can be consulted in both Portuguese and English. It allows the patient to report the symptoms presented in the last 15 days as well as their clinical data. It returns the probability of having the diagnosis of COVID-19. Probability value less than 50% was considered low probability, between 50 and 69% medium probability, and 70% and above high probability. The platform does not solicit or store user registration information, nor does it collect information from the devices or devices used to access the website and the application. However, the user is required to agree to its terms of use and privacy, which include the purpose of the tool, its limitations, and compliance with the General Data Protection Law. The authors declare no conflicts of interest. The study was conducted following the Declaration of Helsinki and followed ethical standards.

Phase 3: use of the platform in teleconsultation service

The ML tool was tested under the "Seacor Digital" project from March 23, 2020 to June 16, 2020. The project's idea was to help patients receive medical care from a distance in order to avoid unnecessary crowds, which was mainly due to the fear of many patients when seeking in-person care. Teleconsultations were carried out on a platform developed for this purpose and lasted 30 min. If the physician felt the need, the patient was referred to the emergency room for immediate care or was instructed to carry out a face-to-face consultation. In addition, consultation with specialists was carried out, if necessary. If COVID-19 was suspected, the ML tool was used to estimate the probability of a diagnosis of the disease. Patients with other clinical suspicions received general guidance on COVID-19 and were instructed to use the ML tool in case of symptoms. Patients were invited to answer an anonymous survey to assess their satisfaction with the project. They were asked to evaluate five aspects of care: ease of scheduling; the professional's interest in their health status; punctuality of the health professional; resolution of the main complaint by the professional; and access to the virtual room (on a scale of 0-5). In this survey, it was also asked how much (on a scale of 0-10) the patient would recommend the project to a friend or relative. This allowed the calculation of the Net Promoter Score (NPS). It was published in 2003 by Frederick Reichheld⁷. The idea is simple and consists of asking the customer what grade he recommends the service of a particular company, on a scale of 0-10. A customer who gives a grade of 9 or 10 is called a promoter. Grade 7 or 8 was classified as neutral, and a score of 6 or below represents a detractor. The NPS is the result of the percentage difference between promoters and detractors.

RESULTS

The tool was advertised on the main television channels in Brazil. The number of accesses in the period was 4,722 (16,400 pageviews). In the "Seacor Digital" project, 126 assistances were



Figure 2. Output screen with probability estimation.

carried out and 107 satisfaction survey returns were received. Professional's interest in their health status and resolution of the main complaint received the maximum grade, while all other items received a score of 4.83 (ease of scheduling), 4.85 (access), and 4.92 (punctuality of the health professional). There were 101 promoters and 6 neutral. The NPS was 94.4 (Figure 3).

DISCUSSION

In the present study, a decision-support algorithm capable of evaluating the probability of a diagnosis of COVID-19 in patients with the suspected disease was developed. To the best of our knowledge, this is the first application of its kind that presents a probabilistic assessment of suspected disease using ML models exclusively based on the symptoms and clinical characteristics of users. The application of ML tools to estimate the probability of a disease has been of great value not only within the scope of this study but also in several different clinical contexts. In addition, the tool developed here does not require the use of adequate information for additional exams and, as it is free, allows people to use it free of charge if they have access to the internet. The user's exemption from filling in personal information such as name, telephone, and email, as well as the need to agree to the terms and conditions and the privacy policy add additional security concerning user anonymization and the security of sensitive data, which aligns the needs of transparency and compliance⁸⁻¹⁰.

In this context, the experience of applying the tool in a telemedicine context was very productive. The results obtained



Figure 3. Evaluation of five aspects of care and Net Promoter Score.

were very promising. The response rate to the questionnaires was 84.92%, and the ratings obtained were higher than 4.8. The worst grades were related to connectivity and access issues. Some important variables in this process may include issues related to infrastructure and digital literacy. Smith and Magnani highlighted that people harmed by the social determinants of health may face difficulties in accessing digital health owing to the lack of means to do so. They also reiterated that in addition to this access barrier, the lack of adequate literacy can contribute to difficulties in understanding the content¹¹. On the contrary, the NPS achieved was high (94.4), which reflects a promoter score. Alismail et al., used NPS in an Outpatient Allergy and Pulmonary Clinic to evaluate its performance. They compared a Tablet-Based Tool (using NPS) and a Traditional Survey Method. The response rate was 37.9% (648 responses) versus 27% (156 responses). They both had similar outcomes regarding patient satisfaction. The NPS was also high and achieved 96%12.

These experiences show that the use of NPS seems to have potential in a clinical context. Another merit of this study was the integration of ML tools in clinical practice since the tool could be tested in practice. The integration of algorithms into practice brings with it several challenges. In this context, this tool had the advantage of being conceived in such a way that it included an important intersection between the team that would be involved in carrying out the telemedicine care and the development team, which certainly contributed to its improvement. Taha et al., pointed out that telemedicine care can achieve the same status as face-to-face consultations from a quality point of view¹³. Despite this, it is important to emphasize that the study had noteworthy limitations. The first one is that the developed tool was validated in a context with a small number of patients in a retrospective study. The pandemic indeed posed severe difficulties for research, whether from a budgetary point of view or regarding its performance per se; however, it is important to increase the number of patients. Furthermore, validation takes place in a single center, which certainly raises the need for validation in other contexts.

CONCLUSION

Our study developed an online platform for screening patients with suspected signs and symptoms of a disease caused by COVID-19. This tool performs an automated calculation of infection risk probability using an ML algorithm after the user has entered the requested clinical information. It was used successfully in a telemedicine project during the pandemic. The results obtained were very promising (NPS=94.4). Despite the various challenges present in the digital ecosystem, we believe that the integration of ML tools in telemedicine activities can bring important benefits to patients and contribute to the generation of value in the health chain.

AUTHORS' CONTRIBUTIONS

EMSF: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **RST**: Conceptualization, Investigation, Methodology, Software, Writing – review & editing. **BJD**: Data curation, Formal Analysis, Investigation, Software. **AHNPG**: Conceptualization, Methodology, Project administration, Writing – original draft. **LCOP**: Conceptualization, Data curation, Project administration. **LGRNP**: Conceptualization, Methodology, Project administration, Writing – original draft. **FBC**: Conceptualization, Data curation, Formal Analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **LGMA**: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **AM**: Methodology, Validation, Writing – original draft, Writing – review & editing.

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Lung and physical function in post COVID-19 and clinical and functional associations: a cross-sectional study in Brazil

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SUMMARY

OBJECTIVE: The purpose of this study was to assess exercise capacity, lung and physical function in COVID-19 survivors, and the association of lesion-level characteristics assessed by chest computed tomography, probable sarcopenia, and percentage of diffusing capacity of the lung for carbon monoxide with clinical and functional variables.

METHODS: This study was conducted in Salvador, Bahia, Brazil. All patients had a laboratory-confirmed SARS-CoV-2 infection. The sociodemographic characteristics, COVID-19 exposure history, pulmonary function, computed tomography, and functionality of the participants between 1 and 3 months of diagnosis of the disease were collected.

RESULTS: A total of 135 patients after COVID-19 recovery were included in this study. Probable sarcopenia, reduction in percentage of diffusing capacity of the lung for carbon monoxide, and a lower 6-min walk distance were observed after COVID-19 infection. Computed tomography>50% was associated with a longer length of stay and a lower percentage of diffusing capacity of the lung for carbon monoxide. Probable sarcopenia diagnosis was associated with a worse percentage of the predicted 6-min walk distance in relation to the predicted, absolute 6-min walk distance (m), percentage of diffusing capacity.

CONCLUSION: Muscle disability and lung dysfunction are common in COVID-19 survivors. Hospitalization was associated with the worst muscle force and diffusing capacity of the lung for carbon monoxide. Computed tomography characteristics could be a marker of prolonged hospital stay after the acute phase of COVID-19. Additionally, the probable diagnosis of sarcopenia could be a marker of impact on walking distance. These results highlight the need for long-term follow-up of those patients and rehabilitation programs.

KEYWORDS: COVID-19. Post-acute COVID-19 syndrome. Functional status. Respiratory function tests. Sarcopenia.

INTRODUCTION

Clinical and functional sequelae after COVID-19 have been described, including abnormalities in pulmonary function tests, chest imaging, and physical performance outcome measures in hospitalized and non-hospitalized patients^{1,2}. Post-covid syndrome, which is not one condition, is defined by the National Institute for Health and Care Excellence (NICE) as "signs and symptoms that develop during or after an infection consistent with covid-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis³."

Based on this, Nalbandian et al.⁴ reinforced the need that a comprehensive understanding of patient care needs beyond the acute phase will help in the development of infrastructure for COVID-19 clinics that will be equipped to provide integrated multispecialty care in the outpatient setting. Furthermore, decreased levels of physical function, muscle strength, and exercise capacity are associated with an increased risk of mortality in the general population and in people with chronic diseases⁵.

In Brazil and around the world, there were a million confirmed cases of COVID-19. Most infected individuals remain asymptomatic or have a mild or moderate form of the disease (85%), with non-specific symptoms such as fever, cough, myalgia, sputum, and fatigue^{6,7}. Thus, most available data focus on symptoms-related events data, and thus data about pulmonary and musculoskeletal functionality are scarce in the national and international literature. Thereby, we aimed to describe the characteristics of patients reporting prolonged symptoms after an infection with COVID-19 and examine the associations and correlations of computed tomography (CT) findings, probable sarcopenia, and percentage of diffusing capacity of

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on October 25, 2022. Accepted on January 02, 2023.

the lung for carbon monoxide (%DLCO) with clinical and functional variables.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study design

The study was approved by the ethics committee of Bahia Medicine of Faculty, Bahia Federal University (FMB/UFBA), Brazil (CAEE: 41132020.4.0000.5577). A cross-sectional study was performed, and data were collected (from April 2020 to August 2021) from post-COVID patients. Written informed consent was obtained from all patients.

Setting and participants

This study was conducted in Salvador, Bahia, Brazil. The diagnosis of COVID-19 was based on CDC criteria. All patients had a laboratory-confirmed SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR). All adult patients, who were diagnosed with COVID-19 between 1 and 3 months and who underwent pulmonology treatment, were consecutively enrolled according to the World Health Organization (WHO) interim guidance. The inclusion criteria were as follows: (a) over 18 years of age; (b) positive RT-PCR assay; (c) no previous neurological sequelae; (d) inability to perform either the test (limited mobility or any joint/mobility pain); (e) hemodynamic stability; and (f) time for COVID-19 diagnosis≥3 months.

Variables/quantitative variable

Sociodemographic characteristics and medical history

The electronic medical record was used to extract the sociodemographic characteristics of the participants [age, gender, height, weight, body mass index (BMI), obesity or overweight (considering the WHO definition), smoking status, exercise activity, medical history (i.e., laboratory results – to help determine comorbidities, medication use, and chronic conditions), and chest imaging (chest CT scans)]. Comorbidities were included in the search. Exclusion criteria were as follows: (1) previous myopathy and (2) previous locomotor limitations.

COVID-19 exposure history

The diagnosis date, main symptoms, oxygen supplementation and/or invasive and noninvasive ventilation (NIV) support, COVID-19-specific therapies, hospitalization, if necessary, ICU admittance history, and outcomes were recorded. The severity of patients with COVID-19 infection was determined according to the WHO classification.

Clinical and functional variables

The specific questionnaire of symptoms-modified Medical Research Council (mMRC) dyspnea scale was used. The mMRC scale is a self-rating tool to measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 to 4⁸. Lung function (spirometry and DLCO) and functionality variable were measured.

Data sources/measurement

Pulmonary function and chest computed tomography

The forced vital capacity, forced expiratory volume at 1 s, FEV1/FVC ratio, total lung capacity (TLC), and DLCO were measured during complete PFT. PFT data were collected as a percentage predicted based on previously published reference equations. FEV1/FVC was reported as the raw number ratio. Interpretation of the obtained values was based on the ATS-ERS criteria⁹. In addition, lesion-level characteristics were assessed by chest computed tomography (CT).

Five times sit-to-stand test

Participants were asked to stand up five times in a row as quickly as possible from a chair without stopping, keeping their arms folded across their chest. Participants had to come to a full standing position each time they stood up and to sit all the way down each time. Time (in seconds) or inability to perform the test was used for the present analyses¹⁰. The cutoff point to probable sarcopenia was $\geq 12 \text{ s}^{11}$.

Short physical performance battery

The lower extremity function was assessed using the short physical performance battery (SPPB) with the predicted normal values of Bergland et al.¹². Following the Asian Working Group for Sarcopenia 2019¹¹ and considering that impaired mobility defined as SPPB score ≤ 9 was more predictive of all-cause mortality in a systematic review¹³, SPPB score ≤ 9 was considered low physical performance.

6-min walking test and 6-min step test

All participants performed 6-min walking test (6MWT) based on the American Thoracic Society/European Respiratory Society standards. The measured 6-min walk distance (6MWD) values were compared with the predicted values using a reference equation¹⁴. The absolute 6MWD was expressed as a percentage of the predicted 6MWD (%6MWD).

6-m gait speed

The gait speed was calculated for each participant using distance in meters and time in seconds. All studies used instructions to walk at a maximal pace and from a standing start. Two cones were placed 10 m apart and provided a 2 m acceleration zone, a 6 m timing area, and a 2 m deceleration zone. The subjects were instructed to "walk as fast as you can safely, without running" from one cone to the other. The time to walk 4 m was measured with a manual stopwatch¹⁵. Low physical performance is predicted when the gait speed is <1.0 m/s¹¹.

Time up and go test

The time up and go test (TUGT) assesses basic mobility skill as well as strength, balance, and agility. Time (in seconds) taken to rise from sitting in an armchair, walk 3 m, turn, walk back to the chair, and then sit down using regular footwear and a walking aid if required was measured¹⁶. Following EWGSOP2¹⁷, sarcopenia cutoff point to TUG is ≥ 20 s.

Bias

Our results may be subject to selection bias.

Study size

The sample size was calculated using the Epi info statistical package version 7. Based on the following parameters for a cross-sectional study – expected post-COVID-19 cases 0.17, with an acceptable margin of error of 0.05, a design effect of 1, and a 95%CI, the required sample size will be 131 patients.

Statistical methods

Data were coded and analyzed using the Statistical Package of Social Science (SPSS) software program, version 22 (IBM SPSS 22 Statistics for Windows, Armonk, NY: IBM Corp). The statistical analysis plan was determined using the Shapiro-Wilk test. Continuous data were reported as mean±standard deviation (SD) or median and interquartile range. Frequency and percentage were used to denote qualitative variables. A comparison of quantitative variables was conducted using the Mann-Whitney test or Student's t-test. The relationships between 6MWD and functional variables were examined using Spearman correlation coefficients (r). P-value≤0.05 was considered substantially significant.

RESULTS

A total of 135 patients after recovery from COVID-19 (1.45±0.69 months after recovery) were included in this study. There were 69.6% men and 30.4% women, with a mean age of 56.9±13.3 years. Demographic, anthropometric, physiological, and clinical characteristics of patients are shown in Table 1.

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| Characteristics | Mean±SD (n) | Value % (n) |
|----------------------------|---------------------------------|-------------|
| Age (years) | 56.9±13.3 (135) | |
| Gender | | |
| Female | | 30.4 (41) |
| Male | | 69.6 (94) |
| BMI | 27.9±4.8 (135) | . , |
| Obese (BMI>30) | | 34.1 (45) |
| Overweight | | 37.9 (50) |
| Obesity or overweight | | 71.2 (94) |
| Comorbidities | | |
| Hypertension | | 35.9 (47) |
| Diabetes | | 16 (21) |
| Cardiopathy | | 10.1 (13) |
| Other comorbities | | 67.9 (91) |
| Tabagism | | 1.5 (2) |
| Internation | | |
| Yes | | 52.6 (71) |
| No | | 47.4 (64) |
| Internation (days) | 16.3±15.9 (2-76 days) (135) | |
| ICU internation | | |
| Yes | | 29.6 (40) |
| No | | 70.4 (95) |
| Mechanical ventilation (IV | or NIV) | |
| Yes | | 12.6 (17) |
| No | | 87.4 (118) |
| ICU days | 124.6±15.4 (1-64 days) (135) | |
| Percentage of lung disease | 2 | |
| Normal | | 5.2 (7) |
| 25 | | 15.6 (21) |
| 25-50 | | 28.1 (38) |
| 50-75 | | 14.1 (19) |
| >75 | | 3.7 (5) |
| Corticosteroids | | 95 (132) |
| Dyspnea post COVID (MR | C) | |
| 0 | | 53.3 (72) |
| 1 | | 29.6 (40) |
| 2 | | 11.1 (15) |
| 3 | | 1.5 (2) |
| 4 | | 4.4 (6) |

BMI: body mass index; IV: invasive ventilation; NIV: noninvasive ventilation; MRC: Medical Research Council.

Hospitalization and ICU admission were observed in 52.6 and 29.6% of sample, respectively. The mean day of hospitalization was 16.3 ± 15.9 . Notably, 12.6% of sample used mechanical ventilation support. Table 2 shows the pulmonary function of the study patients, and 35.1% of sample presented DCLO lower than 80%.

Additionally, the mean of 6MWD in all subjects was 517.7 ± 103.3 m ($86.0\%\pm14.0$ of the predicted walking distance) (Table 2). It is important to highlight that probable sarcopenia was observed in 17.8% of patients. Four patients had the gait speed test lower than cutoff point (<1 m/s), one patient had

Table 2 Long for atting and for atting lite manyles dominance to COVID 10

| Characteristic | Mean±SD (n) | Value % (n) |
|-----------------------|-------------------|-----------------|
| FVC liters | 3.5±1.0 (77) | |
| FVC% | 81.8±15.5 (77) | |
| TLC liters | 5.8±4.9 (74) | |
| %TLC | 82.4±16.0 (74) | |
| FEV1 liters | 2.8±0.8 (76) | |
| FEV1% | 82.7±13.9 (76) | |
| FEV1/FVC % | 81.3±8.3 (71) | |
| FEF 25-75% | 104.8±39.9 (71) | |
| DLCO abs | 18.4±6.2 (77) | |
| %DLCO | 74±17.5 (77) | |
| DLCO<80% | · · · · · · | |
| Yes | | 35.1 (26) |
| No | | 64.9 (48) |
| 6MWD (m) | 517.7±103.3 (124) | |
| Predictive 6MWTD (m) | 598±65.4 (124) | |
| Predictive 6MWD (%) | | 86.0±14.0 (135) |
| 6MWT or 6MST desatura | ation | |
| Yes | | 19.3 (26) |
| No | | 80.7 (109) |
| 6MST | 143.3±40.1 (11) | |
| TUG (s) | 6.1±1.6 (135) | |
| TVM (m/s) | 2.04±0.54 (135) | |
| SPPB | 11.7±0.9 (135) | |
| FTSTST (s) | 8.7±4.5 (125) | |
| Sarcopenia | | |
| Yes | | 17.8 (24) |
| No | | 74.8 (101) |

FVC: forced vital capacity; TLC: total lung capacity; FEV: forced expiratory volume; DLCO: diffusing capacity of the lung for carbon monoxide; MWD: min walk distance; MWT: min walking test; TUG: time up and go; SPPB: short physical performance battery.

SPPB lower cutoff point (\leq 9), and one and four patients had the TUG test>12 s and >10 s, respectively.

Spearman correlation coefficients were calculated from (1) hospital days and 6MWD (m) (r=-0.32, p=0.001); (2) hospital days and DLCO abs (r=-0.53, p<0.001); (3) hospital days and %DLCO (r=-0.76, p<0.001); (4) sit-to-stand test and 6MWD (m) (r=-0.495, p<0.0001); and (5) DLCO abs and 6MWD (m) (0.49, p<0001).

Differences in functional status were observed between hospitalized and non-hospitalized patients (Table 3). Hospital stay was significantly superior to CT>50% compared to CT<50% [median (IQ)=16.5 (23.5) *versus* 9.5 (10.5), p=0.015]. %DLCO was significantly lower to CT>50% compared to CT<50% [median (IQ)=77 (25) *versus* 66 (20.5), p=0.01]. No differences were observed to 6MWD (m), 6MWD, %-predicted, 6-m gait speed, 5xSTS, TUGT, and SPPB. Probable sarcopenia was associated with worse 6MWD, %-predicted in relation to predicted [70 (21.9) *versus* 90.5 (10.0), p<0.0001], 6MWD (m) [396 (174.5) *versus* 551 (103.3), p<0.0001], %DLCO [70(24) *versus* 77.5 (23.5), p=0.018], and percentage of TLC (%TLC) [72(28.5) *versus* 87(20.8), p=0.006].

DISCUSSION

Although most people with COVID-19 get better within weeks of illness, some people experience post-COVID conditions. Post-COVID conditions are common and can involve sequelae, and other medical complications that last weeks to months after initial recovery.

 Table 3. Functional status between hospitalized and non-hospitalized during post COVID-19.

| Characteristics | Hospitalization (n=71) | Non- hospitalization (n=64) | p-value |
|---------------------|---------------------------|-----------------------------------|---------|
| 6MWD (m) | 502±113.2 | 538.4±86.8 | >0.05 |
| Predictive 6MWD (%) | 82.2±15.3 | 90.6±10.5 | 0.01* |
| TUG (s) | 6.3±1.7 | 6.0±1.42 | >0.05 |
| TVM (m/s) | 1.9±0.52 | 2.2±0.51 | >0.05 |
| FTSTST (s) | 9.5±5.1 | 7.6 ±2.7 | 0.04* |
| SPPB | 11.6±1.1 | 11.9±0.47 | >0.05 |
| FEV1/FVC % | 84.4±8.1 | 77.8±7.3 | <0.001* |
| %DLCO | 69.0±16.5 | 80±17.4 | 0.02* |

*Differences between hospitalized and non-hospitalized patients (Mann-Whitney U test or Student's t-test). Statistically significant values are indicated in bold. MWD: min walk distance; TUG: time up and go; FVC: forced vital capacity; FEV: forced expiratory volume; SPPB: short physical performance battery; DLCO: diffusing capacity of the lung for carbon monoxide.

Thus, this study showed a high frequency (46.7%) of dyspnea (MRC score>0) in patients with post-COVID syndrome. Hospitalization and ICU admission were observed in 52.6 and 29.6% of sample, respectively. Notably, 35.1% of sample presented DCLO lower than 80%. Additionally, the mean of 6MWD in all subjects was 86.0%±14.0 of predicted walking distance. It is important to highlight that probable sarcopenia was observed in 17.8% of patients.

In addition, percentage of lesion-level characteristics, assessed by CT, was associated with a worse %DLCO. In this sense, in patients with emphysema, lesion-level chest CT is related to decreased PaO2 but cannot replace the measurements of diffusion capacity in the clinical evaluation of hypoxemia¹⁸. Moreover, multiple variable analysis showed that the visual extent of emphysema and 15th percentile HU were independent significant predictors of DLCO/VA¹⁹. It is also important to highlight that, in post-COVID patients, dyspnea was associated with both DLCO %-predicted and total CT score¹.

Furthermore, in this study, sarcopenia was associated with worse 6MWD, %-predicted, 6MWD (m), and %DLCO. These findings highlight that COVID-19 is a disease that also affects skeletal muscles²⁰ and patient's functionality. Specifically, post-COVID-19 patients showed reduced lung function, muscle strength, and exercise capacity. In this context, recent reviews showed that acute post-COVID-19 patients suffer from changes in respiratory function, fatigue, muscle weakness, and disability²¹⁻²⁵.

Considering the global scale of this pandemic, the sequelae of COVID-19 will continue to increase in the future⁴. There is a critical need to understand the disabilities of patients (in the acute and long-term), aiming to effectively improve the functionality of survivors of COVID-19⁴. We have identified persisting disability and functional and pulmonary abnormalities in a significant proportion of subjects. These data may assist with the detection of post-COVID complications and the identification of patients who could benefit from physical rehabilitation.

CONCLUSION

Physical disability and reduction in lung function are common in COVID-19 survivors. The impact of hospitalization on muscle force and DLCO was observed. Additionally, CT>50% was associated with longer length of stay (LOS) and lower %DLCO. Probable sarcopenia diagnosis was associated with a worse %6MWD in relation to predicted, 6MWD (m), %DLCO, and %TLC. These results highlight the need for a long-term follow-up of those patients and rehabilitation programs.

AUTHORS' CONTRIBUTIONS

IGNA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MGN: Data curation, Formal Analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. SFOJ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. DMM: Investigation, Methodology, Validation, Visualization, Writing – review & editing. WLCN: Investigation, Methodology, Validation, Visualization, Writing – review & editing. KDOA: Investigation, Methodology, Validation, Visualization, Writing – review & editing.

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The effectiveness of preoperative diagnostic methods in predicting intra-abdominal adhesions before repeat cesarean section delivery

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SUMMARY

OBJECTIVE: This study aimed to evaluate the effectiveness of skin appearance, striae gravidarum severity, and ultrasonographic "sliding sign" in predicting preoperative adhesions before repeat cesarean section delivery on the same patient and find the most useful one.

METHODS: This was a prospective cohort study conducted on pregnant women with a history of cesarean section delivery. Davey's scoring system was used for stria evaluation. The scar was assessed using their visual appearance, and transabdominal ultrasonography was applied to detect sliding sign existence. Surgeons blinded to preoperative assessment graded the severity of intra-abdominal adhesions intraoperatively using Nair's scoring system. **RESULTS:** Of the 164 pregnant women with at least one previous cesarean section delivery, 73 (44.5%) had filmy or dense intra-abdominal adhesions. Statistically significant association was found between three groups regarding parity, previous cesarean number, scar appearance, total stria score, and sliding sign existence. Negative sliding sign had a likelihood ratio of 4.198 (95%CI 1.178–14.964) for the detection of intra-abdominal adhesions. Stria score and scar appearance were also valuable for detection adhesions with likelihood ratios of 1.518 (95%CI 1.045–2.205) and 2.405 (95%CI 0.851–6.796), respectively. After receiver operator characteristics curve analysis, striae score cutoff value in adhesion, and sliding sign, as an easy-to-apply, inexpensive, useful sonographic marker, is the most effective adhesion predictor before repeat cesarean section delivery compared to other known adhesion markers.

KEYWORDS: Surgery. Cesarean section. Ultrasonography.

INTRODUCTION

Cesarean section (CS) delivery is currently one of the most common obstetric operation, and its rate increased steadily from 5 to 30–32% over the past 10 years¹. Intra-abdominal adhesions can occur in 46–83% of women who undergo repeat CS, leading to bleeding, bladder and bowel injury, infection, hysterectomy, and neonatal morbidity in subsequent surgeries^{2,3}.

Aiming this, various noninvasive methods including skin scar characteristics, striae gravidarum score, and "sliding sign" on ultrasound have been investigated and found useful to predict adhesions before subsequent surgery⁴⁻⁶.

Since no data comparing these methods exist, the aim of this study was to evaluate the effectiveness of skin appearance, striae gravidarum severity, and sliding sign for predicting preoperative adhesions before repeat CS on the same patient and to define the best predictive tool.

METHODS

This prospective cohort study was conducted in Bursa Yüksek İhtisas Treaning and Research hospital between December 2020 and August 2021 and approved by institutional ethics committee. Patients who had undergone at least one previous cesarean delivery and scheduled for elective CS were included. Patients with conditions such as pelvic inflammatory disease, infections, wound infections, systemic lupus erythematosus, diabetes, endometriosis, and history of corticosteroid that might affect wound healing were excluded from the study. Demographic data, including age, body mass index (BMI), and smoking status, were also recorded.

Davey's scoring system was applied to determine the severity of the striae gravidarum; thus the abdomen was divided into four quadrants, using the umbilicus as references⁷. If the skin was clear, the score was 0; if the number of striae per quadrant was 1–3, the

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on January 13, 2023. Accepted on January 20, 2023.

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score was 1; and if the number of striae was \leq 4, the score was 2. The sum of the scores of all four quadrants was calculated to obtain the total striae score. Patients with no striae were classified into the "no striae" group. Patients with the total score of 1–2 were classified into the "mild striae" group, and patients with scores between 3 and 8 were classified into the "severe striae" group.

According to their appearance, the CS scars were classified as flat, elevated, or depressed.

All pregnant women underwent transabdominal ultrasound using Voluson P6 ultrasound system (GE Medical Systems) with a 2- to 5.5-MHz convex probe for the evaluation of sliding sign. The ultrasound assessment was performed by the same physician with 18 years obstetric and gynecological ultrasound experience who evaluated the patient according to Barons' description for sliding sign⁶. The probe was placed just above the transverse skin scar and the patient was asked to take a deep breath in order for the uterus to be observed sliding caudally under the parietal peritoneum and fascia transversalis. Presence of the "sliding sign" was described when sliding of the uterus against the abdominal wall was observed. When no movement of the uterus under the fascia was noted, the sliding sign was considered "absent" (Figure 1).

As a final step, the surgeon who was blinded to the results of the ultrasound sliding sign assessment performed the CS operations and evaluated all patients for intra-abdominal adhesions using the modified Nair classification system⁸. Nair et al., described their classification system as follows: Grade 0: complete absence of adhesions; Grade 1: single band of adhesion between viscera or from one viscera to the abdominal wall; Grade 2: two bands either between viscera or from viscera to the abdominal wall; Grade 3: more than two bands between viscera or from viscera to the abdominal wall; and Grade 4: multiple dense adhesions



Figure 1. Transabdominal ultrasound images showing the presence or absence of "sliding sign." Top images before deep breath **(A1,B1)**, bottom images after deep breath **(A2,B2)**. "S" represents uterine serosa and "F" represents muscle fascia. **(A2)** After deep breath uterine serosa sliding caudally under the fascia transversalis (positive sliding sign). **(B2)** No movement of the uterus under the fascia transversalis was noted (negative sliding sign).

or viscera directly adherent to the abdominal wall, irrespective of the number or extent of adhesive bands. According to this intraoperative, adhesions were classified as grade 1 or 2 if filmy intra-abdominal adhesions were present and as grade 3 or 4 if dense intra-abdominal adhesions were present.

Statistical analysis

The data were analyzed using the SPSS, version 22.0 program (IBM, Armonk, NY, USA). The descriptive statistics were presented as mean±SD for continuous variables and as a median (minimum-maximum) for discrete numeric variables. Variables were examined using visual (histograms, probability graphs) and analytical methods (Shapiro-Wilk and Kolmogorov-Smirnov test) to determine whether the data showed a normal distribution. Kruskal-Wallis and chi-square tests were used for comparisons between groups. Multiple logistic regression analysis was performed to examine the risk factors affecting the development of adhesion. ROC analysis was performed for the striae score, which was determined as a risk factor, and the cutoff value was determined. A p-value of <0.05 was considered to be statistically significant.

RESULTS

In all, 73 (44.5%) patients had intra-abdominal adhesions (47 had filmy adhesions and 26 had dense adhesions) and 91 (55.5%) were found to have no adhesions. Mean age was 29.6±5.4 years, mean parity was 2 (1–7), and mean BMI was 30.3±5.3. The demographic characteristics of the participants are presented in Table 1. According to adhesion existence, participants were classified into the following three groups: group 1: patients with no intra-abdominal adhesion; group 2: patients with filmy adhesions; and group 3: patients with dense adhesions.

Table 1. Demographic and clinical characteristics of patients.

| | Patients (n=164) |
|----------------------------------|------------------|
| Age (years) (mean±SD) | 29.6±5.4 |
| BMI (kg/m²; mean±SD) | 30.3±5.3 |
| Parity (median; minimum-maximum) | 2 (1-7) |
| Stria score | 3.1±3.2 |
| Previous CS number | |
| 1 | 86 (52.4%) |
| 2 | 48 (29.3%) |
| 3 | 23 (14%) |
| 3+ | 7 (4.3%) |
| | |

CS: cesarean section.

Among these three groups, there was no significant difference regarding various demographic factors, including age, previous cesarean indication, and BMI. However, a statistically significant association was found between three groups regarding parity, previous cesarean number, smoking status, scar appearance, total stria score, and sliding sign existence (Table 2).

Regarding diagnostic performance in predicting presence of intra-abdominal adhesions in women undergoing repeat CS, the sliding sign was the single most valuable method. A negative sliding sign had a likelihood ratio of 4.198 (95%CI 1.178–14.964) for the detection of intra-abdominal adhesions. Stria score and scar appearance were also valuable for detection of adhesions with likelihood ratio of 1.518 (95%CI 1.045–2.205) and 2.405 (95%CI 0.851–6.796), respectively (Table 3). After the ROC analysis, the cutoff value for stria score was determined as 3.5.

DISCUSSION

To the best of our knowledge, this is the first study to compare the effectiveness of preoperative methods for predicting intra-abdominal adhesions before repeat CS. Evaluating striae score, scar appearance, and sliding sign, we found sliding sign as the most effective prediction tool.

Since this study was conducted in a tertiary teaching and research hospital and we included all adhesions, not just severe adhesions, we have an adhesion rate of 44.5% that may be considered high.

Although there are conflicting data, most of the previous studies suggested stria score, scar appearance, and sliding sign as valuable predictors of intra-abdominal adhesions^{6,9-12,13,14}.

The association between cigarette smoking and delayed wound healing is well known, and increased adhesion formations after each repeated CS is also expected^{5,15}. According to our study, smoking and each CS increase the likelihood of intra-abdominal adhesions by 2.82 and 2.73 times, respectively.

Stria gravidarum is a common skin change among pregnant women. In the past years, many studies have been conducted to investigate the effectiveness of stria score for predicting intra-abdominal adhesions before repeat CS. According to Dogan et al., both adhesion formation and the intensity of adhesions were reduced in the presence of abdominal striae, while another study found no difference in peritoneal adhesions in women with or without striae^{5,16}. Jaafar's study suggested that the type of striae rather than its severity is associated with intra-abdominal adhesions and studies such as Abbas et al., and Çakır et al., reported higher rates of intraperitoneal adhesions in women with striae gravidarum⁹⁻¹¹. Our current study

Table 2. Adhesion status of patients.

| | | Adhesion | | | |
|--------------------------|----------------------|-------------|-----------------|-----------------|---------|
| | | No | Filmy Grade 1-2 | Dense Grade 3-4 | p-value |
| Age | | 29.5±5.3 | 29.1±5.7 | 31.1±5.2 | 0.231 |
| Parity | | 1 (1-6) | 2 (1-6) | 2 (1-7) | 0.000 |
| BMI | | 30.0±5.4 | 30.0±5.0 | 32.1±5.4 | 0.175 |
| Previous cesarean number | | 1 (1-3) | 2 (1-4) | 2 (1-6) | 0.000 |
| | Elective | 29 (17.7 %) | 15 (9.1 %) | 6 (3.7 %) | 0.670 |
| Cesarean indication | Emergency | 62 (37.8 %) | 32 (19.5 %) | 20 (12.2 %) | 0.420 |
| | No | 81 (49.4%) | 34 (20.7 %) | 22 (13.4 %) | 0.430 |
| | Flat | 66 (40.2 %) | 26 (15.9 %) | 12 (7.3 %) | |
| Scar appearance | Keloid/hypertrophied | 12 (7.3 %) | 10 (6.1 %) | 1 (0.6 %) | 0.001 |
| | Depressed | 13 (7.9 %) | 11 (6.7 %) | 13 (7.9 %) | |
| | Absent | 48 (29.3 %) | 17 (10.4 %) | 8 (4.9 %) | |
| Severity of stria | Mild | 7 (4.3 %) | 2 (1.2 %) | 2 (1.2 %) | 0.103 |
| | Severe | 36 (22 %) | 28 (17.1 %) | 16 (9.8 %) | |
| Sliding | Negative | 5 (3 %) | 5 (3 %) | 15 (9.1 %) | 0.000 |
| | Positive | 86 (52.4 %) | 42 (25.6 %) | 11 (6.7 %) | 0.000 |
| Stria score | | 2.4±2.9 | 3.8±3.3 | 4.3±3.4 | 0.004 |

BMI: body mass index.

Table 3. Risk factors for adhesion.

| | OR | 95%CI | p-value |
|----------------------------------|-------|--------------|---------|
| Parity | 1.341 | 0.634-2.834 | 0.442 |
| Previous cesarean number | 2.733 | 1.403-5.321 | 0.003 |
| Stria score | 1.518 | 1.045-2.205 | 0.028 |
| Smoking status | 2.821 | 1.048-7.595 | 0.04 |
| Scar appearance | | | |
| Flat | | | |
| Keloid/hypertrophied | 2.405 | 0.851-6.796 | 0.098 |
| Depressed | 1.211 | 0.439-3.338 | 0.712 |
| Severity of stria | | | |
| Absent | | | |
| Mild | 0.327 | 0.057-1.883 | 0.211 |
| Severe | 0.178 | 0.015-2.122 | 0.172 |
| Sliding *R2 Nagelkerke: 0.377 | 4.198 | 1.178-14.964 | 0.027 |

revealed positive correlation with Davey's striae gravidarum score and intraoperative adhesion existence. After ROC analysis, striae score of 3.5 was found as best cutoff threshold value in adhesion prediction similar to the results of Elprince et al., who suggested stria score \geq 3 as cutoff value¹⁶.

Abdominal scar characteristic has been suggested as a possible predictor for intra-abdominal adhesions, suggesting the similarities in healing of skin and peritoneum. Kahyaoglu et al., and Jaafar et al., concluded that depressed scars were the predictors for intra-abdominal adhesions^{9,12}. Additionally, elevated and palpable scars were also found to be associated with more adhesions¹⁷. The present study indicate that both hypertrophied/ palpable and depressed scars were associated with intra-abdominal adhesions and support the results of a meta-analysis suggesting that depressed and elevated scars were positively associated with intra-abdominal adhesions, while flat scars were the predictors to determine the absence of adhesions¹⁸.

In recent years, ultrasound has been proposed as suitable, noninvasive tool for adhesion prediction and "sliding sign" was mostly used to predict pelvic endometriosis-related adhesions. Baron et al., were the first to describe this method in predicting intraoperative adhesions before repeat CS and effectiveness of sliding sign was supported by Drukker et al.^{6,13,14}. Despite promising results, lack of comparison between the effectiveness of sliding sign with other known adhesion predictors was the main limitation of these studies. In this study, we investigated and compared the effectiveness of most known adhesion predictors and showed that the sliding sign predicted intra-abdominal adhesions before repeat CS more accurately than other predictors including stria score, scar appearance, and previous cesarean number. Ultrasound is easily accessible, commonly used noninvasive diagnostic tool in obstetrics and gynecology practice. After a short learning period, it can be applied preoperatively by physicians for the detection of sliding sign. Skin appearance, stria score, and previous CS number were also significant predictors of adhesion, therefore using them together with sliding sign can improve accuracy of intraoperative adhesion prediction before repeat CS.

Using blinded prospective design, utilizing standardized scoring systems, investigating and comparing the effectiveness of these methods on the same patient are the main strengths of the present study. The main limitations are small sample size and not evaluating all known diagnostic tools for adhesion prediction.

In conclusion, predicting intra-abdominal adhesions in pregnant women undergoing a repeat cesarean delivery is still a

challenging issue in obstetric practice. Stria score, scar appearance, and sliding sign are all significant predictors for intraperitoneal adhesions. Furthermore, sliding sign, as an easy-to-apply, inexpensive, useful sonographic marker, is the most effective adhesion predictor compared to other known adhesion markers.

AUTHORS' CONTRIBUTIONS

SS: Data curation, Formal Analysis, Project administration, Resources, Visualization, Writing – original draft. BA: Formal Analysis, Supervision, Visualization, Writing – original draft.
SSK: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – original draft.

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Measurement properties of the Brazilian version of the Kidney Symptom Questionnaire

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SUMMARY

OBJECTIVE: The aim of this study was to measure the reliability, internal consistency, and construct validity of the Kidney Symptom Questionnaire for the Brazilian population.

METHODS: This is a cross-cultural adaptation and questionnaire validation study. We included native Brazilians of both sex aged>18 years, as well as hypertensive and/or diabetic patients. All participants were assessed using Screening for Occult Renal Disease, EuroQol 5 Dimensions, 36-Item Short Form Survey, and the Kidney Symptom Questionnaire. We used Spearman's coefficient (rho) to measure the correlations between the Kidney Symptom Questionnaire and other instruments; Cronbach's alpha to measure internal consistency; and intraclass correlation coefficient, standard error of measurement, and minimum detectable change to measure test-retest reliability.

RESULTS: The sample was formed by 121 adult participants, mostly female, with systemic arterial hypertension and/or diabetes mellitus. We found excellent reliability (intraclass correlation coefficient>0.978), adequate internal consistency (Cronbach's alpha≥0.860), and adequate construct validity on the Kidney Symptom Questionnaire domains; besides, we observed significant correlations between the Kidney Symptom Questionnaire and other instruments.

CONCLUSION: The Brazilian version of the Kidney Symptom Questionnaire has adequate measurement properties to assess chronic/occult kidney disease in patients who do not require renal replacement therapy.

KEYWORDS: Public health. Diabetes complications. Hypertension. Renal insufficiency, chronic.

INTRODUCTION

Systemic arterial hypertension, one of the most common chronic diseases in the world, is divided into two categories, namely, essential hypertension and secondary hypertension. In essential hypertension, increased sodium absorption by the kidneys and a loss of elasticity in the arteries are associated with an increase in blood pressure, and it is estimated that 95% of cases of systemic arterial hypertension are linked to it. Secondary hypertension, in contrast, occurs as a result of other associated pathologies (e.g., renal dysfunctions), and this category is responsible for 5% of the occurrences¹.

Approximately 600 million people live with systemic arterial hypertension, and approximately 7.1 million die every year. Systemic arterial hypertension is responsible for 13% deaths worldwide, 40% deaths from stroke, and 25% cases of acute myocardial infarction. However, in addition to cerebrovascular conditions, systemic arterial hypertension is also related to chronic kidney disease, whose symptoms (fatigue, weakness, musculoskeletal pain) can be identified even in its early stages^{2.3}.

Thus, the identification of symptoms related to systemic arterial hypertension in patients is relevant for clinical management and investigation of the general health situation. Therefore, the use of easy-to-use and low-cost tools (e.g., questionnaires) is essential to ensure an assessment that points out potential occult kidney diseases in their primary stages⁴. The questionnaire

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Received on December 28, 2022. Accepted on January 10, 2023.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was partially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), finance code 001. The funding source had no involvement in the study design, collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

used for this purpose is the Kidney Symptom Questionnaire (KSQ), which was developed in England for patients who do not require renal replacement therapy⁴.

The Kidney Symptom Questionnaire consists of 13 items that assess the frequency and severity of symptoms, and besides its easy application, it identifies current renal diseases and points out the probability of pathological evolution⁴. However, the measurement properties of the KSQ have not yet been evaluated in a Brazilian population. Thus, we aimed to measure the reliability, internal consistency, and construct validity of the KSQ for the Brazilian population under the hypothesis that the aforementioned instrument presents adequate measurement properties.

METHODS

Design

This is a cross-cultural adaptation and questionnaire validation study based on the process of cross-cultural adaptation of self-report measures⁵ and consensus-based standards for the selection of health measurement instruments⁶. Authorization to validate the instrument was granted via email by one of the authors of the questionnaire (Dr. Alice C. Smith).

Participants and study size

The study was disseminated through social media, websites, email, and mobile messaging apps. In addition, the survey was disseminated to basic health units in the state of Maranhão (northeastern Brazil), and participants were recruited from January 2019 to October 2021.

We collected data through an online form (Google Forms, Mountain View, CA, USA) from people residing in all regions of Brazil. Participants were included in the study after signing or agreeing to an informed consent form. All procedures' research was approved by the Ethics Committee for research with human beings at Universidade Ceuma (opinion number 2.853.570).

A minimum sample size of 100 participants was considered⁷, with the following inclusion criteria: native Brazilians, age>18 years, both sex, diagnosed with systemic arterial hypertension and/or diabetes mellitus. We excluded participants who could not understand the questions in the questionnaires and who were in any other situation that made it impossible for them to continue participating in the research.

Data collection

The researchers responsible for the recruitment and assessments did not influence the participants in their respective responses. All participants filled out forms that made it possible to identify clinical and demographic characteristics, in addition to the following instruments: Screening for Occult Renal Disease (SCORED), EuroQol 5 Dimensions (EQ-5D), 36-Item Short Form Survey (SF-36), and Kidney Symptom Questionnaire (KSQ).

Assessment tools

Screening for Occult Renal Disease, an instrument validated for the Brazilian population by Magacho et al.⁸ predicts the development of chronic and/or occult kidney disease. It consists of 11 items based on diagnostic characteristics and has a cutoff point of 4 (the total score ranges from 0 to 17). The higher the score, the greater the probability of kidney disease.

EuroQol 5 Dimensions assesses the quality of life through five dimensions, namely, mobility, self-care, usual activities, painful discomfort, and anxiety/depression. It is a simple, short, easy-to-use instrument capable of obtaining psychometric measurements (profile) and econometric index measurements (utility/index); the score ranges from 0 to 5; and the higher values indicate greater negative implications for quality of life⁹.

36-Item Short Form Survey, an instrument validated for the Brazilian population by Ciconelli et al.¹⁰ consists of 36 items that assess eight dimensions related to the quality of life: physical functioning, role physical, bodily pain, global health, vitality, social functioning, role emotional, and mental health. The score for each domain ranges from 0 to 100; the higher the score, the higher the quality of life.

Kidney Symptom Questionnaire

The Kidney Symptom Questionnaire, a questionnaire developed by Smith et al., at Lancaster University in 2018, has 2 domains (frequency and impact of symptoms), each with 13 items. For each item, there are five response options, generating a score from 0 to 4. For the total score by domain, the scores of each item must be added, generating a value that varies from 0 to 52⁴. Higher values indicate greater frequency/ impact of symptoms.

Statistical analysis

We verified the distribution of variables through the Kolmogorov-Smirnov test. We used Spearman's correlation coefficient to verify associations between the KSQ domains and other instruments (SCORED, EQ-5D, SF-36), and the values for correlation magnitudes are 0.26–0.49=low, 0.50–0.69=moderate, 0.70– 0.89=high, and 0.90–1.00=very high¹¹.

We used Cronbach's alpha to assess internal consistency (considered adequate when obtaining values between 0.70 and 0.95)⁷. Test-retest reliability was evaluated by intraclass correlation coefficient (ICC), standard error of measurement (SEM), and minimum detectable change (MDC). The mathematical equation to calculate SEM is Standard deviation× $\sqrt{(1-ICC)}$. The mathematical equation to calculate MDC is $1.96 \times \text{SEM} \times \sqrt{2^{12}}$.

The interpretation of the ICC is in accordance with Fleiss' classification¹³: <0.40=low; 0.40–0.75=moderate; 0.75–0.90=substantial; and >0.90=excellent. We evaluated the construct validity by comparing the KSQ and other instruments already validated for the Brazilian population (i.e., SCORED, EQ-5D-3L, SF-36). We expect correlations greater than 0.30 between the instruments. We set the significance level at 5% for all statistical tests, which were processed using the Statistical Package for the Social Sciences software, version 17.0 (Chicago, IL, USA).

RESULTS

A total of 128 volunteers were recruited for the study, of whom 7 were excluded based on the eligibility criteria; thus, the final sample consisted of 121 adult participants, mostly female, with systemic arterial hypertension and/or diabetes mellitus. To assess the reliability and internal consistency of the KSQ, 65 volunteers participated in the survey for the second time after 7 days.

Table 1 describes the anthropometric and clinical characteristics of the study participants. Table 2 shows excellent reliability (ICC≥0.978) and adequate internal consistency (Cronbach's alpha≥0.860) for the KSQ domains. Table 3 shows the correlations between the KSQ and other instruments (SCORED, EQ-5D-3L, and SF-36). We observed significant (p<0.05) and adequate values for the construct validity of the KSQ based on confirmation of the previous hypothesis.

Ceiling and floor effects were not observed for the KSQ. For the frequency of symptoms domain, 5 (4.1%) participants had a score of 0, while 17 (14%) participants had a score of 0 for the impact of symptoms domain. The maximum KSQ score was not reached by any participant. The instrument is available at the link: https://questionariosbrasil.blogspot.com.

DISCUSSION

The results of the KSQ in the present study describe excellent test-retest reliability, adequate internal consistency, convergent validity with other instruments for screening for kidney disease, and an assessment of the quality of life and stability among the responses of all volunteers.

Our analyses reinforce the findings of Brown et al.⁴ whose descriptions support this instrument to support regular measurements of symptoms in routine clinical practice; it can also be used as a resource to improve and develop effective future treatments and management in patients with chronic or occult kidney disease through the assessment of symptoms and their respective frequencies.

It seems common to describe that aging is positively related to chronic or occult kidney disease; although an important clinical observation, this may just be a confounding variable

| Table 1. Characte | eristics of | the study | , participant | s (n=121) |
|-------------------|-------------|-----------|---------------|-----------|
|-------------------|-------------|-----------|---------------|-----------|

| Variables | Values | |
|---|---------------|--|
| Sex (female) ^b | 71 (58.7%) | |
| Schooling ^b | | |
| Primary school | 28 (23.1%) | |
| High school | 29 (24%) | |
| University education | 64 (52.9%) | |
| Marital status ^b | | |
| Single | 35 (28.9%) | |
| Married or stable union | 75 (62%) | |
| Divorced | 3 (2.5%) | |
| Widower | 8 (6.6%) | |
| Age (years)ª | 47.14 (16.81) | |
| Stature (m) ^a | 1.65 (0.09) | |
| Body mass (kg)ª | 75.36 (18.79) | |
| Body mass index (kg/m²)ª | 27.45 (5.60) | |
| Physical activity (yes) ^b | 51 (42.1%) | |
| Systemic arterial hypertension (yes) ^b | 73 (60.3%) | |
| Diabetes mellitus (yes) ^b | 51 (42.1%) | |
| SCORED (score, 0-17) ^a | 4.16 (2.47) | |
| EQ-5D (score) ^a | 0.82 (0.16) | |
| SF-36 (score) ^a | | |
| Physical function (0–100) | 70.08 (29.16) | |
| Role physical (0–100) | 60.53 (42.17) | |
| Pain (0-100) | 65.90 (22.55) | |
| Global health (0–100) | 58.18 (24.53) | |
| Vitality (0–100) | 57.43 (22.63) | |
| Social function (0–100) | 73.55 (24.69) | |
| Role emotional (0–100) | 58.40 (42.87) | |
| Mental health (0–100) | 65.38 (22.05) | |
| KSQ (score) ^a | | |
| Symptoms frequency (0–52) | 13.91 (10.01) | |
| Symptoms impact (0–52) | 12.25 (11.45) | |

SCORED: Screening for Occult Renal Disease; EQ-5D: EuroQol 5 Dimensions; SF-36: 36-Item Short Form Survey; KSQ: Kidney Symptom Questionnaire. ^aValues are presented as mean (standard deviation). ^bValues are presented as absolute numbers (percentage).

| Domain | ICC | (95%CI) | SEM (score) | SEM (%) | MDC (score) | MDC (%) | Cronbach's alpha |
|-----------|-------|--------------|-------------|---------|-------------|---------|------------------|
| Frequency | 0.978 | 0.964; 0.987 | 1.59 | 9.05 | 4.41 | 25.09 | 0.860 |
| Impact | 0.985 | 0.975; 0.991 | 1.88 | 10.95 | 5.20 | 30.36 | 0.911 |

Table 2. Reliability (test-retest) and internal consistency of the Kidney Symptom Questionnaire (n=65).

CCI: intraclass correlation coefficient; CI: confidence interval; SEM: standard error of measurement; MDC: minimum detectable change.

Table 3. Correlation between the Kidney Symptom Questionnaire and other instruments (n=121).

| Veriables | КЅѺ | | | |
|---------------------|----------------------|----------------------|--|--|
| variables | Symptoms frequency | Symptoms impact | | |
| SCORED | rho=0.466, p<0.001* | rho=0.444, p<0.001* | | |
| EQ-5D | rho=-0.759, p<0.001* | rho=-0.689, p<0.001* | | |
| SF-36 | | | | |
| Functional capacity | rho=-0.691, p<0.001* | rho=-0.642, p<0.001* | | |
| Role physical | rho=-0.457, p<0.001* | rho=-0.456, p<0.001* | | |
| Pain | rho=-0.650, p<0.001* | rho=-0.632, p<0.001* | | |
| Global health | rho=-0.652, p<0.001* | rho=-0.579, p<0.001* | | |
| Vitality | rho=-0.735, p<0.001* | rho=-0.592, p<0.001* | | |
| Social function | rho=-0.626, p<0.001* | rho=-0.564, p<0.001* | | |
| Role emotional | rho=-0.549, p<0.001* | rho=-0.532, p<0.001* | | |
| Mental health | rho=-0.575, p<0.001* | rho=-0.459, p<0.001* | | |

KSQ: Kidney Symptom Questionnaire; SCORED: Screening for Occult Renal Disease; EQ-5D: EuroQol 5 Dimensions; SF-36: 36-Item Short Form Survey. *Significant correlation (p-value<0.05) – Spearman's correlation coefficient (rho).

(i.e., it is associated with the disease but does not explain the chronification). Our study permeates this aspect by identifying that the participants have a mean age>40 years; however, they have other associated diseases, such as systemic arterial hypertension and diabetes mellitus, which are more related to chronic/occult kidney disease.

In this scenario, in a systematic review, Ameh et al.¹⁴ described an association between the presence of chronic kidney disease (or declining kidney function) and accelerated wear of telomeres and also mainly highlighted the confounding effect of the aging process on the assessment of kidney symptoms.

The relevance of this study consists of its applicability in clinical and scientific contexts. In primary health care (clinical context), it allows us to screen for potential occult kidney diseases in patients with systemic arterial hypertension and/ or diabetes mellitus, making it possible, in necessary cases, to refer them to specialists or perform additional tests, in order to promote, protect, or restore the health of these people. In epidemiological studies (scientific context), it facilitates the assessment of the general state of health for comparisons with other populations also studied.

This study has limitations that must be described. First, the absence of other studies that carried out a similar adaptation made it difficult to construct the discussion in question. In addition, the construction of the database took place through online forms, and we know that not all regions of Brazil participated in this research. Thus, considering the cultural plurality of Brazil, we suggest additional studies for the applicability of this tool in different states of the country in order to confirm the reproducibility of our findings.

Clinical implications

The implementation of a questionnaire that uses the patient's self-report (e.g., the KSQ) to then consider the intervention helps teamwork, communication, and relationships, as well as support for families, consequently improving patient care in health promotion, protection, and recovery environments.

CONCLUSION

The Brazilian version of the KSQ has adequate measurement properties to assess chronic/hidden kidney disease in patients who do not require renal replacement therapy.

ETHICS APPROVAL

The study followed the Declaration of Helsinki guidelines, and all procedures of this study were previously approved by the Ethics Committee in research with human beings at the CEUMA University in Brazil, attending the resolution 466/2012 (opinion number 2.853.570).

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author, but access to these data is restricted because they were used under license for the current study and are thus not publicly available. However, data can be obtained from the authors upon reasonable request and with the permission of the corresponding author.

AUTHORS' CONTRIBUTIONS

LFSA: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. APS: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. RGM: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. CDS: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. WSB: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. WSB: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **JAOB:** Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **MCG:** Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **AVDF:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **DBD:** Conceptualization, Data curation, Formal Analysis, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **DBD:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – original draft, Writing – original draft, Writing – review & editing.

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Revisiting femoral cartilage thickness in cases with Hashimoto's thyroiditis in thyroidology: a single institute experience

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SUMMARY

OBJECTIVE: Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis, is a considerable part of the spectrum of chronic autoimmune thyroid gland disorders which is pathologically associated with various degrees of lymphocytic infiltration. The purpose of the present study was to evaluate whether cartilage thickness is affected in patients with Hashimoto's thyroiditis or not in thyroidology.

METHODS: A total of 61 individuals had been evaluated in this case-control study, including 32 euthyroid Hashimoto's thyroiditis patients and 29 healthy subjects comparable in age, sex, and body mass index. The patients with a history of knee trauma or knee surgery, an additional systemic disease such as diabetes mellitus, or an inflammatory disease like rheumatoid arthritis, systemic lupus erythematosus, and scleroderma had not been included in the study. The thickness of the femoral articular cartilage was measured using B-mode ultrasonography, and the right lateral condyle, right intercondylar area, right medial condyle, left medial condyle, left intercondylar area, and left lateral condyle were also measured.

RESULTS: No statistically significant difference between patients with Hashimoto's thyroiditis diagnosis and healthy controls in terms of age, age groups, gender, and body mass index (p>0.05).

CONCLUSION: As a consequence, no obvious connection between autoimmune markers and cartilage thickness in patients with Hashimoto's thyroiditis was recognized. Although the diverse manifestation of Hashimoto's thyroiditis could be observed, it seems to be no liaison between thyroid autoimmunity and cartilage thickness.

KEYWORDS: Thyroid gland. Thyroiditis. Cartilage. Cytology. Pathology.

INTRODUCTION

Hashimoto's thyroiditis (HThy) is an autoimmune thyroid disorder, which is also known as chronic lymphocytic thyroiditis or struma lymphomatosa, and characterized by lymphoplasmacytic infiltration and lymphoid follicle formation with well-developed germinal centers. Although patients may have euthyroidism, hypothyroidism, and rarely hyperthyroidism, "hashitoxicosis" may accompany them but hypothyroidism is usually observed. The articular cartilage surrounding the joint surface is a worthy issue for the normal function of the joint. The proper formation, development, and maintenance of the cartilage tissue are important in preventing the development of osteoarthritis, which is a degenerative disorder leading to pain and disability. Similarly, thyroid hormones play a crucial role in cartilage homeostasis. To this end, sonographic evaluation of articular cartilage has been performed in patients with hypothyroidism³ and autoimmune diseases such as systemic lupus erythematosus and scleroderma¹⁻⁶.

However, sonographic evaluation of cartilage thickness in patients with HThy has not yet been reported in the literature. Herein, this study aimed to evaluate the femoral cartilage thickness (FCT) in cases with HThy with ultrasonography.

METHODS

The present study enrolled 32 euthyroid HThy and 29 healthy subjects comparable in age, sex, and body mass index (BMI). Patients with a history of knee trauma or knee surgery, an additional systemic disease such as diabetes mellitus, or an inflammatory disease like rheumatoid arthritis, systemic lupus erythematosus, and scleroderma had not been

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on December 05, 2022. Accepted on December 05, 2022.

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included in the study. All the subjects included in the present study signed the informed consent. The present study was approved by the Research and Ethics Committee of Clinical Studies linked to Giresun University, under the 90139838-000-E.28156/2019 approval number. The studied cases had laid down in the supine position, both knees in maximum flexion were examined, and the thickness of their femoral articular cartilage was measured using B-mode sonography (3-13 MHz MyLabSix; Esaote Biomedica, Italy). To this end, the probe was placed in the axial plane on the upper edge of the patella and the right lateral condyle, right intercondylar area, right medial condyle with the left medial condyle, left intercondylar area, and left lateral condyle were measured meticulously (Figure 1). Afterward, cartilage thickness was interpreted as the distance between the thin hyperechoic line at the synovial space/cartilage interface and the sharp hyperechoic line at the cartilage-bone interface⁷.



Figure 1. Sonographic image, exhibiting the right femoral distal cartilage measurements (D1 right lateral condyle, D2 right intercondylar area, and D3 right medial condyle).

Statistical analysis

The research data were uploaded to the computer environment and evaluated using SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc., Chicago, IL). Descriptive statistics were presented as mean±standard deviation (minimum–maximum), frequency distribution, and percentage, and a Pearson chi-square test was used to evaluate categorical variables. The conformity of the variables to the normal distribution had been examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk test). The Mann-Whitney U test was used to determine the statistical significance between two independent groups for the variables found to be non-normally distributed, and the Student's t-test was used to determine the variables with normal distribution. The relationship between the variables was evaluated with the Spearman correlation test and the significance level was accepted as p<0.05.

RESULTS

A total of 61 subjects had been involved in the present prospective study. Of these, 32 cases had HThy, while the remaining 29 were healthy controls. The distribution of age, gender, and BMI between the HThy and control groups showed no statistically significant difference between patients with HThy and healthy controls in terms of age, age groups, gender, and BMI (p>0.05) (Table 1). The distribution of FCT between the HThy and control groups is presented in Table 2. No significant difference between the cases with HThy and the control in terms of both the right and left medial, lateral, and intercondylar FCTs has been detected (p>0.05) (Table 2). In addition, Table 3 reveals the relationship between age and FCT within the HThy and control without a significant correlation between

| | Hashimoto's thyroiditis (n=32) Control (n=29) | | p-value | | | |
|------------------------------|---|--------------------------|--------------------|--|--|--|
| Age, year, mean±SD (min-max) | 33.5±11.2 (18-60) | 32.6±6.8 (19-40) | 0.960ª | | | |
| Age groups (years), n (%) | | | | | | |
| <25 | <25 11 (34.4) 6 (20.7) | | | | | |
| 25-35 9 (28.1) | | 1 (37.9) | 0.466 ^b | | | |
| >35 | 12 (37.5) | 12 (41.4) | | | | |
| Gender, n (%) | | | | | | |
| Male | 7 (21.9) | 5 (17.2) | 0 (4 Ob | | | |
| Female | 25 (78.1) | 24 (82.8) | 0.6495 | | | |
| BMI, kg/m² | 21.73±1.70 (19.54-26.14) | 21.18±1.12 (19.42-23.20) | 0.315ª | | | |

 Table 1. Distribution of age, gender, and BMI between Hashimoto's thyroiditis and control.

n: number of individuals; %: column percentage; SD: standard deviation; ^aMann-Whitney U test; ^bPearson chi-square test.

| | | Hashimoto's thyroiditis (n=32) | Control (n=29) | a valua |
|---------------------|---------------|-----------------------------------|----------------------|--------------------|
| | | mean±SD (min–max) | mean±SD (min−max) | p-value |
| Femoral cartilage t | hickness, mm | | | |
| Right | Medial | 2.13±0.44 (1.3-3.1) | 2.18±0.34 (1.5-2.7) | 0.597ª |
| | Lateral | 2.11±0.38 (1.5-3.1) | 2.02±0.37 (1.5-2.7) | 0.341 ^b |
| | Intercondylar | 2.49±0.80 (0.8-4.0) | 2.50±0.50 (1.6-3.5) | 0.946ª |
| Left | Medial | 2.15±0.57 (1.1-4.2) | 2.18±0.49 (1.0-3.2) | 0.832ª |
| | Lateral | 2.02±0.51 (1.1-3.1) | 2.07±0.46 (1.4-3.0) | 0.701 ^b |
| | Intercondylar | 2.49±0.78 (0.9-4.5) | 2.39±0.51 (1.5-3.2) | 0.811 ^b |

Table 2. Distribution of femoral cartilage thicknesses between Hashimoto's thyroiditis and control.

n: number of persons; SD: standard deviation; "Student's t-test; "Mann-Whitney U test.

Table 3. The relationship between age and femoral cartilage thickness in Hashimoto's thyroiditis and control.

| | | Hashimoto's thyroiditis (n=32) r p-value | | Control (n=29) | |
|-------------------------|---------------|--|-------|-------------------|---------|
| | | | | r | p-value |
| Femoral cartilage thick | ness, (mm) | | | | |
| Right | Medial | 0.221 | 0.225 | -0.088 | 0.648 |
| | Lateral | 0.087 | 0.637 | -0.340 | 0.072 |
| | Intercondylar | 0.323 | 0.071 | -0.239 | 0.211 |
| Left | Medial | -0.001 | 0.998 | 0.232 | 0.226 |
| | Lateral | 0.106 | 0.563 | -0.171 | 0.376 |
| | Intercondylar | 0.172 | 0.346 | -0.126 | 0.513 |

n: number of cases; r: Spearman correlation coefficient.

the ages of the cases with HThy and the healthy controls in the control and all the FCTs (p>0.05).

DISCUSSION

Hashimoto's thyroiditis is now recognized as an autoimmune thyroid disorder that is characterized by high titers of circulating antibodies. Microscopically, it involves lymphoplasmacytic infiltration and lymphoid follicle formation with well-developed germinal centers, although it does not histopathologically possess a homogeneous lesion. Of note, several subtypes of HThy, presenting the clinicopathological features, have been reported, which are quite distinct from that of typical HThy. To this end, the most salient subtype is the fibrous variant of HThy with marked fibrous replacement of the thyroid gland parenchyma and typical microscopic changes of HThy in the remaining tissue, which is contrary to Riedel's thyroiditis, in case of not possessing extrathyroidal fibrosis¹.

To the best of our knowledge, this is the first study in the English-language literature in the era of FCT vs. HThy. It has been revealed that the FCT of the control was recognized to be similar in the cases with HThy, which is the most common autoimmune disorder that frequently affects females. Its clinical features include local and systemic manifestations. Systemic ones frequently result from loss of function of the thyroid gland. Since thyroid hormones have effects on most organs and tissues, the symptoms and signs of hypothyroidism are also quite diverse. The hypertrophic appearance of the muscles is mentioned due to myxedematous infiltration in the connective tissues, which usually causes pain and cramps in its effects on the musculoskeletal system⁸. Although osteoarthritis has a high prevalence and morbidity rate, no effective treatment has yet been found. To prevent and treat this disease effectively, the molecular mechanism of the cartilage structure should be initially recognized⁹. Since the cartilage structure has a very tight connection with the function of its architecture, the ability to reconstruct the structure was found to be necessary

for regeneration¹⁰. To this end, many different methods have been investigated in the treatment modalities of osteoarthritis, including disease-modifying drug treatments¹¹ and marrow stimulation techniques¹², and also cell therapy, tissue engineering, and gene therapy have been the subject of research¹³⁻²⁰. However, these treatment options are quite demanding, so it is important to predict and prevent the causes that may lead to osteoarthritis.

Hypothyroidism is one of the causes of secondary osteoarthritis in thyroidology. Of note, the thyroid hormones are essential and crucial for endochondral ossification, chondrocyte maturation, and matrix synthesis. In fact, the evaluation of the articular cartilage using sonographic and pre-osteoarthritic evaluation of the knees with ultrasound possesses a prognostic value^{2,21-23}. Devrimsel et al.⁴ observed thinner femoral cartilage measurements in hypothyroid cases compared to the healthy volunteers. Based on this result, close monitoring of hormone levels in euthyroid patients is propounded as valuable for the prevention of osteoarthritis.

The thickness of the articular cartilage and possible mechanisms that may cause cartilage degradation have been investigated in some autoimmune disorders. The cartilage thickness was reduced in patients with Behcet's disease, and some authors propounded that it might be related to increased levels of IL-1 β in the synovial fluid²⁴. Serum levels of human cartilage glycoprotein-39 (HC gp-39), an indicator of cartilage damage or degradation, have been found to be increased in early rheumatoid arthritis and systemic scleroderma²⁵. Cartilage oligomeric matrix protein (COMP), a structural component of cartilage, was highly found in patients with scleroderma. In addition, medial condyle cartilage thickness attenuates in cases with scleroderma²⁴. However, decreased cartilage thickness in cases with scleroderma may also be a result of vascular dysfunction or synovial fibrosis in this disease, and the nutritional status of cartilage plays an important role in maintaining normal cartilage balance. In the present study, investigating whether cartilage destruction may emerge in an autoimmune disorder such

as euthyroid HThy, and no significant cartilage thinning was detected in these patients.

Limitations

Some limitations can be detected in our study. Biomarkers that may be associated with cartilage thickness or metabolism in cases with HThy and cartilage volume are the missing parameters in the present study.

CONCLUSION

The outcomes of our preliminary study have revealed that no relation between autoimmune markers and cartilage thickness in the cases with HThy has been recognized. Although the diverse manifestation of HThy could be observed, it seems no relationship exists between thyroid gland autoimmunity and cartilage thickness in thyroidology.

ACKNOWLEDGMENTS

The authors thank all the participants in the article.

AUTHORS' CONTRIBUTIONS

NCY Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. OD: Methodology, Project administration, Resources, Validation, Visualization. FK: Methodology, Project administration, Resources, Validation, Visualization. IFS: Methodology, Project administration, Resources, Validation, Visualization. DS: Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. IS: Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Obstetric simulation for undergraduate medical education: how to improve students' self-confidence and expectation according to gender

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the effects of obstetric simulation training on undergraduate medical students to improve their self-confidence.

METHODS: Fifth-year undergraduate medical students were invited to a 2-week course of simulation in obstetrics during their clerkship. The sessions included were as follows: (1) care for the second and third periods of childbirth, (2) partograph analysis and pelvimetry, (3) premature rupture of membranes at term, and (4) diagnosis and management of third-trimester bleeding. Before the first session and at the end of the training period, a questionnaire about self-confidence in obstetric procedures and skills was applied.

RESULTS: A total of 115 medical students were included, of whom 60 (52.2%) were male and 55 (47.8%) were female. Comparing initial and final scores, the median results of the subscales "comprehension and preparation" (18 vs. 22, p<0.001), "knowledge of procedures" (14 vs. 20, p<0.001), and "expectation" (22 vs. 23, p<0.01) were significantly higher at the end of the training period in all items of the questionnaire than in the beginning. Differences were found based on the students' gender, i.e., female students had a significantly higher sum of scores than the male students in the initial subscale for "expectation" (median, 24 vs. 22, p<0.001) and "interest" (median, 23 vs. 21, p=0.032), and a higher sum of scores in the subscale for "expectation" (median, 23 vs. 21, p=0.010) in the final questionnaire.

CONCLUSION: Obstetric simulation enhances the improvement of students' self-confidence in understanding both the physiology of childbirth and the obstetric care procedures. Further studies are needed to understand the influence of gender on obstetric care.

KEYWORDS: Simulation training. Education, medical. Clinical clerkship. Students, medical. Obstetrics.

INTRODUCTION

Simulation-based medical education is always a challenge for educators. In obstetrics, teaching undergraduate students about childbirth care and management of complications is hampered by the impossibility of inserting them straightaway into reallife clinical practice.

Wang et al.¹ found that students' engagement in a simulation-based learning environment is different from their engagement in a traditional setting. Furthermore, educators need to incorporate new technologies into their teaching methods in order to suit the needs of new generations, who prefer to work in groups and have practical and dynamic experiences. Scholz et al.² found that the students felt well prepared for obstetric practice and performed with better skills in a high-fidelity than in a low-fidelity simulation. The simulation training is able to increase students' satisfaction by providing a safe environment for them to practice their skills³.

In the literature, we found a variety of studies of simulation training in operative vaginal delivery, obstetric emergencies, and surgical skills for obstetrics and gynecology residents⁴. Specific obstetric scenarios for undergraduate medical students are less developed and do not present a variety of learning contents. This study was conducted to evaluate the effects obstetric simulation training in different scenarios had on undergraduate medical students, aiming at improving their self-confidence and motivation and encouraging their engagement and interest in the study of obstetrics.

METHODS

This research was developed at the University Simulation Center. The study protocol was approved by the local research ethics committee (CAAE n°: 71373317.2.0000.5505), and all participants signed an informed consent form.

Between August 2018 and April 2019, a total of 115 fifth-year undergraduate medical students were recruited to participate. They were classified into groups of 5–6 students and assigned to a 2-week course of simulation in

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

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Received on December 07, 2022. Accepted on December 10, 2022.
obstetrics during the 4-week clerkship rotation in their fifth undergraduate year. Simulation training took place in 3–4 sessions of approximately 3 h each. Every session included three steps as follows: (1) orientation, which encompassed an introduction to the learning objectives; (2) simulation, when students managed the cases; and (3) debriefing. Before the beginning of the first simulation session, a questionnaire about self-confidence in obstetric procedures, skills, and expectations was applied to each student. The same questionnaire was applied at the end of rotation. The student had predetermined tasks to carry out.

In the simulation-training sessions, a NoelleS575, a fullsized female anthropomorphic birth simulator, and models of cervical dilation and pelvis were used. For the scenarios that simulate a woman's admission, standardized speeches were prepared with specific topics, challenging the student caring for the simulated patient. The students were trained in the following scenarios.

Scenery 1: care for the second and third stages of childbirth

A 25-year-old primiparous at term with 39+4 weeks' gestation went through maternity triage in spontaneous labor. She was known to have a baby of normal weight, and maternal and fetal signs were also normal. The contractions are strong, and she is fully dilated. She was transferred to a labor and delivery room, and a student was given the task to assist the parturient with only one nursing technician in training to help in this scenario. The supervising professor plays the role of the nursing technician, pushing the fetus through the birth canal in the mannequin until the baby is out. A third person (usually a postgraduate student) performs the woman's dialogues, voicing complaints and doubts and letting out screams and sounds to make the scenario more realistic. The fetal head station initially is at +3 of De Lee in occiput anterior position, and it gradually progresses to delivery. To simulate the third stage, the placenta is manually pushed when appropriate. Each student performed the scenario individually. The scenario lasted for an average of 20 min. In this scenario, the student was expected to do the following: to perform a vaginal exam and correctly identify the head station and position; to guide pushes, "hands-on" perineal protection maneuver; to promote delayed umbilical cord clamping; to check the baby's conditions for keeping the skin-to-skin contact; to perform active management of the third stage; to perform a placental rotation maneuver, and a placental and perineal revision; and to demonstrate effective communication with the mother.

Scenery 2: partograph analysis and pelvimetry

A 29-year-old primiparous woman at 40+2 weeks' gestation was in labor for 9 h in the delivery room. Cervical dilation was progressing slowly, and a student was called to evaluate the mother. The progress of labor is shown on the partograph, which reveals a secondary arrest of dilation suggestive of cephalopelvic disproportion. The student is asked to outline the clinical pelvimetry. The scenario lasts for an average of 15 min and the following skills are evaluated: guided anamnesis, effective communication to perform the examination with the woman's consent, evaluation of cervical dilation, demonstration of how to perform a clinical evaluation of the pelvis, filling out of the partograph detection of cephalopelvic disproportion, and management planning.

Scenery 3: premature rupture of membranes at term

This scenario is developed with the participation of an actress (usually a postgraduate student) representing a woman at 39 weeks' gestation who tests positive for group B streptococcus. She complains of fluid loss from her vagina which started 8 h before and is now experiencing contractions every 30 min. The student is tasked with conducting an anamnesis to establish the full extent of the situation, including the woman's expectations. A physical examination should be performed on the simulator to verify maternal and fetal status and to reach a clinical diagnosis by conducting a specular examination and using diagnostic tests. In addition, calculation of the Bishop's index to determine obstetric management, organize the treatment, and prepare a medical prescription is also a required task. In this scenario, a cervical dilation effacement simulator and a medical prescription form are used.

Scenery 4: diagnosis and management of thirdtrimester bleeding

In this scenario, the student is asked to assist a pregnant woman who has just been admitted presenting third-trimester bleeding. An actress representing the woman gives a history of 32 weeks' gestation and reports two previous episodes of painless vaginal bleeding at 26 and 28 weeks. The student has to decide between a diagnosis of placenta previa and placental abruption and manage the case accordingly. The student should be able to interact with the patient, obtain medical history, perform an accurate examination (uterine height, obstetric palpation, FHR auscultation, and evaluation of contractions), and carry out a pelvic examination, while simultaneously gaining the patient's confidence and cooperation. The student should also be able to communicate the results of the examination to the patient and describe the initial management plan for the case. In this scenario, the cervical dilation effacement simulator and a medical prescription form are also used.

Instruments

A self-assessment questionnaire based on the instrument proposed by Scholz et al.² was used to evaluate the students. This questionnaire was translated into Brazilian Portuguese and adapted to medical students in the clerkship. The self-assessment questionnaire contains 26 items divided into five subscales: comprehension and preparation (5 items), knowledge of procedures (5 items), motivation (6 items), expectation (4 items), and interest (6 items). The participants' scores on each item indicate their level of agreement with the item as expressed by their responses on the following 5-point Likert scale. Reliability analyses were performed to determine the internal consistency of the scale. The following variables were reversed prior to the analysis of Cronbach's alpha: 15, 18, 19, 20, 23, and 26. Cronbach's alpha for questionnaire results was 0.823 (95% lower confidence limit: 0.781).

Statistical analysis

Data were analyzed using the MedCalc® Statistical Software version 19.5.3 (MedCalc Software Ltd., Ostend, Belgium; 2020). The sample size was calculated based on the total number of fifth-year students. Descriptive statistics are presented as mean and standard deviation (SD), median (95% confidence interval [CI]), or frequency and percentage (%). The comparison between the moments before and after the simulation sessions was performed using the Wilcoxon test of paired samples. The comparison between proportions was drawn using the chi-square test or Fisher's exact test. The statistical significance was set at p<0.05.

RESULTS

A total of 115 medical students were included in this study, of whom 60 (52.2%) were male and 55 (47.8%) were female. The mean age was 24.6 years (SD=2.3 years), and the median age was 24.0 years (interquartile range [IQR]=2.0 years).

The results of the before and after self-confidence questionnaires are presented in Table 1. At the end of the clerkship rotation, the median scores of all items of the subscales "comprehension and preparation," "knowledge of procedures," and "expectation" were significantly higher. In the "motivation" subscale, the median of the final score was significantly higher in the items addressing overload, understanding of scenarios, and actual performance but significantly lower in the item involving curiosity about the next stage. In the subscale "interest," the median of the final score was significantly higher in items that addressed not having to deal with childbirth care and interest in childbirth care but significantly lower when the topic was knowing more about childbirth care and understanding that it is a challenge to learn about childbirth care.

The sum of the scores on the items of each subscale showed that in the final assessment (Table 2), the median score was significantly higher on the subscales "comprehension," "knowledge of procedures," and "motivation," but significantly lower on the subscale "expectation." No difference was observed in the subscale "interest."

Table 3 displays the scores of each subscale according to the students' gender. Scores differed by gender. On the questionnaire filled out by the female students prior to the clerkship, the subscales "expectation" and "interest" had a significantly higher score than those of the male students, and so did the subscale "expectation" on the final questionnaire.

DISCUSSION

The present study demonstrates that learning based on obstetric simulation increases the self-confidence of medical students in understanding, preparing, and learning obstetric procedures. We found gender-related differences; however, they need to be investigated by specifically designed studies. The practical activities in a simulation environment allow the students to experience possible situations in day-to-day obstetric practice with a view to improving self-confidence and knowledge about childbirth care, as was the case in the present study. The assessment and correction of the students' skills in the simulated scenarios allowed for greater understanding and knowledge retention.

We found that the sum of the scores increased on the subscales "comprehension," "knowledge," and "motivation," demonstrating an improvement in the learning process. Once the necessary tools for better acquisition of competencies are offered, the students' enthusiasm for new knowledge in obstetrics is expected to increase. One can think of different ways to further arouse students' interest, such as by extending the course or offering a greater diversity of practice scenarios, enabling them to have contact with different aspects of the specialty of obstetrics.

Obstetric simulation is of potential interest in medical education, as it allows students to practice new skills

| Comprehension and preparation | | Initial | | Final | |
|--|---|---------|--------|-------|---------|
| | | IQR | Median | IQR | p° |
| 1. I understand the course of events of a physiological delivery. | 4 | 0 | 5 | 1 | <0.001 |
| 2. I understand fetal position and fetal rotation during labor. | 4 | 0 | 5 | 1 | < 0.001 |
| 3. I feel confident assisting a doctor during labor. | 4 | 2 | 5 | 1 | < 0.001 |
| 4. I feel well prepared for a internship in obstetrics. | 3 | 2 | 4 | 1 | < 0.001 |
| 5. I am confident that I am going to have a significant role in intrapartum care. | 3 | 2 | 4 | 1 | < 0.001 |
| Knowledge of procedures | · | | | | |
| 6. I feel confident delivering the fetal head. | 2 | 2 | 4 | 1 | < 0.001 |
| 7. I feel confident delivering the fetal shoulders and body. | 2 | 2 | 4 | 1 | <0.001 |
| 8. I am able to palpate the fetal presentation. | 3 | 2 | 4 | 1 | < 0.001 |
| 9. I am able to palpate the fetal position. | 3 | 2 | 4 | 1 | < 0.001 |
| 10. I am able to palpate the fetal station. | 2 | 2 | 4 | 1 | < 0.001 |
| Motivation | | | | | |
| 11. I feel overcharged. | 3 | 2 | 3 | 2 | 0.014 |
| 12. I am able to understand the clinical case scenarios. | 4 | 1 | 4 | 1 | <0.001 |
| 13. I think that my actual performances are very good. | 3 | 2 | 4 | 1 | < 0.001 |
| 14. Learning gives pleasure. | 4 | 1 | 5 | 1 | 0.170 |
| 15. I am curious what comes in the next internship stage ^b | 5 | 1 | 4 | 1 | 0.001 |
| 16. I am quite bored. | 2 | 2 | 2 | 2 | 0.168 |
| Expectation | | | | | |
| 17. I think that I am able to understand childbirth care. | 4 | 1 | 5 | 1 | < 0.001 |
| 18. I will never be able to fully understand childbirth care. ^b | 1 | 1 | 1 | 1 | 0.013 |
| 19. Childbirth care is too complicated for me. ^b | 2 | 1.5 | 2 | 1 | 0.001 |
| 20. The correct interpretation of obstetric findings is too difficult for me. $^{\scriptscriptstyle \mathrm{b}}$ | 2 | 1 | 2 | 1.5 | <0.001 |
| Interest | | | | | |
| 21. I am interested in the topic childbirth care. | 5 | 1 | 5 | 1 | 0.794 |
| 22. I enjoy dealing with the topic childbirth care. | 4 | 1 | 4 | 1 | 0.117 |
| 23. I am glad, if I do not have to deal with the topic childbirth care. $^{\scriptscriptstyle b}$ | 2 | 2 | 2 | 2 | 0.048 |
| 24. I am fascinated by the topic medical care during childbirth. | 3 | 2 | 3 | 1 | 0.015 |
| 25. I would like to learn more about childbirth care. | 4 | 1 | 4 | 1 | 0.002 |
| 26. It poses a challenge for me to learn more about childbirth care. ^b | 4 | 1 | 3 | 2 | 0.001 |

Table 1. Scores on the self-confidence questionnaire items before and after the obstetric simulation training (n=115).

^aWilcoxon test (paired samples); ^bvariables detected as reversed by Cronbach's alpha analysis.

Table 2. Total scores on the self-confidence questionnaire subscales before and after the obstetric simulation training (n=115).

| Catazami | Initial | | Fii | | |
|-------------------------------|---------|-----------|--------------|-----------|--------|
| Category | Median | 95%CI | Median 95%CI | | |
| Comprehension and preparation | 18 | 17.0-8.0 | 22 | 22.0-23.0 | <0.001 |
| Knowledge of procedures | 14 | 13.0-15.0 | 20 | 20.0-21.0 | <0.001 |
| Motivation | 22 | 21.0-23.0 | 23 | 22.0-23.0 | <0.001 |
| Expectation | 9 | 8.0-10.0 | 8 | 8.0-9.0 | 0.046 |
| Interest | 23 | 22.0-23.0 | 22 | 21.0-23.0 | 0.234 |

^aWilcoxon test (paired sample).

| | Male (n=55) | | Female | | |
|-------------------------------|-------------|-----|--------|-----|--------|
| | Median | IQR | Median | IQR | P- |
| Initial | | | | | |
| Comprehension and preparation | 18 | 3.8 | 18 | 3.0 | 0.953 |
| Knowledge of procedures | 14 | 6.0 | 14 | 7.0 | 0.690 |
| Motivation | 9 | 2.0 | 8.5 | 4.5 | 1.000 |
| Expectation | 22 | 3.8 | 24 | 5.0 | <0.001 |
| Interest | 21 | 4.0 | 23 | 4.5 | 0.032 |
| Final | | | | | |
| Comprehension and preparation | 22 | 4.0 | 23 | 3.0 | 0.078 |
| Knowledge of procedures | 20 | 3.8 | 20 | 4.5 | 0.632 |
| Motivation | 8 | 3.0 | 8 | 4.0 | 0.194 |
| Expectation | 21 | 3.0 | 23 | 4.0 | 0.010 |
| Interest | 22 | 4.0 | 23 | 4.0 | 0.053 |

Table 3. Total scores on the self-confidence questionnaire before and after the obstetric simulation training according to the students' gender.

^aMann-Whitney test. IQR: interquartile range.

in a safe environment. The simulation can be interrupted at any time to point out errors or correct them⁵. In addition, training teams with different health professionals in scenarios where simulations are performed repeatedly has demonstrably succeeded in terms of cost-effectiveness in managing emergencies⁶.

Learning projects using obstetric simulation scenarios that can be integrated into the medical curriculum for the development of skills will also promote students' self-confidence⁷. In addition, the importance of spreading knowledge by training programs for health professionals must be recognized⁸. Simulation can help standardize education and ensure quality and comparability in an ever-expanding educational environment⁹.

Communication skills can be practiced in a simulated environment using standardized patients¹⁰. In our obstetric simulation sessions, we observed that medical students immerse themselves in clinical reasoning when they see a standardized patient interpreted by a member of the teaching team with whom they have no connection. Issues of ethical and professional conduct are easily addressed, as in real-life obstetric practice when, for example, there is a demand for a cesarean section or a refusal to allow a pelvic examination¹¹. Academic achievement was found to be the main learning stimulus for medical students.

A limitation of this study is the before-and-after design; also, there was no control group and no randomization. A further limitation is that the study design did not allow for an evaluation of the students' learning achievements and performance. This research focused on the students' experiences and subjective feelings in the simulation sessions. However, we cannot foretell their reactions in the real world, nor are we able to know whether the learning experience in the simulation center will affect their performance in real life.

CONCLUSION

Obstetric simulation supports the improvement of students' self-confidence in terms of understanding the physiology of childbirth and the obstetric care procedures. Further studies are needed to understand the influence of gender on obstetric care. The available technologies in simulation training support the acquirement of the required competencies. Activities in obstetric simulation have a positive impact on learning and on the development of students' self-confidence in basic obstetric care. Simulation-trained students felt better prepared for obstetric work and obstetric skills assessments.

AUTHORS' CONTRIBUTIONS

RMYN: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **CMP**: Conceptualization, Data curation, Writing – review & editing. **FMDR**: Formal Analysis, Writing – original draft, Writing – review & editing. **AMG**: Formal Analysis, Writing – original draft, Writing – review & editing.

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Does enteral nutrition through a percutaneous endoscopic gastrostomy, attenuate *Helicobacter pylori* colonization?: is it worth mentioning?

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SUMMARY

OBJECTIVE: In patients who experience difficulties in oral feeding, alimentary intake can be supported by creating direct access into the stomach through a percutaneous endoscopic gastrostomy. The present study purposed to compare naïve and exchanged percutaneous endoscopic gastrostomy tubes in terms of *Helicobacter pylori* infection and other clinical characteristics.

METHODS: A total of 96 cases who underwent naïve or exchanged percutaneous endoscopic gastrostomy procedures with various indications were incorporated into the study. The patients' demographic data, such as age and gender, etiology of percutaneous endoscopic gastrostomy, anti-HBs status, *Helicobacter pylori* status, the presence of atrophy and intestinal metaplasia, biochemical parameters, and lipid profiles, had been analyzed. In addition, the anti-HCV and anti-HIV statuses had also been evaluated.

RESULTS: The most common indication for percutaneous endoscopic gastrostomy placement was dementia in 26 (27.08%) cases (p=0.033). The presence of *Helicobacter pylori* positivity was significantly lower in the exchange group compared to the naïve group (p=0.022). Total protein, albumin, and lymphocyte levels were significantly higher in the exchange group compared to the naïve group (both p=0.001), and the mean calcium, hemoglobin, and hematocrit levels were statistically significantly higher in the exchange group (p<0.001).

CONCLUSION: Preliminary outcomes of the present study revealed that enteral nutrition attenuates the incidence of *Helicobacter pylori* infection. Considering the acute-phase reactant, the significantly lower ferritin values in the exchange group suggest that there is no active inflammatory process in the patients and that immunity is sufficient.

KEYWORDS: Enteral nutrition. Gastrostomy. Immune system. Helicobacter pylori. Pathology.

INTRODUCTION

Patients who experience difficulties with oral feeding often require enteral or parenteral nutrition. In some cases, oral intake can even be dangerous in cases of obstructive or neurological conditions¹. Enteral feeding has several advantages, including preserved enteral function, suppression of bacterial translocation, and reduced cost expenditure². In these cases, alimentary intake can be supported by creating direct access into the stomach through a percutaneous endoscopic gastrostomy (PEG) application. On a case-by-case basis, recently published European Society of Gastrointestinal Endoscopy guidelines recommends enteral feeding through a PEG tube application in cases for whom enteral feeding is required for longer than 3–4 weeks³⁻⁵. The 3–4-week cutoff is arbitrary and has been chosen to avoid numerous adverse events associated with percutaneous access, such as infections.

Percutaneous endoscopic gastrostomy was performed for the first time on 12 pediatric and 19 adult patients by Gauderer et al. using a mushroom catheter⁶. Since then, multiple efforts have been made to improve the efficiency of the PEG procedure and reduce the rate of procedure-related complications. There has been a worldwide spread of this technique and an increase in indications for this medical approach. Of note, PEG allows the maintenance of normal physiological activities of the gastrointestinal tract and avoids long-term complications associated with intravenous nutritional support⁷. A gastric route through

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Conflicts of interest: tThe authors declare that there are no conflicts of interest. Funding: none. Received on December 28, 2022. Accepted on January 04, 2023.

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a PEG tube is advantageous over a jejunal approach due to its better tolerance, ease of the procedure, and possibility of being performed in a bedside model⁸. Albumin and transferrin levels have been reported to improve after inserting a PEG tube in patients with dementia⁹. Park et al.¹⁰ reported that weight gained by patients who underwent the PEG procedure were significantly higher than those who underwent the nasogastric intubation. Moreover, PEG was associated with a significantly faster time to start feeding.

Although the benefits of PEG have been reported, several controversies and major concerns still exist regarding this procedure⁷. Previously placed PEG tubes can dislodge or be inadvertently removed, blocked, or damaged. PEG tube replacement is not performed infrequently¹¹. An endoscopic replacement is recommended as it becomes dislodged within a month after placement. However, bedside replacement is usually sufficient if the tube is dislodged after 4–6 weeks, when tract maturity is expected¹². To the best of our knowledge, the remarkable effect of enteral nutrition fluid in comparing patients who underwent PEG replacement and those who underwent PEG for the first time was that it caused a decrease in *Helicobacter pylori* colonization.

METHODS

A total of 96 patients who underwent naïve or exchanged PEG procedures in our clinic with various indications between January 01 and December 31, 2021 had been included in the study. Patients were divided into two groups as naïve and exchanged PEG, and the results were compared between the two groups. In addition, the demographic data, such as age and gender, etiology of PEG, anti-HBs, anti-HCV, anti-HIV, *H. pylori* status, the presence of atrophy and intestinal metaplasia, biochemical parameters, and lipid profiles, had been reevaluated in cases.

Percutaneous endoscopic gastrostomy tube placement

The technique of PEG tube placement had been performed in line with the British Society of Gastroenterology (BSG) practice guidelines¹³. Briefly, PEG tube insertion using the pull technique had been performed under sterile conditions, and 2 g of ceftriaxone was administered intravenously as prophylaxis 30 min before the interventional procedure. The weight-adjusted midazolam and propofol were administered as sedation was required depending on the patient's condition. After a skin shave was performed, a 1-cm skin incision just before insertion of the PEG was performed with a positive transillumination in all patients. The PEG tube insertion was performed by using the PEG 24[®] Pull Method (Cook Medical, Bloomington, IN, USA), and the tube was fixed using an exterior retention plate without sutures after its insertion. The dressing was made three times a day for the first 7 days after the procedure, and water was given through the PEG tube 24 h after the tube placement. Initially, 100 mL of food was injected to ensure that there were no complications. If this was tolerated, an additional 50 mL of food was added to the previous volume as described by Jung et al.³.

Percutaneous endoscopic gastrostomy exchange procedure

If the PEG tube is not dislodged completely but has been clogged or malfunctioning, the old tube needs to be exchanged. If resistance is felt during the attempted removal of the old tube by gentle traction, it is best to remove the tube after the endoscopic cutting of the internal mushroom cap and removal of the rest of the tube through external puling. A similar-diameter PEG tube as the old tube should be used as an exchange tube. The final step in PEG tube exchange is to confirm the placement. For this purpose, water-soluble contrast is placed through the exchanged tube, and a contrast-enhanced abdominal X-ray is obtained to confirm placement in the stomach¹⁴.

Statistical analysis

Data obtained in this study were statistically analyzed using the SPSS version 25.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, USA) statistical software. The normal distribution of the variables was tested using the Kolmogorov-–Smirnov method. Normally distributed continuous variables were compared between the groups with the independent t-test and non-normally distributed variables with the Mann––Whitney U test. Categorical variables were compared using the χ^2 test. Normally distributed continuous variables are expressed as mean±standard deviation and non-normally distributed variables are given as a frequency (number, percentage), and p-values < 0.05 were considered statistically significant for the study.

RESULTS

A total of 96 patients who underwent placement or replacement (exchange) PEG procedures due to various etiologies in our clinic were included in the study. The patients were divided into two groups, namely, naïve and exchange. Patients with a PEG inserted before ≤ 1.5 months were considered to have naïve PEGs, while the others were included in the exchange group. Accordingly, the naïve group consisted of 44 cases, and the exchange group consisted of 52 cases. The median PEG exchange duration was 9 months (min-max: 0.5–6). Of all patients, 37 (38.5%) were male and 59 (61.5%) were female.

The median age was found to be 83 years (min–max: 35–96) in the exchange and 79 years (min–max: 26–95) in the naïve. Of the patients in the exchange, 14 (26.9%) were male and 38 (73.1%) were female, while in the naïve, 23 (52.3%) were male and 21 (47.7%) were female. There was a statistically significant difference between the two groups in terms of gender (p=0.020), while no significant difference was observed in terms of age (p=0.179). The most common indication for PEG placement was dementia in 26 (27.08%) cases (p=0.033). The other etiologies are shown in Figure 1.

When the clinical features of the patients were examined, the presence of *H. pylori* positivity was significantly lower in the exchange compared to the naïve (p=0.022). Clinical features of the patients are given in Table 1. Among laboratory parameters, glucose was significantly lower in the exchange group (p=0.05). Similarly, ferritin levels were statistically significantly lower in the exchange compared to the naïve (p=0.001). The exchange group's lymphocyte count was significantly higher (p=0.001) (Table 2). Total protein and albumin levels were statistically significantly higher in the exchange compared to



Figure 1. Etiologies of the percutaneous endoscopic gastrostomy application.

| Variable | | Exchange | Naïve | | |
|--------------------------|----------|-----------|-----------|---------|--|
| | | n (%) | n (%) | Р | |
| Anti LIDe | Positive | 10 (29.4) | 8 (44.4) | 0.437 | |
| ANU-HBS | Negative | 24 (70.6) | 10 (55.6) | | |
| Helicobacter | Positive | 1 (2.6) | 10 (19.2) | 0.022 | |
| pylori | Negative | 37 (97.4) | 42 (80.8) | | |
| Atrophy | Yes | 3 (6.4) | 5 (11.6) | 0.472 | |
| Atrophy | No | 44 (93.6) | 38 (88.4) | | |
| Intestinal metaplasia | Yes | 6 (12.8) | 3 (7) | 0.400 | |
| | No | 41 (87.2) | 40 (93) | 0.489 | |

Table 1. Clinicopathological features of the cases.

the naïve (both, p=0.001). The mean calcium, hemoglobin, and hematocrit levels were statistically significantly higher in the exchange (for all, p<0.001). The PNI value calculated as [albumin (g/dL)×10+lymphocyte (×10⁹/mL)×0.005] was also statistically significantly higher in the exchange compared to the naïve (p<0.001).

DISCUSSION

Nutritional support is essential in patients who have a limited capacity to maintain their normal body weight through a normal diet⁷. Enteral nutrition is indicated for patients who have a functional gastrointestinal tract and whose oral nutritional intake is insufficient to meet the estimated nutritional needs¹⁵. The placement of a PEG tube is one of the most commonly used methods to provide enteral feeding. PEG is usually indicated when a period of inadequate nutritional intake exceeding 2–4 weeks is expected, such as in patients with malignancies (mainly head and neck) or neurological diseases (e.g., cerebrovascular stroke and brain hemorrhage)². Since its introduction, PEG has become a very well-established endoscopic procedure for the enteral feeding of patients.

In the present study, we evaluated the efficacy of the enteral feeding system by comparing naïve and exchanged PEGs. Our results indicated that enteral feeding was maintained through the PEG system. No evidence-based guidelines regarding the replacement of PEG tubes have been reported. Our study's median PEG exchange duration was 9 months (0.5–6). Similarly, in a study by Bouchiba et al.¹⁶ the median follow-up was found to be 8.9 months. In our study, the median age was found to be 83 years (35–96) in the PEG exchange group, while Jung et al.² reported the mean age of 77 years.

Helicobacter pylori is a gram-negative, microaerophilic, spiral-shaped, and active bacteria that possess the ability to colonize in gastric mucosa, causing histopathological alterations in some cases, such as persistent inflammation, even peptic ulcus, chronic active gastritis, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. *H. pylori* remains one of the most common bacterial infections in humans. It has been suggested that *H. pylori* infection may influence intake and caloric homeostasis¹⁷⁻²². It has been reported that the bacterial content of the gut and the presence of relevant antigens influence the rate of recovery of host pathophysiology induced by chronic *H. pylori* infection²³. Histopathologically, a high ratio of gastric mucosa abnormalities, chronic active gastritis, and reactive gastropathy have been reported in cases with *H. pylori* colonization^{21.24}.

In the present study, *H. pylori* positivity was significantly lower in the exchange compared to the naïve (p=0.022). In addition,

| Veriable | Exchange | | | n — | | |
|------------|----------|--------------------|----|-------------------|-------|--|
| Variable | n | Median [min-max] | n | Median [min-max] | 4 | |
| Glucose | 52 | 106 [80-266] | 44 | 118 [83-380] | 0.005 | |
| AST | 52 | 22.5 [9-67] | 44 | 23[7-167] | 0.342 | |
| ALT | 52 | 14[3-76] | 44 | 18 [5-257] | 0.053 | |
| ALP | 42 | 80.5 [16-217] | 23 | 88 [54-416] | 0.38 | |
| GGT | 43 | 23 [2-197] | 31 | 26 [6-268] | 0.507 | |
| Urea | 52 | 43.5 [16-203] | 44 | 54[13-269] | 0.27 | |
| Creatinine | 52 | 0.64 [0.24-2.6] | 44 | 0.615 [0.15-7.29] | 0.724 | |
| Uric acid | 34 | 4.23[1.4-9.9] | 33 | 3.92 [1.41-13.65] | 0.985 | |
| WBC | 52 | 7.565 [4.14-20.95] | 44 | 7.81 [4.52-19.88] | 0.492 | |
| Lymphocyte | 42 | 1.765 [0.63-4.22] | 44 | 1.34 [0.33-2.67] | 0.001 | |
| Ferritin | 37 | 143[12.6-2000] | 28 | 607.55 [9.2-2000] | 0.001 | |
| TSH | 36 | 1.255 [0.01-6.97] | 18 | 1.835 [0.2-25] | 0.283 | |
| FT4 | 37 | 1.35 [0.9-12.1] | 18 | 1.215 [0.28-1.94] | 0.074 | |
| PT | 51 | 9.99 [7.81-22.1] | 44 | 9.87 [8.08-20.6] | 0.979 | |
| HbA1c | 23 | 5.48 [4.69-7.95] | 11 | 5.3 [4.71-10.08] | 0.821 | |

Table 2. Laboratory parameters of the cases.

H. pylori prevalence varies concerning ethnicity and geographic regions worldwide^{19,21}. Lee et al.²⁴ reported that *H. pylori* positivity was detected in 48.3, 67.4, and 77.9% of Americans, Korean, and Japanese, respectively. They also stated the antrum location dominancy. In the study conducted in December 2018, Sengul and Sengul^{19,21} reported 55.2% overall positivity of *H. pylori* with the antrum dominancy, 57.9%, in our studied city region. Their reported positivity was between the positivity of American and Korean-Japan groups with the frequent location of the antrum, concerning the corpus.

Several markers are used to evaluate nutritional status in the enteral feeding system through a PEG. In the present study, glucose and ferritin levels were significantly lower in the exchange group (p<0.05). The lymphocyte count was significantly higher in the exchange group (p=0.001). Similarly, in a study by Jung et al.² lymphocyte count was higher in the post-PEG group compared to the pre-PEG group.

In the present study, total protein and albumin levels were statistically significantly higher in the exchange group versus the naïve group (p=0.001). Total protein was also significantly higher in the post-PEG group in the Jung et al.² study. The mean calcium, hemoglobin, and hematocrit levels were statistically significantly higher in the exchange group (for all, p<0.001). The PNI value was also significantly higher in the exchange group than in the naïve group (p<0.001). However, since this is the first study in the literature comparing naïve and exchange PEGs, we could not compare our findings exactly.

Study limitations

The main limitations of the current study include its retrospective nature and the relatively small number of patients. In addition, we could not measure pre-PEG values. However, given the lack of a similar study in the literature, we believe that our findings will serve as a guide for future, more comprehensive studies.

CONCLUSION

Our findings indicate that dementia was the most common etiology for PEG placement, enteral feeding was maintained, and this decreased the incidence of *H. pylori* infection. Total protein, glucose, albumin, and lymphocyte counts were statistically higher, while ferritin levels were significantly lower in the PEG exchange group, showing that enteral feeding was maintained and continued to provide nutritional support through PEG. To the best of our knowledge, this is the first study in the English literature stating that enteral nutrition through PEG might lead to attenuating *H. pylori* colonization. However, further comprehensive prospective studies are needed to confirm our findings. .

ACKNOWLEDGMENTS

The authors thank all the participants involved in this study.

AUTHORS' CONTRIBUTIONS

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

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Vulnerability of lesbian and bisexual women to HIV: a qualitative meta-synthesis

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INTRODUCTION

The concept of vulnerability in the field of health is understood as the possibility of exposing a person to illness, considering individual and collective factors contextualized around a disease. According to the exposition, three dimensions of vulnerability are individual, social, and programmatic¹.

The configuration of literary productions on the vulnerability and/or sexual practices of women who have sex with women is still less present in studies on sexuality and sexual health^{2,3}.

The AIDS epidemic strengthened the LGBT movement by enabling the social debate on sexuality and homosexuality, enabling public health policies that contemplated the specificities of this population^{4,5}. Sexual practices among women who have sex with women (a universe that includes both lesbians and bisexuals) were made invisible in the context of HIV infection due to the initial idea of contagion, in which it was thought that the spread of the virus occurred only through the sharing of body fluids².

HIV/AIDS is a topic widely studied in scientific research. However, these studies related to the field of sexuality still present a panorama predominantly focused on male sexual practices in relation to female sexual practices, either in the context of heterosexuality or still relatively incipient when focused on female homosexuality. Given the above, it is essential to identify and analyze the production of knowledge in the health literature on vulnerabilities to HIV in the context of lesbians and bisexual women. This study aimed to analyze scientific evidence on the vulnerability of lesbian and bisexual women to HIV, compared to heterosexual women.

METHODS

The methodology of systematic review (SR) of the meta-synthesis type was adopted⁶. Initially, in the elaboration of the guiding question, the PICo strategy was used, proposed by the Joana Briggs Institute for qualitative SR, where P corresponds to the participants=lesbians and bisexual women; I corresponds to the phenomenon of interest=vulnerability to HIV/AIDS; and Co corresponds to the context of the study=HIV vulnerability of lesbians and/or bisexuals.

The review protocol was submitted to the International Prospective Registry of Systematic Reviews, with registration number CRD42021274780. The searches were carried out in February 2021 in the databases (CINAHL), SciELO, and National Library of Medicine (PubMed/Medline). Controlled descriptors and keywords in English were used: Female Homosexuality, Lesbian, Sexual and Gender Minorities, Gay, Health Vulnerability, Vulnerability, and HIV; and their correlates in Portuguese and Spanish according to the classification of Health Sciences Descriptors (DeCS) and Titles of Medical Subjects (MeSH/PubMed) crossed with the Boolean operators AND, OR, and NOT.

Inclusion criteria are as follows: only primary studies that addressed vulnerability related to HIV in lesbian and/or bisexual women, available in full, in Portuguese, English, and Spanish (because they are the most predominant languages in the databases used). Furthermore, exclusion criteria include publications of the editorial type, letters to the editor, books and/or book chapters, monographs, dissertations, theses, experience reports, systematic and/or integrative reviews, gray literature, and predatory publications.

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Conflicts of interest: The authors declare there is no conflicts of interest. Funding: none.

Received on January 15, 2023. Accepted on January 21, 2023.

The period of publication was limited to the years 2010–2020 due to the publication of scientific evidence in 2009 of the first confirmed case of exclusive HIV infection among women⁸. The selection was performed using the Rayyan Application with two independent reviewers, and, when necessary, a third reviewer was requested in articles where there was disagreement. After this careful evaluation, a final sample of 16 studies was obtained. The level of evidence of the articles was evaluated based on the proposal by Melnyk and Fineout-Overholt⁷. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) instrument was used to search and select the articles described in Figure 1. The analysis of the results was based on a thematic analysis⁹.

RESULTS

Among the 16 selected articles, which were predominantly published in English, as for the methodology used, there were 9 articles with a quantitative approach^{10-13,17,19,20,23-25} and 7 articles with a qualitative approach^{10,14-16,21,22}. Table 1 summarizes the information on the articles included in the final sample.

DISCUSSION

Vulnerability in women who have sex with women is revealed in the contexts of vulnerability that permeate the social and pragmatics, in addition to the contexts of individual invisibility



Figure 1. Flowchart of study selection process.

| Authors/Year | Methodological design | Evidence level |
|---|--|----------------|
| Batista and Zambenedetti ¹⁰ (2017) | Intervention research, following the analytical-institutional framework | LE=VI |
| Lyons et al. ¹¹ (2014) | Prospective cohort study and bivariate and multivariate logistic regressions | LE=IV |
| Poteat et al. (2013) | Cross-sectional cohort study, with mixed method | LE=IV |
| Logie et al. (2019) | Multicenter, nonrandomized pilot study | LE=IV |
| Mora and Monteiro ¹⁴ (2010) | Qualitative research with ethnographic observations and in-depth interviews | LE=VI |
| Daly et al. ¹⁵ (2016) | Qualitative analysis of health policies | LE=VI |
| Sandfort et al. ¹⁶ (2013) | Qualitative field research | LE=VI |
| Herrick et al. ¹⁷ (2010) | Cross-sectional descriptive study | LE=VI |
| Muzny C.A. et al. ¹⁸ (2013) | Qualitative study through focus groups | LE=VI |
| Andrade et al. (2019) | Cross-sectional descriptive study | LE=VI |
| Paschen-wolff et al. (2019) | Prospective cohort study and multivariate logistic regression | LE=IV |
| Muzny A. et al. ²¹ (2013) | Qualitative study | LE=VI |
| Poteat et al. (2017) | Exploratory study, through spoken narrative | LE=VI |
| Palma et al. (2015) | Cross-sectional mixed method study | LE=VI |
| Zaidi et al. (2012) | Cross-sectional descriptive study | LE=VI |
| Wang et al. ²⁵ (2012) | Cross-sectional descriptive study | LE=VI |

Table 1. Distribution of articles regarding methodological design, authors, and level of evidence.

and identity invisibility expressed in the situations identified in the research that composed the sample of this review.

In the contexts of vulnerability category, it was found that although there are policies that affirm the importance of promoting sexual rights and the promotion and prevention of HIV, women who have sex with women, lesbians, and bisexual women, in addition to sex workers in a particular way, remain with their rights unexplored. In terms of epidemiology and structural factors of social and pragmatic vulnerabilities, this may mean the need for more targeted approaches to the demands from different policy approaches aimed at the LGBTQI public identified in the deficiency in the service of this population¹⁴.

Historically, individuals who experience practices that differ from the heterosexual norm with different expressions of sexual orientation, that is, desire or effective attraction to the same sex or both, have been positioned in a restricted place. Very less is known about lesbian and their past experiences, as well as the patterns of seeking health care, leading them to avoid and be reluctant to seek help and medical advice²⁶⁻²⁸.

Understanding how to provide appropriate and comprehensive counseling for lesbian and bisexual women is essential in preventing and controlling the transmission of the virus to their female sexual partners. In addition, reporting their sexualities and sexual practices with same-sex partners should not impede trained health professionals in addressing the potential sexual risks for these women¹⁶. Perspectives on issues of social and pragmatic vulnerability are consistent with social networks and the training of health professionals involved in assisting this group¹⁹. Particularly in parts of the world where HIV prevalence is high, women who have sex with women and other sexual minorities face various forms of homophobic violence. All these women must receive adequate information about sexually transmitted infection (STI) prevention and HIV²⁰.

When analyzing the different contexts of vulnerability, different perspectives are opened which allow judgments and understanding of individual and collective differences and how everyone faces the health-disease process²⁹. Moreover, this will be effective only if the heterogeneity in the population of lesbians and bisexual women is recognized, with health programs adapted to meet the needs of these women in an integral and targeted way²⁵.

Thus, for these women, the perception of the vulnerabilities in which they are inserted occurs through their relationships with society, often surrounded by taboos and prejudices rooted in historical contexts established from heteronormative standards. For health professionals and services, these women are recognized only during the provision of care that has already been instituted and guided as subjects framed in the pattern of sexual practices positioned in heteronormative issues, seen as the central axis of care, displacing their sexual practices between women by a context of subordination to the dominant model, because men and women assume that they are different in the exercise of their sexuality, especially for men, sexuality is linked to power²⁹.

In the Invisibility Processes category, although there is an understanding of the aspects that make women who have sex with women vulnerable to STIs, there is still no consideration that the methods and means of prevention made available to this public are unfeasible, because they consider these methods out of context, with the perception that the methods are linked to the reduction of their sexual pleasure. In addition to having this idea of prevention, the biomedical and prescriptive nature of the interventions always follows the heteronormative bias, where the information given do not match the context and demands of these women, prioritizing what would be more or less important, which ends up accentuating the dimension of programmatic vulnerability¹⁰⁻¹⁴.

This idea is also present when they point out that the risks for these women are even more intensified because their peculiar characteristics are neglected by many health professionals, who are still outdated and prejudiced, which can influence their search patterns for health care^{25,12}.

Throughout the history, HIV infection has been unique in that its modes of transmission are primarily related to human behavior with drug use and unprotected sex⁸, which ends up making women who have sex with women even more vulnerable, as gender relations and relations that generate social constructions end up bringing severe repercussions to the health of these women involved³⁰.

Another perceived point is the relationship of influence in trust between social and sexual interaction on the risk of HIV, the bonds with their sexual partners and social networks among women end up transmitting confidence, minimizing the perception of the risks of HIV contamination among them. Women denote the forms and meanings attributed to their sexual and prevention practices between partnerships as a result of a historical production centered on heterosexual practices¹⁸. Thus, socially and economically disadvantaged populations experience greater capacity and risk of acquiring HIV, as the burden

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of disease and prevention innovations are not evenly distributed among populations²⁷⁻²⁹.

CONCLUSION

It was noted that the existing belief about sexual practices between women, which is still widely understood as illegal or out of the ordinary, has as its reference the heteronormative standards of society, which ends up resulting in contexts of discrimination and stigma, thus bringing negative consequences for women.

The contexts of vulnerability found in the articles point to the contexts of stigma generated by the lack of empowerment and low social support of these women.

Their relationships enhance these vulnerabilities, especially with regard to reception and care, in addition to illness and exposure to various diseases.

STUDY LIMITATION

The probable limitations in this study are the limitations of time and language, which may have reduced the scope of findings in the sample. The definition of not having included the term "bisexuality" in the crossings in the databases may have also limited the research, but it was decided not to use it due to the possibility of including studies that addressed male bisexuality. This bias was controlled with the use of "NOT GAY" in the crossings performed with the other DESC and MESH.

AUTHORS' CONTRIBUTIONS

CAAA: Conceptualization, Data curation, Methodology, Project management, Writing – original draft, Writing – review & editing. RLA: Conceptualization, Data curation, Methodology, Writing – original draft. KRFS: Conceptualization, Methodology, Writing – original draft. GBM: Conceptualization, Methodology. AMC: Project administration, Supervision, Validation, Writing – review & editing. FMSA: Project administration, Supervision, Validation, Writing – review & editing.

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In the manuscript "Cannabis products: medical use", DOI: 10.1590/1806-9282.2023D693, published in the Rev Assoc Med Bras. 2023;69(3):358-364, on page 358:

Where it reads:

César Eduardo Fernandes¹ ⁽¹⁰⁾, José Eduardo Lutaif Dolci¹ ⁽¹⁰⁾, Leonardo Sobral Navarro² ⁽¹⁰⁾, Marcelo Allevato³ ⁽¹⁰⁾, Clóvis Francisco Constantino⁴ ⁽¹⁰⁾, Rodrigo Pastor Alves Pereira⁵ ⁽¹⁰⁾, Carlos Roberto de Mello Rieder⁶ ⁽¹⁰⁾, Flávia Torino² ⁽¹⁰⁾, Wanderley Marques Bernardo^{1*} ⁽¹⁰⁾

It should read:

César Eduardo Fernandes¹, José Eduardo Lutaif Dolci¹, Leonardo Sobral Navarro², Marcelo Allevato³, Clóvis Francisco Constantino⁴, Rodrigo Pastor Alves Pereira⁵, Carlos Roberto de Mello Rieder⁶, Flávia Torino², Wanderley Marques Bernardo^{1*}, Antônio Geraldo da Silva³



In the manuscript "Low-dose paclitaxel modulates the cross talk between the JNK and Smad signaling in primary biliary fibroblasts", DOI: 10.1590/1806-9282.20210777, published in the Rev Assoc Med Bras. 2022;68(2):159-164:

Page 160, where it reads:

As shown in Figure 1C, 3 ng/mL TGF- β 1 increased the phosphorylation level of JNK as compared to the control group (p<0.05), whereas 5 ng/mL TGF- β 1 increased the phosphorylation level of JNK by 3.85 times compared with the control group (p<0.01).

It should read:

As shown in Figure 1C, 3 ng/mL TGF- β 1 increased the phosphorylation level of JNK as compared to the control group (p<0.05), whereas 10 ng/mL TGF- β 1 increased the phosphorylation level of JNK by 3.85 times compared with the control group (p<0.01).

Page 162 on Figure 2, where it reads:



ERRATUM

Page 162 on Figure 2, it should read:



