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Editors-in-Chief: Renato Deláscio Lopes, José Maria Soares Jr and Roseli Nomura.
Managing Editor: Cesar Teixeira
E-mail: ramb@amb.org.br
Website: www.ramb.org.br

ADDRESS: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
Postal Code: 01333-903
Phone no.: (+55 11) 3178-6800 Ext. 177
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Safe transport of organs and tissues for transplants: technological innovation product validation method

Bartira de Aguiar Roza[1*], Sibele Maria Schuantes Paim[1], Renata Leite[1], Adriana Ferraz Carbonel[2], Murched Omar Taha[3], André Ibrahim David[3], José Maria Soares Junior[4], Manuel de Jesus Simões[2], Janine Schirmer[1*]

Brazil is a country with expressiveness and relevance in the organ and tissue donation and transplantation scenarios. Numerical indicators regarding the rate of transplants demonstrated this importance. During 2021, 23,929 cells, tissues, and organs transplants were performed[1].

However, despite this numerical indicator, the waiting list for transplantation is still lengthy. During the first semester of 2022, 51,674 people were registered waiting for the treatment, which often means a chance for continue living[2].

Due to the difference between the number of transplants and the number of people on the waiting list, strategies are developed to look for problems and failures in the cells, tissues, and organs donation and transplantation processes, as well as improvement opportunities. Regarding these strategies, it was identified that organs and tissues were lost ofdue to logistical problems. According to the Brazilian Association of Organ Transplantation (Associação Brasileira de Transplantes de Órgãos – ABTO), in 2022, 15% of the organs offered were not transplanted for various reasons. Some of these reasons were related to fragilities during the packaging for transport[2].

Currently, the organs are packaged in three primary packages and then in a thermal box filled with ice for transport[3]. Identification is done with labels standardized in current legislation[4], and the internal temperature is not controlled. Furthermore, the packaging route is not shared.

The problems with this type of transport are related to the lack of temperature control, causing the organs to freeze when in contact with the ice or, due to the thawing of the ice, the temperature increase. Both situations result in tissue death and, thus, there is not control over the quality of the transplanted organ.

Being faced with the identified problem, a group of researchers started to develop a package that would meet the requirements and safety criteria for this type of transport, including temperature control and industry 4.0 enabling technologies, that is, an interactive system with data collection and storage using cloud, and artificial intelligence[5].

The research idea as well as the development and production of this package arose from nurses' concern on the quality during their assistance to transplants. In their routines, nurses experienced and still experience the impact of these problems on the life of patients and on the health systems. The project is developed in two other public institutions and in a private one in the state of São Paulo, Brazil[5].

However, to ensure that the technological product is safe and widely used, a clinical validation method was developed. For this purpose, organs and ocular tissues obtained from Landrace line pigs (due to the similarity with humans' organs and ocular tissues) will be used in simulated organ extraction surgeries. Twelve experiments will be conducted, of which two pilot tests are used to improve the method and 10 experiments using the case-control method are adapted for clinical validation purpose.

Studies using this method aim to compare the individual's exposure to some factors that can trigger an outcome of interest. Normally, it is a retrospective study that aims to identify the existence of casual association between the factor's exposure and the disease under study[6,7]. In this case, for the technological product validation, the study's object is the new packaging that works differently from the packaging used in the Brazilian reality. Therefore, the main risk factor is the integrity maintenance of the organs and tissues transported.

[1]Universidade Federal de São Paulo, Escola Paulista de Enfermagem – São Paulo (SP), Brazil.
[2]Universidade Federal de São Paulo, Escola Paulista de Medicina, Department of Morphology and Genetics – São Paulo (SP), Brazil.
[3]Universidade Federal de São Paulo, Escola Paulista de Medicina, Discipline of Operative Technique and Experimental Surgery – São Paulo (SP), Brazil.
[4]Laboratório de Ginecologia Estrutural e Molecular - LIM 58 da Disciplina de Ginecologia, Departamento de Obstetrícia e Ginecologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – São Paulo (SP), Brazil.
*Corresponding authors: bartira.roza@unifesp.br; schirmer.janine@unifesp.br
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To determine the package's capacity to maintain organs and tissues viable to transplant, operational analysis will be performed. Safety issues, temperature, transport conditions, ergonomics, histomorphology, and microbiology will be evaluated.

Data collection will be done following the standardized organ and tissue extraction process performed in humans. Anesthetic procedures in pigs will be carried out, followed by the removal of the heart, liver, pancreas, kidneys, and ocular globes. Then, organ perfusion, macroscopic analysis regarding the organs and tissues characteristics using an instrument made for this purpose, and, finally, samples collection for the histomorphological and histomorphometric analysis will be performed. Finally, packaging organs and tissues in primary packages with preservation solutions and in secondary packages for transport will be carried out in test (experimental package) and in the package already in use (control package) with ice.

Ground transport will be carried, and once returned to the surgical place, the same analyses described above will be performed. In addition, before and after transport, to compare microbiological growth, swabs will be collected in both packages using a protocol developed for this study (three collections at the bottom of the box, three in the top of the box, and three in the support for biological samples inside the box), totaling 18 samples each package.

Regarding the morphological analysis, it will present important data about the morphology of the transported organs and tissues. In this way, in the heart, the cardiac striated muscle tissue (cardiomyocytes), nuclei, intercalated disks, and the entire cardiac stroma will be evaluated. In the liver, central lobular vein, hepatocytes, portal space (branches of the portal vein and hepatic artery, respectively), bile ducts, lymphatic vessels, and nerves will be evaluated. In the pancreas (exocrine and endocrine portion), lobules, septa, and glands in the pancreatic stroma will be evaluated. In the kidney, glomeruli, proximal and distal convoluted tubules, and entire renal stroma will be evaluated. In the ocular globes, the cornea (dense modeled connective tissue), anterior and posterior epithelium, the sclera (dense non-modeled connective tissue), vascular tunic (uvea comprising the iris, choroid, and ciliary processes), and retina will be evaluated.

Thus, with these data, it is intended to see the tissue morphology and quantify it using specific software. This type of analysis is called histomorphometry, which constitutes the first step in carrying out the approach to new tissues. This analysis will allow to quantify and statistically show the comparison of organs and tissues between the two packages under test.

In addition, immunohistochemistry technique will be performed to search for cellular and tissue antigens in order to analyze proteins that participate in the cell death process, seeking to analyze the specific proteins that participate in cell proliferation and apoptosis in the evaluated organ[8,9].

Finally, the main purpose of this process is to guarantee the entry into the market of a new and safe innovative product to be used in the transport of organs and tissues for transplants. Therefore, reducing the loss of these organs caused by logistical and transport problems and, consequently, increasing the number of patients with access to this treatment and reducing the waiting period for an organ or tissue will all impact the lives of these people.

AUTHORS' CONTRIBUTIONS

BAR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **SMSP:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **RL:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **AFC:** Methodology, Project administration, Supervision, Validation, Writing – original draft. **MOT:** Resources, Supervision. **AID:** Software, Validation, Visualization, Writing – original draft. **JMSJ:** Writing –original draft, Writing – review & editing. **MJS:** Writing – original draft, Visualization. **JS:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing.

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GUIDELINE

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The use of esketamine in the treatment of patients with oral antidepressant-resistant depression: systematic review and meta-analysis

Idevaldo Floriano[1*], Antônio Silvinato[2], Wanderley Marques Bernardo[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 conditions and the clinical condition of each patient.
Guideline conclusion: April 2023.
Societies: Brazilian Medical Association.

INTRODUCTION

Depression is a very common disabling mental illness and can be assessed through the application of several questionnaires, one of the most commonly used being the Montgomery-Asberg rating scale[1], scoring from 0 to 60, where 7–9 ranks mild depression, 20–24 ranks moderate depression, and greater than 34 ranks severe depression. Approximately one-third of patients with major depression do not experience remission when treated with up to two or more oral antidepressants (OAD), being considered treatment-resistant[2].

In *post-mortem* analysis, in vivo gene expression studies and brain imaging data suggest abnormalities in glutaminergic signaling in the pathophysiology of depression[3,4], allowing the use of new antidepressants with a mechanism of action outside the monoaminergic system.

Esketamine, which is the S-enantiomer of racemic ketamine, is an antidepressive drug with a novel mechanism of action. This active drug is a non-selective, non-competitive *N*-methyl-*D*-aspartate receptor (NMDAR) antagonist; being an ionotropic glutamate receptor, it promotes increased stimulation of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and neurotrophic signaling that restore brain synaptic function. However, the mechanism by which esketamine exerts its antidepressive effect is unknown. Unlike other antidepressive treatments, the primary antidepressive action of esketamine does not directly involve monoamine, GABA, or opioid receptors[5].

The aim of this systematic review was to evaluate the use of esketamine in comparison with placebo in patients with resistant depression.

Clinical doubt

What is the efficacy and safety of using esketamine in the treatment of patients with resistant depression?

METHODOLOGY

Eligibility Criteria:

1. Patients with resistant depression;
2. Compared to placebo plus standard care;
3. Outcomes – improvement in the state of depression, evaluated with appropriate scores;
4. Included randomized controlled trials (RCTs);
5. No restrictions on the date of publication, age of participants, and language;
6. Full text available for access;
7. Follow-up time: minimum of 28 days.

The search for evidence will be carried out in the virtual scientific information database Medline/Pubmed, CENTRAL COCHRANE, and ClinicalTrials.gov, using the search strategy:

[1]Cooperativa Baixa Mogiana, Evidence-Based Medicine – Mogi-Guaçu (SP), Brazil.
[2]Brazilian Medical Association, Evidence-Based Medicine – São Paulo (SP), Brazil.
[3]University of São Paulo, School of Medicine – São Paulo (SP), Brazil.
*Corresponding author: idfloriano@hotmail.com
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(Depressive Disorder OR Depressive Disorder, Major OR Depressive Disorder, Treatment-Resistant) AND Esketamine AND Random*. The search in these databases was carried out until December 2022. This systematic review will be prepared according to the recommendations contained in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[6], and the protocol of this study has been registered in PROSPERO (CRD42023403453).

The risk of bias for randomized clinical trials will be assessed using the items in version 2 of the Cochrane risk of bias tool for randomized clinical trials RoB 2[7] plus other fundamental elements and expressed as low risk, some concerns, and high risk of bias. The risk of bias assessment will be conducted by two independent reviewers (AS and IF), and in case of disagreements, 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 there is no meta-analysis) using the terminology GRADE[8] in very low, low, moderate, and high and through the GRADEpro software[9] (if meta-analysis) into very low, low, moderate, and high.

The measures used to express benefit or harm varied according to the outcomes, being expressed through continuous variables (mean and standard deviation (SD)) or categorical variables (absolute number of events). For continuous measurements, the result will be the difference in means (DM) and its 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 among the included studies, patients and results will be added together, with different doses (esketamine 28–84 mg/week) for comparison with placebo. For calculation in absolute numbers or averages that can be paired, the results will be meta-analyzed using the RevMan 5.4 software[10], 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 doubts. The estimation of the size of the combined effects will be carried out by a fixed or random effect model after the evaluation of the heterogeneity results. Heterogeneity was calculated using the I^2 value.

RESULTS

In the search for evidence, 90 studies were retrieved, 27 being selected by title and abstract, of which 3[11-13] 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 and Table 2.

The population included was 703 patients, aged over 18 years, diagnosed with recurrent depression or a depressive episode for a period ≥2 years, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria (DMS-5 criteria) and without associated psychotic disorders, confirmed by the Mini International Neuropysichiatric Interview (MINI) (Table 1 – ANNEXES). Participants had episodes of moderate to severe depression, with a score≥28 when assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) or a score≥34 when assessed using the Inventory of Depressive Symptomatology.

Exclusion criteria were bipolar psychiatric disorder, drug addiction, intellectual disability, antisocial personality disorder, *borderline personality*, and psychotic disorder.

A total of 415 participants received esketamine for 4 weeks (28–84 mg, nasal route, 3 *puffs* in total, alternating nostrils, 5 min apart, twice a week) associated to treatment with oral antidepressants, individualized for each patient (*standard of care*), and 288 received placebo plus *standard of care*.

The primary outcome considered was the reduction in depressive symptoms assessed by the MADRS and the secondary ones were remission of depression (MADRS score ≤12) and response ≤50% in the reduction in the MADRS score initial and adverse events.

Regarding the risk of bias (Figure 2), two studies did not present analysis by intention to treat[10,11], and the overall risk of bias can be considered moderate. The evaluation was through the ROB 2 tool.

Results of comparing esketamine versus placebo in patients with resistant depression at 28-day follow-up

The evaluation of MADRS score reduction included three studies[11-13] with a total of 681 patients. The meta-analysis for this outcome showed a mean reduction of 4.09 points in favor of using esketamine compared to placebo (MD=-4.09, 95%CI -5.73 to -2.45, I^2=0%, p=0.00001, Figure 3; moderate evidence certainty, Table 3 – ANNEXES).

The meta-analysis for the outcome rate of patients in "remission" (MADRS≤12 points) included three studies[11-13] with a total of 703 participants. Compared with placebo, esketamine increased the number of patients with "remission" by 10% (RD=0.10, 95%CI 0.03–0.17; I^2=8%, p=0.004), requiring treatment (NNT) of 10 patients for one get "remission" (Figure 4; moderate evidence certainty, Table 3 – ANNEXES).

Three studies[11-13], including a total of 703 patients, were included to meta-analyze the outcome "≥50% reduction in baseline MADRS score." Compared to placebo, esketamine increased the number of patients with "≥50% reduction in

baseline score" by 11% (RD=0.11%, 95%CI 0.05–0.16, I^2=8%, p=0.0001; NNT=9), (Figure 5; moderate evidence certainty, Table 3 – ANNEXES).

Serious adverse events were evaluated in three studies[11-13], with a total of 703 participants, in a 28-day follow-up and showed no difference when comparing esketamine versus placebo (RD=1%, 95%CI -0.01 to 0.03, I^2=8%, p=0.36; NNH=NS) (Figure 6; very low certainty of evidence).

Evidence summary

The use of esketamine over a period of 4 weeks (28–84 mg, nasal route, 3 *puffs* in total, alternating nostrils, with an interval of 5

Table 1. Characteristics of clinical studies evaluating the use of esketamine compared to placebo.

Studies	Population	Intervention	Comparison	Outcome	Follow-up
Fedgchin (TRANSFORM-1) 2019	The study was randomized, double-blind and multicenter, with 346 participants aged between 18 and 64 years old with recurrent major depression or a single episode of depression for more than 2 years, without psychotic characteristics according to DSM-IV-TR criteria and confirmed by Mini International. ***Neuropsychiatric Interview(MINI)***. Participants scored ≥28 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and scored ≥34 on the ***Inventory of Depressive Symptomatolgy***. Several psychiatric comorbidities were exclusionary: suicidal ideation, current diagnosis of bipolar disorder, moderate to severe substance use disorder, and substance use.	Esketamine 56 and 84 mg, nasal spray twice a week for 4 weeks, combined 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	4 weeks
Popova (TRANSFORM-2) 2019	Phase 3, double-blind multicenter study, conducted between June 2017 and December 2018, N=227 adult participants (18–64 years old) diagnosed with major depressive illness (DMD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), without psychotic features confirmed by application of the ***Mini International Neuropsychiatric Interview*** (MINI); having a score ≥34 on the "***Inventory of Depressive Symptomatolgy (IDS-C)***" scale. Exclusion criteria: suicidal ideation, psychotic disorders, and drug use.	Esketamine 56–84 mg nasal spray twice a week for 4 weeks plus 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	4 weeks
Ochs-Ross (TRANSFORM-3) 2019	Randomized, phase 3, double-blind, actively controlled, multicenter study conducted in 13 countries between August 2015 and August 2017. 138 participants were selected (N=72 esketamine/antidepressants and N=66 placebos/antidepressants. Eligible patients were aged ≥65 years old, diagnosed with major depressive illness (DMD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), treated with ≥2 oral antidepressants, without psychotic features confirmed by applying the Mini International ***questionnaire Neuropsychiatric Interview*** (MINI) Exclusion criteria were suicidal ideation, psychotic disorders, and drug use.	Esketamine 28–84 mg nasal spray twice a week for 4 weeks plus 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	4 weeks

min, twice a week) associated with treatment with oral antidepressants, in patients with drug-resistant depression treatment with oral antidepressants compared to placebo:

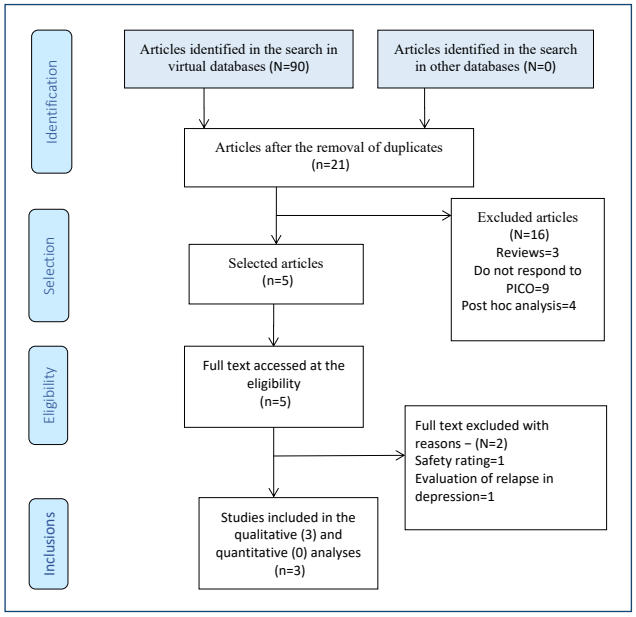

Figure 1. Diagram in recovery and selection of evidence. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097

- It reduces depression rating scale scores (MADRS), standardized mean of 4.09 points on the MADRS. Moderate evidence certainty.
- It increases the "remission" rate by 10% (MADRS≤12 points); NNT=10. Certainty of moderate evidence.
- It increases the number of patients with reduction by 11%≥50% points on the MADRS initial; NNT=9. Certainty of moderate evidence.
- There is no difference in the number of serious adverse events. Very low certainty of evidence.

DISCUSSION

In this systematic review with meta-analysis, only randomized clinical trials were included, which evaluated the use of esketamine in comparison with placebo, in patients with depression resistant to treatment with two or more oral antidepressants (OAD).

The use of esketamine plus individualized antidepressants compared to placebo showed a reduction standardized mean of 4.09 points on the Montgomery-Asberg scale for depression. It should be noted that all patients included had scores≥28 points on the MADRS. In secondary endpoints, the remission rate (MADRS score≤12) and the ≥50% reduction in the baseline MADRS showed a benefit of 10% (NNT=10) and 11% (NNT=9), respectively, at the 28-day follow-up.

Table 2. Studies with exclusion reasons.

Studies	Reason for exclusion
Agboola 2020	Cost-effectiveness analysis
Anees Bahji 2020	Systematic review
Nickname 2019	Protocol
Correia-Melo 2020	Does not meet eligibility criteria
Daly 2017	Purpose of the study was to evaluate the relapse of depression in stable patients who do not meet the PICO
Diekamp 2021	Post hoc analysis of two ASPIRE I and ASPIRE II studies
Fedghin 2019	Depression resistant to conventional antidepressants
Jason Ng 2021	Systematic review
Jones 2022	Post hoc analysis, secondary outcome
Katz 2020	Post hoc analysis of three studies
Nijs 2020	Post hoc analysis
Papakostas 2020	Review article
SD Targum 2019	Pilot study
Singh 2016	Does not meet eligibility criteria
Takahashi 2021	Depression resistant to conventional antidepressants
Turkoz 2021	Post hoc analysis of the Transform study.
Vazquez 2021	Does not meet eligibility criteria
Wajs 2020	Depression resistant to conventional antidepressants

Esketamine has a rapid mechanism of action and an often transient response. With a short follow-up time (28 days), evaluated in this review, it is not possible to extrapolate, in the long term, the result obtained from the treatment of severe depressive illness with resistance to ADO, which is often chronic, demanding treatment for long and indeterminate periods.

As limitations of this study, first, we can mention the number of the tested population, which is relatively small and may lead to publication bias. According to the evaluation through the questionnaire (MARDS), with results in mean and SD, it may not reflect a categorical improvement in absolute and individual terms of these patients.

CONCLUSION

The use of esketamine and *standard of care* compared to placebo and *standard of care,* in patients with resistant depression, reduces baseline MADRS and increases the number of patients with ≥50% reduction MADRS initial as well as remission (MADRS score≤12), in a period of up to 28 days, in patients with ADO-resistant depression. Esketamine is shown to be safe, without increasing serious adverse events.

Therefore, it is concluded that patients with ADO-resistant depression benefit from the use of esketamine 28–84 mg, nasal *spray,* twice a week, for 4 weeks, associated with oral antidepressants.

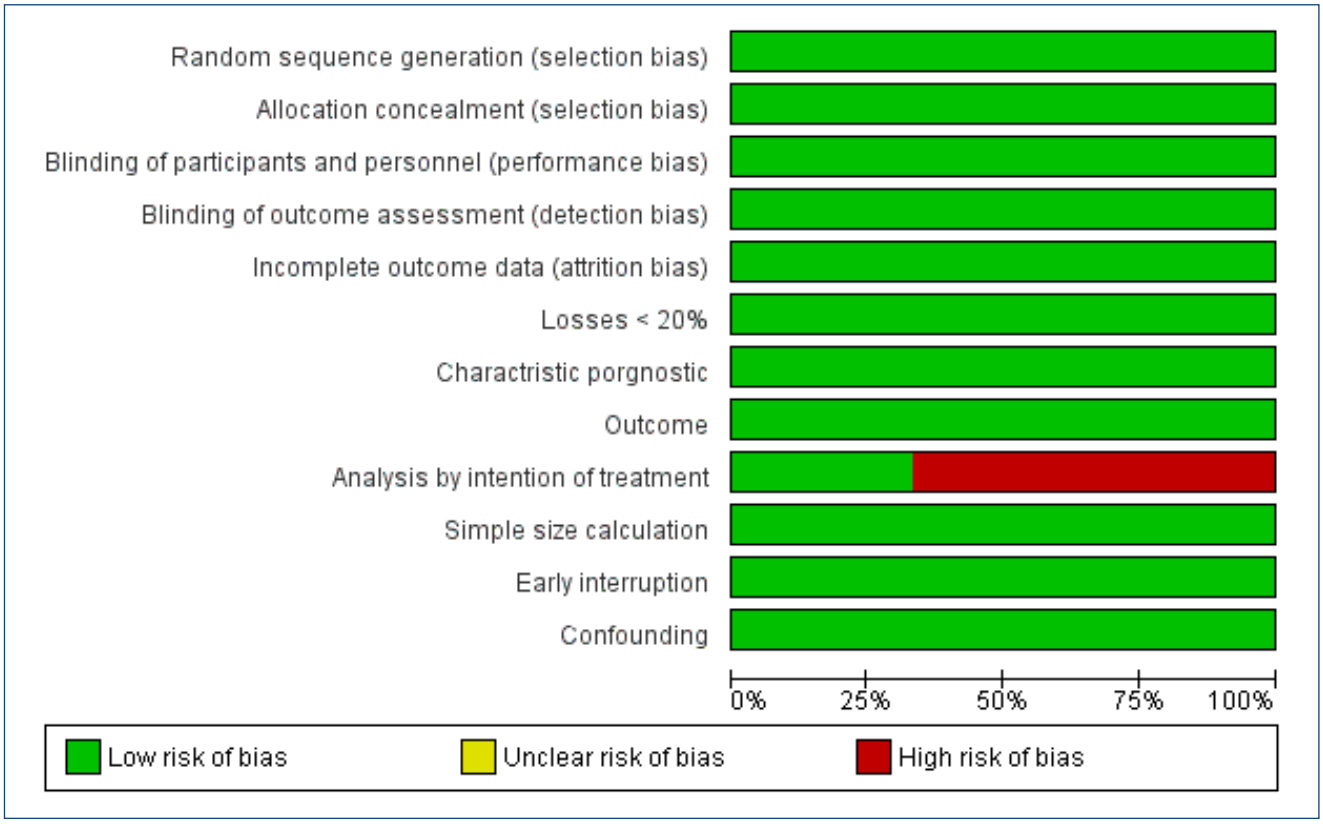

Figure 2. Risk of bias (red=presence; green=absence; and yellow=risk of unclear bias).

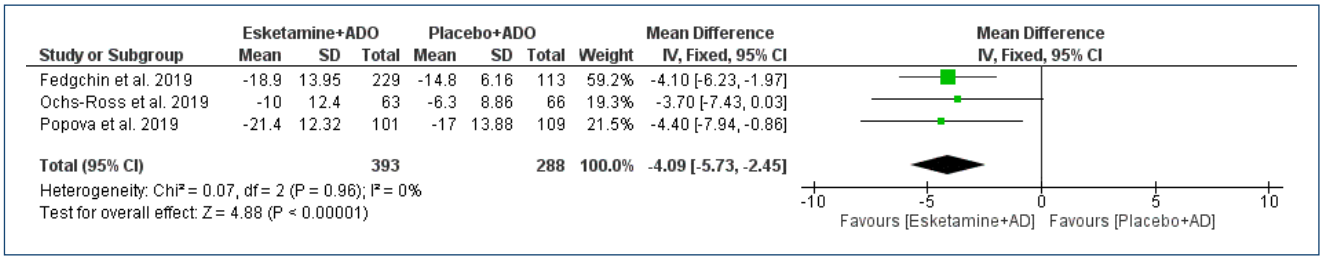

Figure 3. Meta-analysis of the mean reduction in Montgomery-Asberg Depression Rating Scale.

Table 3. Quality of evidence (GRADE).

Summary of findings:					
Evaluate the efficacy and safety of using esketamine and AD in elderly participants with treatment-resistant depression compared to placebo for treatment-resistant depression.					
Patient or population: Patients with treatment-resistant depression **Setting:** **Intervention:** Evaluate the efficacy and safety of using esketamine and AD in participants with treatment-resistant depression. **Comparison:** Placebo					
Outcomes	**Anticipated absolute effects* (95%CI)**		**Relative effect (95%CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with placebo	**Risk with esketamine**			
Mean change from baseline in MADRS total score up to endpoint	The mean change from baseline in MADRS total score up to endpoint was **0**	MD **4.09 lower** (5.73 lower to 2.45 lower)	–	681 (3 RCTs)	⊕⊕⊕O Moderate[a]
Participants in remission (MADRS£12)	243 per 1,000	**340 per 1,000** (267–430)	**RR 1.40** (1.10–1.77)	703 (3 RCTs)	⊕⊕⊕O Moderate[a,b]
Participants who achieved ³50% reduction from baseline in MADRS total score	215 per 1,000	**336 per 1,000** (265–428)	**RR 1.56** (1.23–1.99)	703 (3 RCTs)	⊕⊕⊕⊕ Moderate[b]
Adverse events serious	17 per 1,000	**27 per 1,000** (10–79)	**RR 1.58** (0.55–4.55)	703 (3 RCTs)	⊕OOO Very low[c]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI: confidence interval; MD: mean difference; RR: risk ratio. GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be slightly different from the estimate of the effect. Very low certainty: We have very less confidence in the effect estimate: the true effect is likely to be slightly different from the estimate of effect. [a]Does not apply analysis by the intent of treatment. [b]Wide confidence interval. [c]Confidence interval crosses the nullity line.

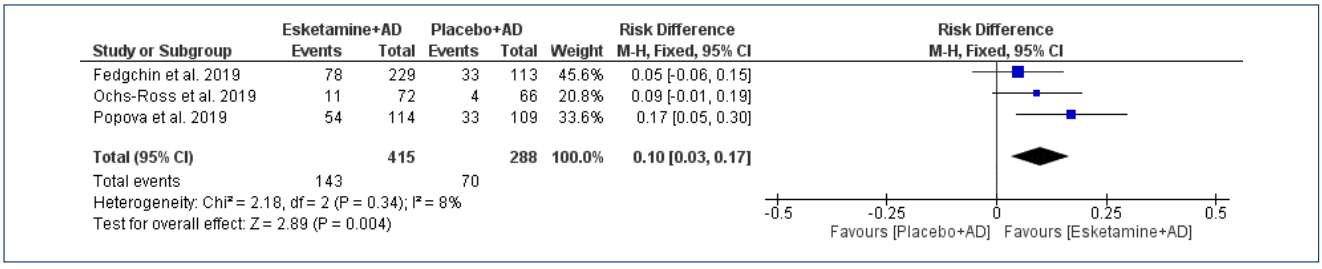

Figure 4. Meta-analysis of the "remission" rate (reduction to ≤12 points on the Montgomery-Asberg Depression Rating Scale), fixed effect.

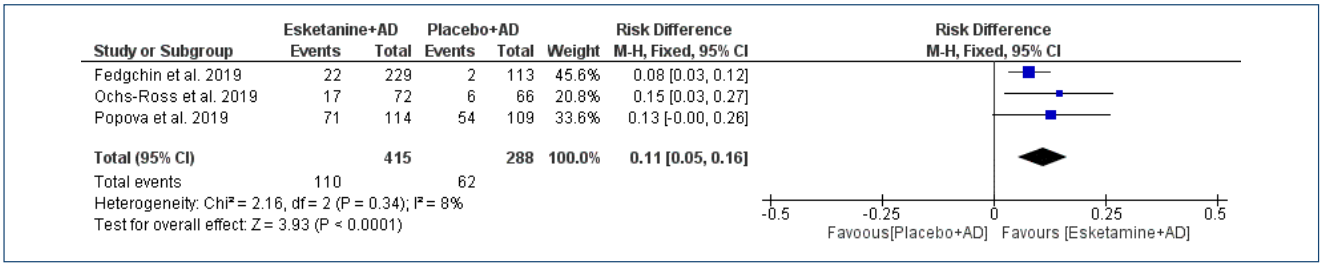

Figure 5. Meta-analysis of the rate of patients with a ≥50% reduction in Montgomery-Asberg Depression Rating Scale, fixed effect.

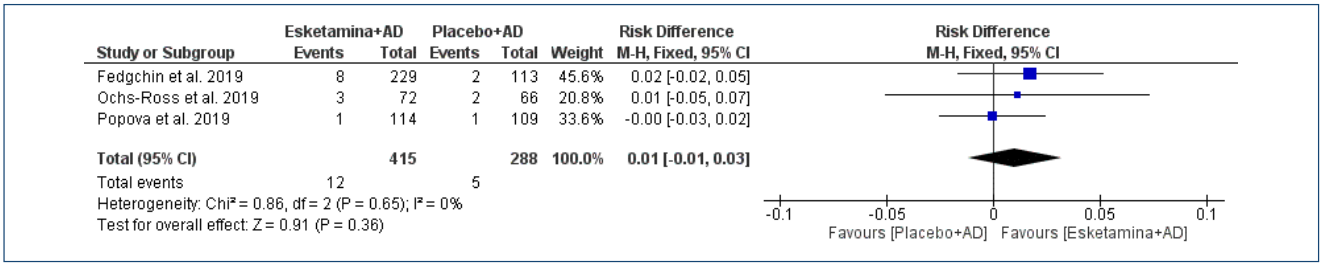

Figure 6. Meta-analysis of serious events, fixed effect.

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, Writing – original draft, Writing – review & editing.

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Comments on "Demonstration of kinesio taping effect by ultrasonography in neck pain"

André Pontes-Silva[1]*

Dear Editor,

Ceylan et al.[1] showed that the Visual Analog Scale (VAS) and Neck Disability Index (NDI) scores in the kinesio taping group were statistically significantly improved when compared to the exercise group ($p<0.05$). According to the authors, "the combination of kinesio taping and exercise therapy was effective in reducing nonspecific neck pain and neck disability". Unfortunately, the authors' conclusion is different from the results presented. By the way, they themselves recognized that "in this study, there was no group that did not receive treatment to show the true effect of the kinesio taping" (p. 1456). That is, it was not possible to know if kinesio taping helped to reduce pain and disability.

Besides, the study did not present the minimal clinically important change (MCIC) of the disability and the pain for patients with neck pain. We know that comparisons of outcomes (e.g., pain and disability) must consider the MCIC of the differences because the p-value only shows statistical significance, whose interpretation translates just a hypothesis test governed by a probability of previously defined error (α)[2]. Most persons interpret $p<0.05$ to mean that the probability that chance is responsible for the finding is less than 5% and that the probability that the finding is a true finding is more than 95%. Both these interpretations are incorrect; unfortunately, they are widely prevalent because they are an easy way to explain and understand a slightly tricky concept[3].

The MCIC for the NDI (scale range, 0–50) is 10.5 points, and for the pain on the Numerical Pain Rating Scale (scale range, 0–10) it is 4.3 points[4]. Regarding disability, the kinesio taping did not show MCIC. Regarding pain, the authors used an instrument (VAS) that does not have an established MCIC for patients with neck pain. In addition, they did not present raw mean difference ($\Delta=\overline{X}^1-\overline{X}^2$) or assess the effect size (Cohen's $d=[M1-M2]/S_{pooled}$) of the comparisons between the groups.

As such, the new conclusion is that kinesio taping added to an exercise program for patients with neck pain is not superior to the same exercise program without the addition of kinesio taping (i.e., kinesio taping seems to be ineffective).

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[1]Universidade Federal de São Carlos, Physical Therapy Department, Physical Therapy Post-Graduate Program – São Carlos (SP), Brazil.
*Corresponding author: contato.andrepsilva@gmail.com

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Brazilian Portuguese version of Eating Pathology Symptoms Inventory

Jônatas de Oliveira[1]*

The identification of eating disorder (ED) symptoms and their diagnosis is still a challenge in the Brazilian scenario, which requires the association of various methodologies to identify symptoms in terms of frequency, association, and an approximation to the clinical diagnosis. The commonly used methods are the Eating Attitudes Test (EAT-26)[1] and the Binge Eating Scale[2], which are self-administered. Also, recently, the questionnaire on Eating and Weight Patterns (QEWP-5)[3], with its Brazilian version, is available for use by clinical interviewers, bringing great advances to the study of binge eating disorders. On the contrary, questionnaires that assess symptoms and risk for ED, such as the EAT-26, present limited features of ED pathology. Also, with the use of the BES, binge eating can be assessed, but not with other aspects such as cognitive restraint and restraint. Fat phobia through negative attitudes toward weight and obesity is also a prominent indicator in the psychopathology of EDs.

In response to this gap, Forbush et al., developed the Eating Pathology Symptoms Inventory (EPSI)[4], which comprises 45 items to assess the frequency of cognitions and behaviors in the last month. An initial pool of 160 items was developed by the researchers to assess 20 dimensions of eating pathology, and after the ensuing analyses were conducted, an 8-factor structure was identified: body dissatisfaction, binge eating, cognitive restraint, excessive exercise, restricting, purging, muscle building, and negative attitudes toward obesity. Bilingual researchers translated the original scale from English to Portuguese version. Then, additional bilingual translators produced two back-translations. The cross-cultural adaptation process of the instrument was carried out, and the final version for use in the Brazilian population is presented in Table 1.

Table 1. Brazilian Portuguese version of Eating Pathology Symptoms Inventory.

EPSI – Brazilian Portuguese version Forbush KT, Wildes JE, Pollack LO, Dunbar D, Luo J, Patterson K, et al. Development and validation of the Eating Pathology Symptoms Inventory (EPSI). Psychol Assess. 2013; 25(3):859. Abaixo estão listadas experiências e problemas que as pessoas às vezes têm. Leia cada item para determinar o quão bem ele descreve suas experiências recentes. Depois, selecione a opção que melhor descreve o quão frequentemente cada afirmação se aplica a você durante as últimas quatro semanas, incluindo hoje. Use a seguinte escala quando estiver respondendo:
0 - Nunca
1 - Raramente
2 - Às vezes
3 - Frequentemente
4 - Muito frequentemente
1. Eu não gostei de como as roupas serviram no formato do meu corpo
2. Eu tentei excluir comidas que "não são saudáveis" da minha alimentação.
3. Eu comi quando não estava com fome.
4. As pessoas me disseram que eu não como muito.
5. Eu senti que precisava fazer atividade física quase todos os dias
6. As pessoas ficariam surpresas se soubessem o quão pouco eu comi.
7. Eu usei suplementos para ganho de músculos.

Continue...

[1]Universidade de São Paulo, Faculty of Medicine, School of Medicine – São Paulo (SP), Brazil.
*Corresponding author: oliveira.jonatas@usp.br
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Table 1. Continuation.

EPSI – Brazilian Portuguese version Forbush KT, Wildes JE, Pollack LO, Dunbar D, Luo J, Patterson K, et al. Development and validation of the Eating Pathology Symptoms Inventory (EPSI). Psychol Assess. 2013; 25(3):859. Abaixo estão listadas experiências e problemas que as pessoas às vezes têm. Leia cada item para determinar o quão bem ele descreve suas experiências recentes. Depois, selecione a opção que melhor descreve o quão frequentemente cada afirmação se aplica a você durante as últimas quatro semanas, incluindo hoje. Use a seguinte escala quando estiver respondendo:
8. Eu me esforcei ao extremo quando me exercitei
9. Eu belisquei alimentos ao longo da noite sem ter me dado conta.
10. Eu fiquei cheio mais facilmente que a maioria das pessoas
11. Eu considerei tomar diuréticos para perder peso
12. Eu experimentei diferentes roupas, porque eu não gostei da minha aparência.
13. Eu pensei que laxantes eram uma boa forma de perder peso
14. Eu pensei que pessoas obesas tem pouco autocontrole
15. Eu pensei em tomar anabolizantes como uma maneira de ficar mais musculoso.
16. Eu usei chás de emagrecimento e chás detox para perder peso
17. Eu usei remédios para emagrecer.
18. Eu não gostei da aparência do meu corpo.
19. Eu comi até ficar desconfortavelmente cheio(a).
20. Eu senti que pessoas que estão acima do peso são preguiçosas
21. Eu contei as calorias dos alimentos que comi
22. Eu planejei meus dias em torno da necessidade de me exercitar
23. Eu pensei que meu bumbum era muito grande
24. Eu não gostei do tamanho das minhas coxas
25. Eu desejei que o formato do meu corpo fosse diferente
26. Eu tive nojo ao ver uma pessoa acima do peso vestindo roupas apertadas
27. Eu induzi o vômito para perder peso.
28. Eu não me dei conta do quanto havia comido até ter terminado de comer
29. Eu considerei tomar suplementos para ganho de músculos
30. Eu senti que pessoas acima do peso não são atraentes.
31. Eu me envolvi em atividades físicas exaustivas pelo menos cinco dias por semana
32. Eu pensei que meus músculos eram muito pequenos
33. Eu fiquei cheio(a) depois de comer uma quantidade de comida que a maioria das pessoas consideraria pouco.
34. Eu estive insatisfeito (a) com o tamanho do meu quadril
35. Eu usei suplementos de proteína.
36. Pessoas me encorajaram para comer mais.
37. Se alguém me ofereceu comida, eu senti que não conseguia resistir em comê-la
38. Eu senti nojo ao ver pessoas com obesidade
39. Eu me enchi de comida até o ponto de passar mal.
40. Eu tentei evitar comidas muito calóricas.
41. Eu me exercitei até o ponto de ficar exausto.
42. Eu usei diuréticos para perder peso
43. Eu pulei duas refeições seguidas
44. Eu comi como se estivesse no piloto automático
45. Eu comi uma grande quantidade de comida em um período curto de tempo (por exemplo, dentro de 2 horas)

Sum the scores: body dissatisfaction (#1, #12, #18, #23, #24, #25, #34), binge eating (#3, #9, #19, #28, #37, #39, #44, #45), cognitive restraint (#2, #21, #40), purging (#11, #13, #16, #17, #27, #42), restricting (#4, #6, #10, #33, #36, #43), excessive exercise (#5, #8, #22, #31, #41), negative attitudes toward obesity (#14, #20, #26, #30, #38), muscle building (#7, #15, #29, #32, #35).

Differentials on the scale are given by the possibility of further Brazilian studies investigating the differences between the diagnoses of anorexia nervosa, bulimia nervosa, and binge eating disorder. All procedures were performed following the ethical standards of the institution (number: 4.886.743). Primary results confirmed the factor structure for the Brazilian population, and the validation process is in progress. EPSI has excellent internal consistency and reliability. In addition, the instrument has the potential to assess changes in EPSI factors after the outpatient segment, focusing on the impact of psychiatric comorbidities, types of associated treatments, and their relationship with more severe eating disorders and longer disease duration. It also presents a potential contribution to the identification of behavioral profiles in non-clinical populations due to its comprehensiveness in eating psychopathology, therefore reducing the need for the association of various instruments.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (05/09/2021 -, Plataforma Brasil -, number: 4.886.743; CAAE: 44615521.9.0000.0068).

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https://doi.org/10.1590/1806-9282.20230122

Answers to comments on "Comparison of severe acute respiratory syndrome coronavirus 2 (COVID-19) vaccine side effects by age groups"

Fadime Tosun[1], Mehmet Bülbül[2*], İsmail Tosun[3]

Dear Editor,

In our study, which was published in your journal, we aimed to compare the side effects of the inactive severe acute respiratory syndrome coronavirus 2 (COVID-19) vaccine according to age groups[1]. According to the results of our study, different types and levels of side effects are seen in all age groups after the administration of inactive COVID-19 vaccine. In terms of side effects, the 20–35 age group and female gender were found to be at more risk.

We thank Wang and Yang et al.[2] for their thoughts on our study. Our response to the request for clarification on two issues in our study is as follows:

First, at the time of the study, there was only one type of coronavirus vaccine available in our country. As explained in the sixth line of the "Method" section of our article, the vaccine "CoronaVac," manufactured by Sinovac Life Sciences, Beijing, China, was used.

Second, in the period when the study data were collected, vaccination was carried out according to the national vaccination calendar within the framework of the pandemic procedure of the Turkish Ministry of Health. For this reason, side effect analysis according to age groups and the number of vaccines could not be performed because there was no two-dose vaccination in each age group.

AUTHORS' CONTRIBUTIONS

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[1]Adiyaman University, Faculty of Medicine, Department of Anesthesiology and Reanimation – Adıyaman, Turkey.
[2]Karabük University, Faculty of Medicine, Department of Obstetrics and Gynecology – Karabük, Turkey.
[3]Adıyaman Provincial Health Directorate, Family Health Center Number 10 – Adıyaman, Turkey.
*Corresponding author: mehmetbulbulmd@gmail.com

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Clinical effects of knee arthroplasty

Josiane Costa Pereira Bezerra[1], Maristela Linhares Costa dos Santos[1], Emannuel Alcides Bezerra Rocha[1], Gerônimo Bouza Sanchis[2], Johnnatas Mikael Lopes[3*]

Osteoarthritis (OA) is a rheumatological disease of gradual origin that can cause pain, joint stiffness, and decreased functionality and that affects elderly individuals in a greater proportion. This event is characterized by the involvement of cartilage, bone, and muscles that can be affected by the disease. Its development can be caused by the imbalance between tissue degradation and repair, which can be aggravated by several factors, the main ones being genetic predisposition, tissue overload, aging, obesity, and previous injuries[1,2].

In addition, arthroplasty is a surgical procedure in which the compromised joint is replaced by an artificial prosthesis, which can be partial or total, and its main objective is to reduce painful symptoms, restore function, and increase joint mobility. This technique is indicated in cases of severe pain, impairment of functionality, instability, and decreased range of motion in the joint[3].

When reading the article entitled "Functional and biochemical improvement following total knee arthroplasty in early postoperative period" by Erden et al.[4], we identified some evidence that deserves to be highlighted and that were not cited and discussed, mainly in clinical application. The first is the absence of a measure of clinical effect and not just a probabilistic effect in multiple comparisons of groups such as Cohen's d[5]. This clinical effect measure is based on the difference in magnitude of the investigated parameter and its variability. Cohen's d values of less than 0.5 reveal a small clinical impact, probably with less utility. Values between 0.5 and 0.08 are considered moderate, and values above 0.8 imply a strong clinical effect[5]. Cohen's d would help healthcare professionals to identify which parameters are more or less expected to improve after the arthroplasty and how to expect these results in patient monitoring.

Anyway, we made these estimates based on the information provided by Erden et al.[4] in Tables 1, 2, and 3. It is evident that the main outcome to be modified with knee arthroplasty is the WOMAC questionnaire (d=-3.27), followed by pain when walking (d=-2.52), valgus angle (d=-1.55), misalignment (d=-1.37), and pain at rest (d=-1.31). As for IL-6, the reduction effect is also great (d=-0.82), but lower than the biomechanical and functional measures.

On the contrary, despite not showing a statistical difference, TNF-α showed a reduction of moderate clinical magnitude (d=-0.55); this may be caused by the insufficient sample size for the probabilistic significance of the outcome and/or the effect of this variable can be perceived in a larger temporal space. In view of this, we believe that the biochemical effects of arthroplasty are slower to be identified than the biomechanical and functional ones.

So, we understand that clinicians need to know that WOMAC is the clinical measure of greatest change after knee arthroplasty because it is a composite indicator for pain, stiffness, and functionality and that biochemical measures may not be useful in the postoperative period of up to 6 weeks.

AUTHORS' CONTRIBUTIONS

JCPB: Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **MLCS:** Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **EABR:** Formal Analysis, Writing – original draft, Writing – review & editing. **GBS:** Formal Analysis, Writing – original draft, Writing – review & editing. **JML:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – Original draft, Writing – review & editing.

[1]Universidade Federal do Rio Grande Do Norte – Natal (RN), Brazil.
[2]Universidade Federal de Minas Gerais – Belo Horizonte (MG), Brazil.
[3]Universidade Federal do Vale do São Francisco – Paulo Afonso (BA), Brazil.
*Corresponding author: johnnatas.lopes@univasf.edu.br
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Comment on "Prognostic value of T-wave positivity in lead aVR in COVID-19 pneumonia"

Weihua Chen[1*]

Dear Editor,

The study[1] entitled "Prognostic value of T-wave positivity in lead aVR in COVID-19 pneumonia" investigated the relationship between T-wave positivity in lead aVR and the prognosis of patients with COVID-19 pneumonia. The findings suggest that T-wave positivity in lead aVR is a useful predictor of poor prognosis in COVID-19 patients. While the findings of this study are interesting, I would like to point out some potential limitations.

First, the sample size of this study[1] is relatively small, which limits the generalizability of the findings. The study[1] included only 130 patients (75 in the deceased group and 55 in the living group), which may not be representative of the larger population of COVID-19 patients. Moreover, the lack of a control group of patients without COVID-19 makes it difficult to determine if the observed changes in T-wave positivity are specific to COVID-19 or if they are a result of other factors. For instance, a study[2] involving 6,354 participants found that the prevalence of a positive T wave in lead aVR (aVRT+) was 2.2%, suggesting that aVRT+ can be found in the general population and that aVRT+ is not a unique factor in COVID-19 patients. In addition, another nationwide population study[3] showed that aVRT+ is also related to the prognosis of hypertensive patients. As described in Table 1, 70% of the participants in this study had hypertension. In this case, the occurrence of aVRT+ may be caused by other confounding factors, not by COVID-19 itself. Therefore, it is necessary to set up a control group without COVID-19 to balance other confounding factors.

Second, this study did not account for the potential effects of medications on T-wave positivity in lead aVR. It is well-known that many medications can cause changes in the electrocardiogram (ECG) and lead to T-wave abnormalities. For example, medications such as hydroxychloroquine and chloroquine[4] have been reported to cause T-wave changes in the ECG. Additionally, the medications that the patients were taking may have influenced the results. It is possible that the observed changes in T-wave positivity were due to medication use rather than COVID-19 pneumonia. Therefore, it is important to consider medication use as a potential confounding variable in the analysis of T-wave positivity in lead aVR.

Third, COVID-19 is a complex disease that can manifest in a wide range of clinical presentations, from mild symptoms to severe respiratory failure[5]. It is important to consider the severity of the disease when interpreting prognostic markers, as the risk of adverse outcomes, such as death, may be related to the severity of the disease. This study suggests that T-wave positivity in lead aVR may be a useful prognostic marker for COVID-19 pneumonia, but it does not provide a clear definition of disease severity. It is possible that the observed changes in T-wave positivity are related to the severity of COVID-19 and not necessarily to COVID-19 pneumonia itself. Furthermore, the deaths were more likely to occur in patients with severe COVID-19, while the surviving patients were more likely to have mild COVID-19. Therefore, the severity of COVID-19 should be considered a prognostic factor for death, but not aVRT+. It is necessary to describe the severity of COVID-19, thereby reducing the influence of confounding factors.

[1]Yichang Yiling Hospital, Infectious Diseases Department – Yichang, China.
*Corresponding author: 19907203849@163.com

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Comment on "What is the effect of tumor diameter, lymph node metastases, and maximum standardized uptake value on prognosis in limited-stage small cell lung cancer?"

Hongyan Yu[1*]

Dear Editor,

I read with great interest the article entitled "What is the effect of tumor diameter, lymph node metastases, and SUVmax value on prognosis in limited-stage small cell lung cancer?" by Çimen et al.[1]. While the study sheds light on important factors that may affect prognosis in patients with limited-stage small cell lung cancer, I would like to raise some concerns.

First, it is unclear how many patients in the study[1] died versus how many survived. This information is critical in understanding the impact of tumor diameter, lymph node metastases, and the maximum standardized uptake value (SUVmax) value on prognosis. A potential hypothesis is that only 5 patients experienced fatal events while 72 patients survived. This significant disparity in death and survival rates could result in inaccurate conclusions. Therefore, it is necessary to clearly describe how many patients died and how many patients survived. Additionally, it would be helpful to know the duration of follow-up in the study, as this information is crucial for accurately interpreting the study findings and drawing conclusions regarding the prognostic factors in limited-stage small cell lung cancer.

Second, another concern that needs to be addressed is the lack of information on the surgical treatment strategy adopted for the patients. Limited-stage small cell lung cancer[2] is a highly aggressive malignancy, and the prognosis of patients is heavily influenced by the choice of treatment. Surgery is a key component of the multimodal approach for limited-stage small cell lung cancer and can significantly impact survival rates. According to a study[3] conducted on a cohort of 14,179 patients with limited-stage small cell lung cancer, it was found that surgical intervention, particularly the use of lobectomy, was associated with better survival outcomes for a specific subset of patients with limited-stage small cell lung cancer. This study[3] suggests that careful patient selection may be key in determining the effectiveness of surgery as a treatment option for limited-stage small cell lung cancer. Therefore, the absence of information on the surgical treatment strategy employed for the patients in this study is a significant limitation that needs to be acknowledged, since this information is crucial for an accurate interpretation of the study results and for drawing appropriate conclusions. Without this critical information, the reliability and generalizability of the study results are likely to be affected.

Third, this study lacks information on the clinicopathological features of the patients. These factors can significantly affect the prognosis of limited-stage small cell lung cancer, and therefore their omission limits the interpretability of the study results. To better understand the clinicopathological features of small cell lung cancer and their impact on prognosis, a previous study[4] conducted a comprehensive analysis on 247 patients who had undergone surgery. The study revealed that certain features, such as spindle cell type and tumor-infiltrating lymphocytes >30%, were independent prognostic factors in patients with small cell lung cancer. Therefore, it may be helpful to consider exploring the clinicopathological features of the patients in more detail to better understand their impact on prognosis. Therefore, it is necessary and interesting to further explore the relationship between clinicopathological features and the prognosis of NSCLC patients.

AUTHOR'S CONTRIBUTIONS

HY: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing.

[1]The First People's Hospital of Chun'an County, Department of Respiratory Medicine – Hangzhou, China.
*Corresponding author: rm1234567892023@163.com

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Correspondence on the evaluation of patients with COVID-19 vaccine side effects

Amnuay Kleebayoon[1*], Viroj Wiwanitkit[2,3]

Dear Editor,

We would like to share ideas on the publication entitled "Evaluation of patients of vaccine side effects after the COVID-19 vaccine"[1]. Gedik et al. sought to create a scientific database to catalog possible vaccination adverse effects[1]. Although fatigue was the most frequent complaint in 29.7% of cases admitted to the emergency room following immunization, Gedik et al. discovered that the most frequent diagnoses following an emergency room assessment were myalgia in 32.1% of cases and upper respiratory tract infection in 28.6% of cases[1].

Comorbidities are rarely mentioned in clinical records, even when they do exist. It can occasionally be challenging to identify the specific patho-immuno-pharmacological relationship due to ignorance. It could also be challenging to comprehend how persistent medical conditions impact clinical results. Concern should also be expressed about the preceding asymptomatic COVID-19, which is not unusual[2]. It is possible for the response to the vaccination and the result in a prior COVID-19 case to differ. Without proper laboratory testing, the effects of prior asymptomatic COVID-19 are often impossible to rule out. Genetics also plays a crucial role[3]. As the study's findings are not supported by any prior research, obtaining new evidence is challenging. There may be a need for additional study that takes other issues into account. A further prospective study and an accurate assessment of the patient's comorbidity are needed in order to draw a firm conclusion.

AUTHORS' CONTRIBUTIONS

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[1]Private Academic Consultant – Samraong, Cambodia.
[2]Chandigarh University – Punjab, India.
[3]Joseph Ayo Babalola University – Ikeji-Arakeji, Nigeria.
*Corresponding author: amnuaykleebai@gmail.com

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Comment on "Continuous clonidine infusion: an alternative for children on mechanical ventilation"

Yanxue Zhao[1], Li Shang[1*]

Dear Editor,

We read with great interest the article entitled "Continuous clonidine infusion: an alternative for children on mechanical ventilation" by Neves et al.[1]. This study highlights the potential benefits of using clonidine infusion as a sedative for mechanically ventilated children, which is a welcome addition to the current options available for pediatric sedation. The authors have done an excellent job of providing a detailed account of their experience with clonidine infusion in pediatric patients. The study's findings indicate that clonidine infusion was an effective sedative with a lower incidence of adverse effects compared to the commonly used sedatives such as benzodiazepines and opioids. The results are significant and can have a considerable impact on the care of mechanically ventilated pediatric patients. However, we would like to raise the following potential concerns.

First, the authors stated that the target sedation level was determined subjectively based on the individual patient's clinical status and therapeutic goals. However, it is unclear which indications were used to determine the target sedation level. This subjectivity may introduce bias into the study results and limit the generalizability of the findings. We believe that it would have been better if the authors had used a well-known sedation score, such as the Richmond Agitation-Sedation Scale (RASS)[2,3] or relevant pediatric sedation score[4], to determine the target sedation level. This additional information would have provided a more objective measure of the level of sedation and allowed for more accurate comparisons with other studies using similar sedation methods.

Second, it would be beneficial to discuss the potential advantages and disadvantages of continuous clonidine infusion compared to other methods using sedatives such as benzodiazepines or propofol. For example, clonidine has been shown to have less impact on respiratory drive compared to benzodiazepines, which could be particularly relevant in children on mechanical ventilation. Additionally, the potential for rebound hypertension and bradycardia should be considered when using clonidine for sedation, and appropriate monitoring and dose adjustments should be implemented. Furthermore, it would be interesting to discuss the potential implications of this study on the future of sedation management in critically ill children. Could continuous clonidine infusion become a first-line option for sedation in this population, or should it be reserved for specific patient populations or situations? Could this approach lead to fewer adverse events associated with sedation in critically ill children, and could it lead to shorter durations of mechanical ventilation and ICU stay?

Third, this study collected data on heart rate (HR), mean arterial pressure (MAP), diastolic blood pressure (DBP), and systolic blood pressure (SBP) in three time periods. However, since the study was performed in a pediatric intensive care unit (PICU), it is crucial to monitor these parameters continuously throughout the entire procedure of continuous clonidine infusion. This is because transient hypotension, tachycardia, or bradycardia can easily be missed if only measured in three time periods. It is suggested that future studies on this topic should consider continuous monitoring of HR, MAP, DBP, and SBP to ensure accurate and comprehensive data collection. This will provide a more detailed understanding of the safety and efficacy of clonidine infusion for sedation in mechanically ventilated children.

AUTHORS' CONTRIBUTIONS

YZ: Conceptualization, Investigation, Supervision, Writing – original draft. **LS**: Conceptualization, Investigation, Supervision, Writing – review & editing.

[1]Shiyan Maternal and Child Health Hospital – Shiyan, China.
*Corresponding author: maohaiyu123456789@163.com

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

André Pontes-Silva[1]*, Yury Zharikov[2]

The article entitled "Overweight status, abdominal circumference, physical activity, and functional constipation in children" by Dias et al.[1] assessed the prevalence of functional constipation and its relationship with food intake, overweight status, and physical activity in children. First, in the scientific context, we need to use technical terms, e.g., "circumference" is wrong; measurements of body surfaces are called "perimeters"; "height" must be "stature"; and "weight" should be "body mass" (note that the concept of BMI is body [mass] index, not body [weight] index)[2]. Besides, the authors used the abdomen perimeter divided by stature; however, this mathematical measurement is wrong because the literature recommends the waist perimeter (waist-to-stature ratio)[3].

The use of the waist perimeter to assess the risk of metabolic diseases[4,5] is also used to measure the waist–hip ratio[6,7]. However, the waist–hip ratio uses two variables (the waist and hip) that change during body mass loss. Furthermore, the waist–hip ratio disregards body proportionality. For example, patients with smaller stature (e.g., 150 cm) have waist areas with smaller perimeters compared to taller patients (e.g., 185 cm). This must be considered in the clinical assessment, as body proportionality is supported by Cube law[8]. Therefore, I recommend that researchers and clinicians to use the waist-to-stature ratio[3]. The cutoff point is <0.50 (i.e., the waist perimeter must be less than 50% of the patients' stature)[9-12].

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[1]Universidade Federal de São Carlos, Physical Therapy Department, Physical Therapy Post-Graduate Program – São Carlos (SP), Brazil.
[2]I.M. Sechenov First Moscow State Medical University (Sechenov University) – Moscow, Russia.
*Corresponding author: contato.andrepsilva@gmail.com

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LETTER TO THE EDITOR

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Comment on "The prognostic impact of tumor necrosis in non-muscle invasive bladder cancer"

Dexin Wang[1*], Yiming Liu[1]

Dear Editor,

We read with great interest the article entitled "The prognostic impact of tumor necrosis in non-muscle invasive bladder cancer[1]." The study[1] aimed to investigate the predictive value of tumor necrosis in patients with non-muscle-invasive bladder cancer and its impact on disease progression and recurrence. The conclusion of this study stated that the presence of tumor necrosis is a significant predictor of disease progression (p=0.00) in patients with non-muscle-invasive bladder cancer, which highlights the importance of considering tumor necrosis as a prognostic factor in patients with non-muscle-invasive bladder cancer. While we found the study to be informative and valuable, we would like to raise some potential limitations that should be considered.

First, as body mass index (BMI) is a well-established risk factor for bladder cancer, with obesity being linked to a higher incidence of this type of cancer, it is crucial to understand the impact of BMI on the prognostic value of tumor necrosis in patients with non-muscle-invasive bladder cancer. A previous study[2] revealed that patients with T1G3 non-muscle-invasive bladder cancer with an increase in BMI had a significantly higher likelihood of experiencing disease progression and a higher risk of bladder cancer-related death, emphasizing the importance of considering BMI in prognostic assessments for patients with non-muscle-invasive bladder cancer. Furthermore, another study[3] conducted on a cohort of survivors with bladder cancer demonstrated that adiposity may play a role in the recurrence of bladder cancer, particularly among smokers. The study[3] demonstrated that individuals with a high BMI and a history of smoking had a significantly higher risk of bladder cancer recurrence compared to those with a low BMI and no history of smoking. The potential mechanisms underlying this association include the impact of adipose tissue on inflammation, insulin resistance, and hormone production, which can create a favorable environment for tumor growth and progression. These findings suggest that BMI should be taken into account when assessing the risk of bladder cancer recurrence and developing personalized treatment plans for survivors with bladder cancer. Therefore, the absence of BMI data in this study[1] limits the ability to draw comprehensive conclusions about the prognostic impact of tumor necrosis in patients with non-muscle-invasive bladder cancer.

Second, the conclusion of this study cannot be considered definitive regarding the impact of tumor necrosis on the prognosis of non-muscle-invasive bladder cancer. While this study suggests that tumor necrosis was associated with cancer progression (p<0.001), as shown in Table 1, a subsequently more rigorous analysis using multivariate Cox regression has shown that there is no association between tumor necrosis and the recurrence (p>0.05) and progression (p>0.05) in patients with non-muscle-invasive bladder cancer, as described in Table 2 of this study[1]. Statistically, the evidence level of multivariate Cox regression analysis is higher than that of Kaplan-Meier analysis, because Cox regression analysis takes into account the influence of all confounding factors (such as age, gender, tumor number, and tumor size) while Kaplan-Meier analysis does not. Therefore, the conclusion that tumor necrosis is related to tumor progression may not be entirely appropriate. It is crucial to acknowledge the study's limitations and the need for further research to achieve a clear and definitive conclusion regarding the prognostic impact of tumor necrosis in non-muscle-invasive bladder cancer. Further research may need to focus on identifying other factors that may be more closely associated with cancer progression in patients with non-muscle-invasive bladder cancer. Additionally, future studies may need to incorporate more rigorous analyses, such as multivariate Cox regression analysis, to provide a more accurate understanding of the

[1]Tianjin Beichen Traditional Chinese Medicine Hospital, Department of Urology – Tianjin, China.
*Corresponding author: wangdexin198192@163.com
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prognostic impact of tumor necrosis. Until then, the current study's results should be interpreted with caution, and further investigation is required to clarify the prognostic significance of tumor necrosis in non-muscle-invasive bladder cancer.

AUTHORS' CONTRIBUTIONS

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Mean arterial pressure and outcomes in critically ill patients: is there a difference between high and low target?

Diana Cristina Buendía Palacios[1], João André Freitas Silva[1], Ana Francisca Torres Sarmento[1], Michael Gregorio Ortega Sierra[2*]

Adult critical illness is one of the conditions that generates the substantial burden of disease and is expensive globally. Sepsis, acute lung injury, and mechanical ventilation are the most representative conditions in this specialty[1]. The barriers and deficiencies of health systems in low- and middle-income countries make the approach to this type of disease even more complex, forcing the reproduction of the best evidence-based decision-making with the least use of resources[1]. This contemplates the ongoing discussion of emerging evidence and the evolution of traditionally used clinical concepts that are essential in the pathophysiology and health care of critically ill patients. Systemic mean arterial pressure (MAP) is a hemodynamic parameter that reflects the perfusion pressure of vital organs. In critically ill patients with resolution therapy, supportive care is essential to ensure survival, reduce morbidity, and reduce the risk of sequelae[2,3]. There has been much discussion on the MAP value that is most appropriate to maintain in critically ill patients[2,3]. However, the scientific evidence shows that this may vary depending on the baseline characteristics of the patients, the disease being treated, and the goal the intensivist wants to achieve. Some guidelines differ between these values, recommending values ranging from 65–70 mmHg to 80–85 mmHg but relying mainly on 30- or 90-day mortality outcome[2-4]. Then, is there a difference between high and low target? What does the evidence say about it?

Recently, Carayannopoulos et al.[4] conducted a meta-analysis of randomized controlled trials, including six trials with a total of 3,690 patients, in order to assess whether the target of higher vs. lower MAP in adults with shock produces significant differences in outcomes in critically ill patients. The authors found that high vs. low target MAP does not produce significant differences in mortality outcome (RR: 1.06; 95%CI: 0.98–1.15, I2=0%, p=0.12), nor in renal replacement therapy (RR: 0.96; 95%CI: 0.83–1.11, I2=24%, p=0.57). However, it was evident that a high target MAP in patients with a history of arterial hypertension may reduce the risk of renal replacement therapy (RR: 0.83; 95%CI: 0.71–0.98, I2=0%, p=0.02) compared to those without arterial hypertension (RR: 0.83; 95%CI: 0.71–0.98, I2=0%, p=0.02). Thus, the authors concluded that there is no difference between the MAP targets in terms of mortality, but a higher MAP can be considered in patients with arterial hypertension[4]. Another similar meta-analysis[5], which evaluated additional outcomes in 3,753 patients with the same conditions, showed that there was no significant difference between MAP targets and duration of mechanical ventilation (SMD: 0.51; 95%CI: -0.29 to 1.31, p=0.21), or length of stay in intensive care (SMD: 0.22; 95%CI: -0.07 to 0.5, p=0.14). However, there was a statistically significant difference in the reduction of ICU length of stay in post-cardiac arrest patients with high MAP targets (SMD: 0.55; 95%CI: 0.31–0.80, p<0.000001)[5].

Other recent studies useful in understanding the impact of MAP variation on outcomes in critically ill patients include those by How et al.[6] and Yoshimoto et al.[7] In the first one, the authors explored the relationship between MAP variability and short- and medium-term mortality in a cohort study. They included a total of 12,867 patients (1,320 died in-hospital, 1,399 died within the first 28 days, and 2,734 died within 1 year), finding that the average real variability of MAP ≥7. 2 mmHg was associated with higher in-hospital (OR: 1.44; 95%CI: 1.21–1.72), 28-day (HR: 1.28; 95%CI: 1.1–1.5), and 1-year mortality (HR: 1.27; 95%CI: 1.14–1.42)[6]. This association was maintained independently of the sequential organ failure assessment (SOFA) score. In the Yoshimoto et al.'s[7] study, in which three randomized controlled trials on 3,357 patients with vasodilator shock were meta-analyzed and the optimal

[1]Centro Hospitalar Universitário Lisboa Norte – Lisbon, Portugal.
[2]Universidad Centroccidental Lisandro Alvarado, Hospital Central Antonio María Pineda – Barquisimeto, Venezuela.
*Corresponding author: mortegas2021@gmail.com
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blood pressure target was evaluated, there was no difference in mortality (RR: 1.06; 95%CI: 0.98–1.16) between the two groups evaluated (60–70 mmHg vs. >70 mmHg), nor in patients with arterial hypertension or older than 65 years. There were also no differences in adverse events observed between the two groups (RR: 1.04; 95%CI: 0.87–1.24). However, it was observed that the frequency of supraventricular arrhythmias was significantly higher in the higher MAP group (RR: 1.73; 95%CI: 1.15–2.60) and that the need for renal replacement therapy in hypertensive patients was lower in this same group (RR: 0.83; 95%CI: 0.71–0.98)[7]. Although these results allow us to observe a heterogeneous trend in terms of MAP targets and mortality, the positive association between higher MAP and a lower need for renal replacement therapy in hypertensives is more evident. However, the risk of supraventricular tachycardia was also reported, which may be an important factor in patients with a history of heart disease. Also, there were no differences in terms of duration of mechanical ventilation or length of stay in intensive care. However, differences were found in post-cardiac arrest patients.

Other variables to consider, which have been studied but not evaluated in the meta-analyses described above, are the time of day of the measurement or MAP variability. A cohort study involving 5,185 individuals found that nocturnal MAP rising was significantly associated with intensive care (OR: 1.34; 95%CI: 1.10–1.65), in-hospital (OR: 1.35; 95%CI: 1.12–1.63), 28-day (HR: 1.27; 95%CI: 1.10–1.48), and 1-year mortality (HR: 1.24; 95%CI: 1.10–1.40). Similar to the evidence discussed previously, this estimate was independent of the SOFA score[8]. Likewise, differences have also been found in the outcomes of surgical patients with hypotensive events during the postoperative stay in intensive care. Those with events with MAP values ≤65 mmHg had up to 1.52 times higher risk of suffering an adverse cerebrovascular or cardiac event at 30 days[9]. Thus, care must be taken in the interpretation and critical reading of the evidence, since numerous additional factors may be associated with the control of MAP in intensive care, as well as mortality outcomes, duration of mechanical ventilation, and length of hospital stay.

In Latin American countries, such as Brazil, the quality of labor contracting, barriers, and economic and infrastructure limitations of the health system impedes the systematic reproduction of decision-making[10-12], which would explain the lack of data available to perform similar studies on this topic and to corroborate if the hemodynamic behavior and its association with short- and long-term outcomes are similar to those reported in the literature. A significant prevalence of burnout has been described in nurses and intensive care technicians in Brazil, which can make it difficult to strictly monitor MAP in a personalized way by disease or patient, in a unit with a large volume of patients[12]. The Brazilian Research in Intensive Care Network[11] highlighted the progressive and relevant advances that the country has made in recent years. However, among the future perspectives proposed is to strengthen the country's research, education, and infrastructure in order to further reduce mortality from critical illnesses[11]. The monitoring and regulation of MAP is an indicator associated with outcomes in intensive care; therefore, its constant evaluation and control should also be included in the technical challenges in order to reduce the burden of critical illnesses in adults.

AUTHORS' CONTRIBUTIONS

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What is important in family counseling in cases of fetuses with congenital heart disease?

Marcela Bezerra Dias[1], Luisa Tiemi Souza Tuda[2], Luana Izabela Azevedo de Carvalho[3], Thayla Lais Estevam[1], Bruno Mori[4], Ana Luiza Menezes Teles Novelleto[1], Edward Araujo Júnior[5,6*], Luciane Alves da Rocha Amorim[1]

INTRODUCTION

Fetal medicine has opened up new ways to examine, diagnose, and treat the fetus. The increased demand for fetal ultrasound has helped increase the number of congenital malformations diagnosed. Since congenital heart disease (CHD) is the most common fetal malformation[1] and considering the great evolution of congenital heart surgery worldwide, adequate therapeutic planning should be required with the goal of always reducing the risk of infant morbidity and mortality[2]. Therefore, good counseling of these family members during the prenatal period is essential[3] because this emotional support helps the parents make decisions that allow for better birth planning and more favorable neonatal care.

EMOTIONAL STATE OF PREGNANT WOMEN RECEIVING A FETAL DIAGNOSIS OF CONGENITAL HEART DISEASE

The prenatal diagnosis of a fetal anomaly is a traumatic event in the life of future parents, resulting in intense grief and psychological distress. Therefore, good counseling is important because this emotional support strengthens not only the doctor–patient relationship but also the trust between family members and health care professionals. This process provides security in the therapeutic management and guides the parents in making any decision, whether or not to interrupt the pregnancy, depending on the laws and sociocultural characteristics of the country[4,5].

Following the diagnosis, prospective parents express a need for ongoing support and information as they are concerned about the future of this child[6]. Particularly at the first visit, the initial reactions of shock and sadness to an abnormal finding can inhibit the parents' ability to retain information, making the initial consultation challenging. It is necessary to explain potentially complex anatomical details to a family when stress levels are very high. Ideally, there will be an opportunity for follow-up appointments to adequately complete the counseling and to reinforce points that may have been missed in the midst of an emotional first encounter[7].

However, such counseling is not free of difficulties and ethical dilemmas. This is mainly because we have to inform very distressed parents about the nature and consequences of CHD, early and late outcomes, possible complications at the time of delivery, the need or not for medical treatment, the timing of surgical or hemodynamic intervention, and the risks associated with each step of the procedures. Sometimes, the information obtained from the fetal examination is incomplete or refers to injuries that may evolve during the gestational period to improve or worsen the prognosis[8]. In addition, the information provided cannot take into account possible therapeutic advances that may occur in the future, as they may alter the quality of life and outcomes of affected individuals.

In view of the above, adequate family counseling should be considered a fundamental step in the management of CHD in the fetus, requiring health care professionals' skills and abilities beyond the confirmation of the heart disease and also including continuous monitoring that guarantees the welcoming and safe outcomes needed for each case. Therefore, specialists in fetal cardiology have an ethical obligation to keep their theoretical knowledge and practical skills up to date to ensure good counseling for these family members[9].

[1]Universidade Federal do Amazonas, Medical School, Postgraduate Program in Health Sciences – Manaus (AM), Brazil.
[2]Universidade Federal do Amazonas, Medical School, Medical Course – Manaus (AM), Brazil.
[3]Universidade do Estado do Amazonas, Medical School, Medical Course – Manaus (AM), Brazil.
[4]Universidade Federal do Amazonas, Institute of Health and Biotechnology – Manaus (AM), Brazil.
[5]Universidade Federal de São Paulo, Paulista School of Medicine, Department of Obstetrics – São Paulo (SP), Brazil.
[6]Universidade Municipal de São Caetano do Sul, Medical Course – São Caetano do Sul (SP), Brazil.
*Corresponding author: araujojred@terra.com.br
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IMPORTANCE OF FAMILY COUNSELING

Family counseling involves guiding fetal heart disease. It is therefore a complex skill that requires in-depth knowledge of normal cardiac physiology and CHD, treatment and prognosis data, communication skills, and emotional intelligence. It is pervasive in describing the heart disease, the child's expected course, typical outcomes, and genetic associations and communicating the most evidence-based data related to prenatal and postnatal outcomes[10].

Studies show that family members who receive information about a fetal anomaly immediately have less understanding of the information and an inability to manage their feelings[11] and show more anxiety and depression compared to family members who receive the postnatal diagnosis[12]. These characteristics emphasize the importance of family counseling from the detection of the first sign of alteration in the fetus, and it is also very important to consider the self-medication experience for the relief of anxiety and stress of these mothers[12], giving more time for family members to understand about heart disease and the necessary neonatal care. Some reports show an improvement in the bond between the pregnant woman and her partner, and between the parents and the child, with the awareness of their cardiological condition[13].

Other members of the affected family may want to be involved in the decision-making process. In addition, health care professionals, with their sociocultural beliefs, may influence family members by taking into account the emotional burden on the family, possible surgical procedures, future hospitalizations, the risk of complications, and the financial costs that the family may need during this period[14]. Therefore, care must be taken to ensure that counseling of these family members is done impartially by the welcoming team, as all of these factors can interfere with the free will of parents and family members[14].

Prenatal counseling of families with CHD is one of the main tasks of fetal cardiologists or maternal-fetal medicine specialists after diagnosis[15]. However, we consider the need for the presence of other health care professionals in this emotional support, considering that we must holistically help these families, knowing that, in addition to the medical aspects, there are psychological and sociocultural conditions that must be addressed.

Lee[7] presents important elements for prenatal counseling for these family members. She describes important topics for communicating information about the diagnosis of CHD, considering possible complications and necessary treatments. This model promotes a more assertive follow-up by presenting important aspects that should be part of the counseling of the pregnant woman. A proposed model of emotional support for pregnant women who receive a diagnosis of fetal heart disease is presented, taking into account the point of view defended by the authors with a multidisciplinary approach (Table 1).

The abovementioned elements help the professionals of the multidisciplinary team carry out family counseling, covering different dimensions of management, from the technical guidance on the disease to the basic and complex requirements

Table 1. Multidisciplinary counseling for family members diagnosed with congenital heart disease.

Medical aspects
1)Medical explanation of the diagnosis. 2)Medical clarification on follow-up. 3)Medical clarification on the treatment. 4)Preparation for favorable and unfavorable outcomes in the case of evolution or termination of pregnancy. 5)Suggestion of preventive treatment for new pregnancies. 6)Medical clarification on the association with genetic alterations.
Psychological aspects
1)Anamnesis and post-diagnosis reception. 2)Verification of the degree of understanding and adherence to the medical information suggested in the case. 3)Verify the psychic structure for the treatment and the experience of the outcomes of the case. 4)Emotional follow-up support for the pregnant woman and her family. 5)Clarification for the multidisciplinary team about the follow-up of the case.
Social aspects
1)Provide written materials on the diagnosis and treatment of CHD. 2)Provide information about support groups. 3)Check family financial issues and psychological support. 4)In case of hospital discharge, check the medications, the possible need for home monitoring, and the outpatient follow-up of the pregnant woman. 5)In matters of long-term surgical interventions, consider cardiological follow-up in the other phases of life.

Adapted from Lee[7].

that are expected to be promoted in facing the crisis situation: the essential emotional embrace. Therefore, it is necessary to appreciate the role of each professional, including doctors, psychologists, and social workers.

In view of the above, we would like to make a small reflection on the kind of advice we give to these family members: are we really welcoming these pregnant women?

We must consider that we are not facing an isolated problem, especially when we talk about parental relationships. Because when the mother makes this decision alone, whether without the father of the child or considering the extension of the family, for example, grandparents, aunts, uncles, and siblings, communication is fundamental and must be taken into account so that the decision is assertive, precise, and clear. In any case, opinions and positions must be taken into account, especially if one or more family members close to the parents concerned have a very strong opinion about how the pregnancy should proceed[16].

PSYCHOLOGICAL AND SOCIAL ASPECTS OF FAMILY COUNSELING WITH FETAL DIAGNOSIS OF CONGENITAL HEART DISEASE

Psychological counseling is an intervention by a health care professional that differs from clinical intervention in certain aspects, such as it is situational in nature, it is focused on solving the subject's problems, it is an intervention focused on the present, it has a shorter duration, and it is more action-oriented than reflection-oriented. It consists of a helping relationship that aims to facilitate the subject's adaptation to the situation in which he finds himself by optimizing his personal resources, self-knowledge, self-help skills, and autonomy in facing his difficulties and problems[17].

There are several theoretical perspectives of psychological counseling such as psychodynamic, humanistic, cognitive-behavioral, phenomenological-existential, feminist, constructivist, and systemic. The cognitive-behavioral perspective is the most recommended in the context of health and illness because it is the one that best fits the context and rhythm of health care.

Parents' cognitive activity after receiving the diagnosis can influence their behavior and emotions, which can lead to psychological disorders resulting from cognitive distortions, the way parents understand events and make them their central beliefs, which are not very adaptive and invariant to change.

Therefore, the cognitive-behavioral theory can help the patient adhere to the treatment by offering emotional support and improving quality of life[18]. In this way, the goal is to show that the influence on us is not directly the daily events and situations, but the way we interpret each of these situations so that we can act consciously, elaborating feelings and emotions in the promotion of new behaviors within a broader view of the internal and external world.

Counseling for pregnant women who receive a fetal diagnosis of CHD can be conceptualized as the process by which affected parents go through a grief response with the familiar components of sadness, shock, denial or disbelief, anger, guilt or shame, and grief with a sense of being alone. There is also a desire, or "negotiation", for a delay with the miraculous loss of the problem, followed by eventual resolution and reconstruction[16].

One of the first goals of the cognitive-behavioral approach in the process of accepting a diagnosis is to identify the patient's interpretations of their health-disease process in order to begin to restructure dysfunctional thoughts, adopting interpretations that are based on existing evidence in reality rather than considering irrational premises[19].

Most cognitive therapists begin the client's treatment by identifying automatic thoughts and cognitive distortions in the face of a crisis and, in the long term, by examining intermediate beliefs. In this way, cognitive therapy demonstrates the importance of developing the patient's autonomy, which is achieved through the process of training the patient to have the skills to modify dysfunctional thoughts, behaviors, and/or emotions[18].

The role of the therapist, at this point, is to help the patient think and act in a more realistic and adaptive way considering his psychological problems and, in this way, reduce the symptoms[20]. Therefore, it is up to the psychologist to analyze the variables that interfere with the life of each patient in order to understand how these variables influence their behavior and feelings in the face of the new situation and possible illnesses such as depression and anxiety.

In clinical practice, we have observed social difficulties that should be considered important. The first observation is the language barrier: the lack of understanding of the cardiologic situation due to the lack of fluency in the foreign language, which requires the presence of an interpreter to help clarify the issue[21]. Another very important concern is to provide information about the disease in a didactic way, using drawings, templates, or reliable information websites[21]. Professionals must avoid using confusing medical terms, as many family members, especially those with less education, have difficulty understanding CHD[22]. Contact with other family members with similar diagnoses can provide emotional support during the stages of this process. Family situations such as lack of emotional or financial support can make it difficult for this pregnant woman to progress to more appropriate treatment, for example, when there is a need for transfer. The cultural and

religious aspects can help with the acceptance of the fetus with heart disease[23]. There are countless social conditions that can influence this decision-making process, so there is also a need for good social support.

We suggest that family counseling in these cases of fetal diagnosis of CHD should follow a biopsychosocial approach, that is, it should consider health status, psychological well-being, and social skills, promoting the combination of specialized psychosocial intervention with medical intervention[24]. The history of the pregnant woman, her environmental conditions, personal experiences, and religious and financial aspects must be taken into account, as they are questions to be therapeutically elaborated, the source of which will present the solution to promote the psychic and emotional balance of coping with the demand now manifested, in this case, the heart disease of the child.

CONCLUSION

Counseling family members who receive a diagnosis of congenital heart disease during pregnancy is complex, mainly because of the positive focus on health rather than disease. In this regard, we support the idea that a multidisciplinary team is necessary for good counseling, as we must be able to meet the medical, psychological, and social needs of these individuals. It is also worth mentioning that it is important to evaluate the way this counseling is done and to observe its results, understanding that this is a contemporary issue and that we have a learning curve to develop.

AUTHORS' CONTRIBUTIONS

MBD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology. **LTST**: Formal Analysis, Investigation, Methodology, Writing – original draft. **LIAC**: Formal Analysis, Investigation, Methodology, Writing – original draft. **TLE**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology. **BM**: Investigation, Methodology. **ALMTN**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology. **EAJ**: Validation, Visualization. **LARA**: Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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SHORT COMMUNICATION

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Palliative extubation experience in a community hospital in southern Brazil

Ana Carolina Peçanha Antonio[1,2*], Juliana Peçanha Antonio[1]

INTRODUCTION

Sustaining invasive mechanical ventilation may inappropriately prolong the dying process and perpetuate states worse than death in end-of-life care. Even though withdrawing the ventilator in this circumstance is a well-established practice worldwide[1], Brazilian physicians are far more likely to withhold than withdraw life-sustaining treatments[2-5].

In 2018, the Brazilian Ministry of Health enacted Resolution No. 41/2018[6], spotlighting palliative care as a high-priority public health policy. We here explore the experience of a community intensive care unit (ICU) in Brazil after implementing a local protocol for palliative extubation.

METHODS

This prospective cohort study was conducted in a non-academic 10-bed ICU inside a 100-bed public community hospital in Porto Alegre, southern Brazil, from August 2019 to July 2020. The enrollment ended in August 2020 due to team rearrangement and permutations of staff rostering during the COVID-19 pandemic.

In July 2019, the interdisciplinary ICU team developed an institutional protocol of palliative extubation based on previous literature[7-9], targeting patients on invasive mechanical ventilation with terminal illness, progressive organ failure, chronic frailty, or catastrophic neurological event. Family members were approached regarding goals of care within 24 h of ICU admission, and at least two conferences on separate days were required for the decision process. The withdrawal of mechanical ventilation was always preceded by tapering all life-sustaining interventions, including the ventilatory parameters. Opioids were used immediately before extubation to reduce respiratory distress[10]; neuromuscular blocking agents and no comfort-centered routine measures were permanently discontinued. The medical team performed the procedure only during the daytime on weekdays and documented it in full detail on the electronic medical record.

Clinical and epidemiological data of patients submitted to palliative extubation were prospectively acquired to audit compliance with the protocol and obtain performance and quality indicators for the unit. The Institutional Review Board recently approved the data publication and waived the need for informed consent. The first author also reviewed medical records in case of any missing variables. We excluded patients with a tracheostomy or who were dead during the gradual reduction of life-sustaining treatments prior to extubation. The endpoint of primary interest was the period from extubation to hospital death or discharge.

Continuous variables were reported as mean±standard deviation, median, and interquartile range, and categorical variables were represented as numbers and proportions. We plotted a Kaplan-Meier curve to illustrate the time to death. Data were analyzed using STATA version 14.2 (Stata-Corp LP, College Station, TX, USA).

RESULTS

During the 1-year study period, 18 patients underwent protocolized palliative extubation. No family member or surrogate approached by the ICU team disagreed with the procedure. All included patients had been transferred from external emergency care units or rural hospitals due to a medical condition. Sepsis was the main reason for intubation. Table 1 displays the characteristics of the study cohort.

All patients eventually died during hospitalization, although six (33.3%) were discharged alive to the ward. The time between palliative extubation and in-hospital death ranged from 10 min to 11 days, with a median of 79 h (Figure 1).

[1]Hospital de Clínicas de Porto Alegre – Porto Alegre (RS), Brazil.
[2]Rede de Saúde Divina Providência, Hospital Independência – Porto Alegre (RS), Brazil.
*Corresponding author: aantonio@hcpa.edu.br, @anacarolpecanha
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Table 1. Characteristics of the study cohort.

Variables	n=18*
Age (years)	63.3±13.1
Male (%)	13 (72.2)
SAPS 3 (points)	76.5 (66–87)
Comorbidities (%)	
Moderate/severe COPD	2 (11.1)
Systolic heart failure	4 (22.2)
Cirrhosis	2 (11.1)
Cognitive impairment	2 (11.1)
Stroke sequelae	4 (22.2)
Metastatic cancer	4 (22.2)
End-stage renal disease	0
Reason for mechanical ventilation (%)	
Respiratory sepsis	5 (27.8)
Non-respiratory sepsis	3 (16.7)
Decompensated heart failure	2 (11.2)
Cardiac arrest	4 (22.2)
Stroke	2 (11.2)
Coma (other causes)	2 (11.2)
Palliative Performance Scale (%)	65 (30–80)
Charlson comorbidity index	6 (3–9)
Hemodynamic dysfunction at ICU admission (%)	10 (55.6)
Renal dysfunction at ICU admission (%)	10 (55.5)
Renal replacement therapy (%)	1 (5.6)
Duration on mechanical ventilation (days)**	5 (4–15)
ICU length of stay (days)***	7.5 (4–11)
Hospital length of stay (days)***	8 (4–14)
Use of opioids and/or sedatives after extubation (%)	11 (61.1)
Interruption of artificial nutrition (%)	16 (88.9)
Main surrogate decision-maker (%)	
Offspring	7 (38.9)
Spouse	5 (27.8)
Nephew/niece	3 (16.7)
Other	3 (16.7)

*Data are presented as mean±standard deviation, median (interquartile range), or n (%). **The first day on the ventilator is being considered. ***Day 0 represents the day of admission to our hospital due to inconsistent external medical records. SAPS 3: Simplified Acute Physiology Score 3; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit.

No patient was educated above the high school level. A total of 13 (72.2%) decedents had no advanced care planning, thus relying on third parties to align medical treatments with likely patients' wishes and preferences. Offspring and spouses were the family members most frequently involved in those shared decisions.

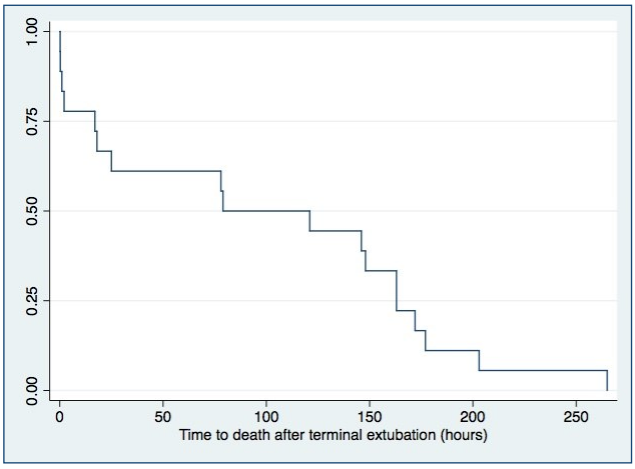

Figure 1. The Kaplan-Meier plot shows the survival time (hours) after palliative extubation of 18 patients, all of whom died in the hospital. 50% died within 79 h.

DISCUSSION

Rigorously executed, protocolized palliative extubation had no association with immediate death in this single-center cohort of 18 critically ill medical patients. Our experience is encouraging: the small, resource-limited, and non-teaching center provided culturally challenging end-of-life care to a considerable number of patients in a short time frame, despite the low prevalence of explicit advance care planning and the presumably low educational level.

Clinicians might consider removing the endotracheal tube as a strong determinant of immediate death. Compared with the previous studies[11-16], the longer survival after withdrawal of mechanical ventilation in our report likely reflects the role of gradual removal of life-support treatments rather than extubation merely in anticipation of imminent death, i.e., quite near the end of life, thus attenuating the residual effect of acutely severe illness. Previous cohorts with lower mortality[10,12,16,17] included patients who were successfully weaned from the ventilator and were probably not representative of the sicker segment of the ICU population.

Most family members would likely prefer the choice to shorten the dying process of the patients by withdrawing the ventilator[18]. In Brazil, however, palliative extubation is seldom performed[3-5]: 50.2% of Brazilian intensivists admit fear of litigation, although over 75% claim to have received specific palliative care training[19]. A survey[20] collected responses from 105 ICU physicians in Brazil in

2012 regarding a case vignette of a critically ill patient with post-cardiac arrest encephalopathy and sepsis: none would perform palliative extubation.

We failed to capture the exact moment when providers decided to recommend palliative extubation to patients, but the median duration of mechanical ventilation in our cohort is comparable to contemporary reports[3,10,17,21]. We were also unable to assess death cases after withdrawing vasopressors, renal replacement therapy, and other life-sustaining interventions while preparing for palliative extubation. We neither addressed the satisfaction of families nor the confidence and perceptions of the healthcare team. Palliative weaning without extubation was not a local practice in end-of-life care. No included patient had been intubated in the community hospital, which denotes the inclination of the hospital staff toward avoiding potentially disproportionate interventions.

Our findings might overcome misperceptions and mitigate potential moral conflicts among healthcare professionals. Professional competency and acceptance matter because they directly affect how patients will die. By integrating palliative care principles into daily care practice, this feasible initiative underscores how palliative extubation could be more frequently approached in the Brazilian health system to promote more humanized and affordable care.

AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

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A retrospective analysis: the outcome of renal replacement therapies in critically ill children

Kübra Çeleğen[1]*, Mehmet Çeleğen[2]

SUMMARY

OBJECTIVE: A few pediatric studies were present which focused on renal replacement therapy used for critically ill children. This research aimed to determine the ratio of utilization of intermittent hemodialysis, continuous renal replacement therapy, and peritoneal dialysis, and to study the properties and outcomes of critically ill pediatric patients who underwent renal replacement therapy.

METHODS: Critically ill children admitted to the intensive care unit and received renal replacement therapy from February 2020 to May 2022 were included. The children were divided into three groups: hemodialysis, continuous renal replacement therapy, and peritoneal dialysis.

RESULTS: A total of 37 patients (22 boys and 15 girls) who received renal replacement therapy met the criteria for this study. Continuous renal replacement therapy was used in 43%, hemodialysis in 38%, and peritoneal dialysis in 19%. In all, 28 (73%) children survived and 9 (27%) died in intensive care unit. The mean systolic blood pressure was significantly lower among children who received continuous renal replacement therapy ($p<0.001$). The need for inotropic medications and a higher PRISM III score were found to be the greatest indicators of mortality.

CONCLUSION: The outcome of children receiving renal replacement therapy seems to be related to their needs for vasoactive drugs and the severity of the underlying disease in the continuous renal replacement therapy group relative to the other groups.

KEYWORDS: Acute kidney injury. Continuous renal replacement therapy. Renal dialysis. Peritoneal dialysis. Pediatrics.

INTRODUCTION

Despite technological progressions in intensive care units (ICU) and the presence of different renal replacement modalities in recent years, acute kidney injury (AKI) is associated with high mortality and morbidity in critically ill patients[1]. The prevalence of AKI in pediatric and adult patients in ICU has been regarded at 5% to over 80% depending on the definition, although only around 5% of patients need renal replacement therapy (RRT)[2]. Although increased consciousness and the agreement on consensus descriptions for the AKI diagnosis have increased physicians' focus on milder renal dysfunction and allowed them to make decisions earlier, sometimes it is uncertain which patients are convenient for RRT, which procedures might be more beneficial, what pulls the trigger for beginning, how many ''doses" should be prescribed, and how long therapy should sustain. There is a common agreement that RRT should be started in cases of AKI, which is complicated by serious metabolic disturbances such as uremia, acidosis, and hyperkalemia[3]. Even though there is no definite indication of RRT in ICU, it is usually preferred for fluid overload and sepsis[4]. Typically, different RRTs are used: intermittent hemodialysis (HD), continuous RRT (CRRT), or peritoneal dialysis (PD)[5]. Although PD and HD are still important treatment options in AKI management, advanced CRRT machines capable of balanced fluid volume control have led to an increased preference for CRRT in pediatric ICU patients[1,2]. In particular, the choice of RRT is frequently arranged by several variables, such as the decision of the doctor, the familiarity with the technique, and the hemodynamic status of the patient.

The main purpose of this research was to define the relative ratio of utilization of HD, CRRT, and PD among critically ill pediatric patients admitted to ICU and to represent patient survival parameters based on the RRT technique as well as their sickness course.

METHODS

This retrospective study was enforced to determine the distribution of different RRT in pediatric patients with AKI who were admitted to the ICU from February 2020 to May 2022. Children aged 1 month to 18 years with the diagnosis of acute renal failure (ARF), volume overload, electrolyte abnormality,

[1]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nephrology – Afyonkarahisar, Turkey.
[2]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care Unit – Afyonkarahisar, Turkey.
*Corresponding author: kubractf@hotmail.com

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metabolic diseases of inborn, and intoxication that needed any type of RRT during their ICU stay were included. Exclusion criteria contained all stages of chronic renal disease, acute chronic kidney disease, fluid-responsive prerenal situation, and urinary tract obstruction caused by ARF.

A disposable, pediatric-size, semi-rigid PD catheter was placed into the peritoneal cavity to perform PD. Initially, 5–10 mL/kg of commercially available PD fluid were used to control the filling and drainage of fluid. Afterward, 15–20 mL/kg fluid volume with glucose concentration was preferred, and the fill volume was increased to 20–30 mL/kg in the case of insufficient ultrafiltration. Hemodiafiltration or continuous RRT was achieved using a Gambro Prisma membrane (AN-69). The blood flow rate was adjusted according to the patients' weight. Replacement or dialysate fluid was prescribed between 2,000 and 8,000 mL/h/1.73 m^2 [6,7]. Systemic heparin was used for anticoagulation, and the target pre-RRT activated clotting time (ACT) was between 170 and 220 s[8].

Intermittent HD was accomplished with Fresenius Medical Care 2008® series HD machines. Fresenius Polysulfone® dialyzer was selected. The dialysate bath was adjusted for sodium and potassium. The blood flow rate was set at 4–5 mL/kg/min. The length and frequency of each dialysis period were decided based on the requirements of the patients. Heparin was used to extend the usage of hemofiltration filter. If there is no coagulopathy, 20 units/kg of intravenous heparin are administered. After the loading dose, 10 units/kg/h of heparin infusion is started, and the heparin dose is adjusted to keep the target ACT level between 180 and 220 s.

The children were divided into three groups: HD, CRRT, and PD. The selection of modality was primarily associated with the choice of the physician and the patient's hemodynamic status. Initially, the ratio of the usage of CRRT, HD, and PD groups among seriously ill patients was described. Second, the results contain a comparison of demographic parameters and patient outcomes (mortality ratio, length of ICU stay, duration of RRT treatment, inotropic drug requirements [dopamine, dobutamine, epinephrine, norepinephrine, vasopressin, and milrinone], ventilator days, and complications) between different RRT groups.

Statistical analysis

The variables were investigated using the histogram, Q-Q plots, and analytic methods for normal distribution. Normally distributed data were reported as mean±standard deviation and non-normal distribution as median. Statistical testing of the three RRT groups was undertaken using the chi-square test for categorical variables or one-way analysis of variance with Tukey post-hoc pairwise tests for continuous variables to identify differences between pairs of data. Levene's test was used to assess the homogeneity of variances. Kruskal-Wallis test was performed to analyze the nonparametric data. Mann-Whitney U test was performed to analyze the significance of pairwise differences. Bonferroni correction was used to adjust for multiple comparisons. An overall p-value of less than 0.05 was considered statistically significant. The multivariate logistic regression analysis was performed to identify the most significant parameters.

RESULTS

A total of 37 patients who received RRT were included. A comparison of demographic and clinical parameters in children is shown in Table 1. CRRT was used in 43%, HD in 38%, and PD in 19%. In all, 28 (73%) patients survived and 9 (27%) died. At the time of starting RRT, although the median age of patients who received PD was 5 months (3–9 months), patients who underwent HD was 132 months (3–170 months), and this difference was significant (p=0.049). RRT was used more frequently in males (p=0.76). The median weight was 13.6 kg (3–65 kg). The weight of children who received PD was lower than that of patients who received CRRT or HD (p=0.07). The systolic blood pressure was significantly lower among CRRT patients (69.6±6.1 mmHg) (p<0.001). The admission diagnoses included sepsis (n=15), acute tubular necrosis (n=12), hemolytic uremic syndrome (n=4), metabolic disease (n=3), intoxication (n=2), and bone marrow transplant (n=1). There was no significant difference between the groups in terms of comorbidity (p=0.32). The median length of ICU stay was 18 days (2–62 days). The duration of ICU stay was insignificantly longer in children undergoing PD than in children who received other RRT modalities (p=0.3). The duration of RRT for the sum of 37 cases was 5.8±3.1 days on HD, 3.4±1.8 days on CRRT, and 6.7±5.9 days on PD. There was no difference between the duration of RRT modalities (p=0.52). Overall, 26 patients needed mechanical ventilation. Conventional mechanical ventilation was the most commonly used ventilation modality. The PRISM III score was significantly greater in patients undergoing CRRT 18 (12–21) compared with HD 6 (2–22) and PD 9.5 (6–12) (p=0.02). Depending on the clinical requirements, 85.7% of patients undergoing CRRT, 22.2% of patients requiring HD, and 50% of patients undergoing PD needed vasoactive inotropic drugs (CRRT versus HD or PD, p=0.01).

The total mortality ratio was 24.3% (n=9) (Table 2). The survival ratio was higher in males (p=0.95). The survival rate of children who needed inotropic drugs was significantly lower than that of patients who needed no inotropic drugs (p=0.03).

At admission, nonsurvivors had significantly lower systolic pressure (p<0.001). The systolic blood pressure was described by the percentiles[9]. The PRISM III scores were significantly higher in nonsurvivors (p<0.001). Nonsurvivors required mechanical ventilator support more commonly than survivors (p=0.52).

Multivariate regression analysis was performed to detect independent risk factors. The requirement for inotropic drugs and a higher PRISM III score were found to be the greatest indicators of mortality (odds ratio [OR] 1.8; 95% confidence interval [CI] 1.05–2.1; p=0.04, OR 2.3; 95%CI 1.25–3.2; p=0.03, respectively) (Table 3).

DISCUSSION

RRT is preferred for critically ill pediatric patients for improving clinical outcome[10]. The major outcomes of this study are as follows: First, when we compared our results, we found that CRRT is the most frequently used RRT type, and mortality was higher in children undergoing CRRT. Second, mortality was higher in children who used vasoactive inotropic drugs. Finally, a higher PRISM III score was associated with mortality.

Although different studies have been performed to find the survival advantage of CRRT over HD, the superiority of one modality over the other has not been demonstrated[11,12].

Table 1. Comparison of demographic and clinical parameters of children who received renal replacement therapy.

Variables	HD (n=14)	CRRT (n=16)	PD (n=7)	p-value
Age at admission (month)	132 (3–170)	13 (3–172)	5 (3–9)#	0.049
Sex (female n/%, male n/%)	6 (42.8%), 8 (57.2%)	6 (37.5%), 10 (62.5%)	3 (42.8%), 4 (57.2%)	0.76
Weight at admission (kg)	20 (3–65)	10 (4–63)	5.5 (3–7)	0.07
Systolic blood pressure at admission (mmHg)	109.2±8.3#	69.6±6.1	82.7±8.7	<0.001
Hearth rate	133.6±28.6	137.7±22.8	144.2±21.5	0.09
Primary diagnosis				
Sepsis	1 (7.1%)	11 (68.8%)	3 (42.8%)	0.06
ATN	7 (50%)	4 (25%)	1 (14.2%)	
HUS	3 (21.4%)	–	1 (14.2%)	
Metabolic disease	1 (7.1%)	–	2 (28.4%)	
Intoxication	2 (14.2%)	–	–	
Bone marrow transplantation	–	1 (6.2%)	–	
Comorbidity				
Respiratory disorders	–	2	–	0.32
Neurological disorders	1	1	–	
Renal disorders	1	–	–	
Metabolic disorders	1	–	2	
Hematological-oncological disorders	–	1	–	
Duration of ICU (day)	16 (2–45)	12 (2–48)	33 (12–62)	0.3
Duration of RRT (day)	5.8±3.1	3.4±1.8	6.7±5.9	0.52
Mechanical ventilation support				
CMV	5 (35.7%)	10 (62.5%)	3 (42.8%)	0.27
HFOV	–	5 (31.3%)	1 (14.2%)	
NIV	1 (7.1%)	1 (6.2%)	–	
PRISM III score	6 (2–22)	18 (12–21)#	9.5 (6–12)	0.02
Vasoactive inotropic drug	2 (22.2%)	6 (85.7%)#	2 (50%)	0.01
Outcome				
Survived	13 (92.8%)	9 (56.25%)	6 (85.7%)	0.02
Died	1 (7.2%)	7 (43.75%)#	1 (14.3%)	

The parameter of the group with (#) sign is significantly higher than those in the other groups.

The survival ratio of pediatric patients requiring RRT is mostly not accurately associated with the RRT modality, but rather with the severity of the underlying disease of patients[7]. Similar findings are shown in adult studies, which define underlying conditions requiring RRT and symptoms of multi-organ failure as the most important predictors of survival[13]. A randomized prospective trial showed an increased survival ratio in HD, but the CRRT group had a higher severity of disease despite the randomization[14]. In a meta-analysis trial comparing HD and CRRT, no superiority of either dialysis treatment over the other could be demonstrated[15]. Different studies were performed to determine the efficacy and outcome of PD in comparison to HD. The outcomes of Noshad et al. suggested that patients' quality of life and survival ratio were higher on PD than on HD[16]. Liberek et al. showed that the survival rate was similar when comparing the PD and HD[17]. In this present study, the increased mortality in patients undergoing continuous RRT can be explained by the fact that the intensity of the disease is more severe, and patients are hemodynamically unstable and need more inotropic support.

It has been shown that critically ill patients undergoing HD need much less vasopressor use than other modalities, and the survival ratio was lower in patients who required vasopressor than in patients who required no vasopressor[7]. Smoyer et al. showed that patients with multi-organ failure requiring vasopressors have an increased risk of mortality[18]. This current study found that the requirement for vasopressor drugs was higher in patients receiving CRRT, and the survival rate was lower in children who needed vasopressor drugs. The rationale for why vasopressor drugs are more commonly used in the CRRT mode is that CRRT is preferred in patients with hemodynamic instability.

In infants, vascular access for CRRT or HD is quite complex, and also infants are more sensitive to hemodynamic fluctuations associated with CRRT and HD[19]. For these causes, PD is the first choice of RRT modality among infants[1]. AKI is common after

Table 3. Multivariate logistic regression analysis of survivors versus nonsurvivors.

Variables	Odds ratio	95%CI	p-value
The requirement for inotropic drugs	1.8	1.05–2.1	0.04
PRISM III score	2.3	1.25–3.2	0.03
Systolic blood pressure at admission	0.98	1.12–1.5	0.09

Table 2. Comparison of demographic and clinical parameters between survivors and nonsurvivors.

Variables	Survivors (n=28)	Nonsurvivors (n=9)	p-value
Age at admission (month)*	63 (3–172)	6 (5–84)	0.42
Sex (female n/%, male n/%)	10 (35.7%), 18 (64.3%)	3 (33.3%), 6 (66.7%)	0.95
Weight at admission (kg)*	15 (3–65)	6 (5–24)	0.56
Systolic blood pressure at admission (mmHg)	94.5±18.1	65.0±6.2	<0.001
Primary diagnosis			
Sepsis	9 (32.1%)	6 (66.7%)	0.14
ATN	11 (39.3%)	1 (11.1%)	
HUS	4 (14.2%)	–	
Metabolic disease	2 (7.1%)	1 (11.1%)	
Intoxication	2 (7.1%)	0	
Bone marrow transplantation	–	1 (11.1%)	
Duration of ICU (day)*	15 (2–62)	5 (2–18)	0.2
MV requirement	17 (60.7%)	9 (100%)	0.52
Mechanical ventilation support			
CMV	12 (42.9%)	6 (66.6%)	0.35
HFOV	3 (10.7%)	3 (33.3%)	
NIV	2 (7.1%)	0	
PRISM III score	10.3±6.6	18.3±0.57	<0.001
Duration of RRT (day)	5.6±3.6	2.6±1.1	0.18
Vasoactive inotropic drug	7 (41.2%)	3 (100%)	0.03

*Indicates median (min–max).

complex congenital heart surgery, and PD is a frequently preferred method of RRT in these patients[20,21]. Although CRRT was more frequently chosen as RRT among whole patients, PD was the most commonly preferred RRT model for those with low body weight children and infants in this study. Hemodynamic instability is one of the main reasons for the preference for CRRT in a considerable number of ICU patients with ARF[22]. Augustine et al. showed that mean arterial pressure and vasopressor support were similar between intermittent and continuous dialysis methods in patients with ARF just before starting the dialysis modality[23]. A study showed that the incidence of circulatory failure and inotropic support did not differ between the continuous venovenous hemodiafiltration and intermittent hemodialysis groups[24]. In this current study, the initial systolic blood pressure was significantly lower in the CRRT group.

Bunchman et al. found that the duration of RRTs was similar among critically ill children[7]. A research presented that the duration of RRT was similar between CRRT and HD patients[24]. In the current study, there was no difference between the duration of the RRT modalities.

Beltramo et al. showed that children who received CRRT stayed in the hospital 7 days longer than those who received HD[1]. In a study conducted by D. E. Uehlinger et al., although the length of hospital stay was longer in the HD group, there was no statistically significant difference between CRRT and HD groups[1,24]. This study showed that the ICU stay was insignificantly longer in the PD group.

A study interested in RRT modalities in critically ill children claimed that requiring mechanical ventilation was associated with higher mortality on multivariate logistic regression analysis[1]. In a study comparing the effects of continuous and intermittent RRTs on acid-base balance, no difference was found in terms of mechanical ventilation need[25].

In this current research, mechanical ventilation support was insignificantly more common in the CRRT group.

This research had some limitations. First, this is a retrospective study performed by using records gathered from the hospital's electronic data system. Second, the timing of renal-replacement therapy initiation was not standardized. Finally, the amount of inotropic drug support was not evaluated, while the inotropic drug requirement was found to be an independent risk factor in regression analysis.

CONCLUSION

The outcome of patients receiving RRT seems to be associated with their requirements for vasoactive drugs and the severity of the underlying disease. CRRT is the most prevalent therapy for RRT in critically ill pediatric patients in ICU. The utilization of CRRT mode is related to raising mortality. Additionally, prospective studies are needed to determine the ideal RRTs in critically ill children.

ETHICAL ASPECTS

This research was approved by University Medical Faculty Ethical Committee (date: April 01, 2022, decision no: 2022/4).

AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

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Immunostaining of stromal CD56 cells in ovarian malignancies

Cid Almeida de Lima[1], Millena Prata Jammal[1], Renata Margarida Etchebehere[2], Eddie Fernando Candido Murta[1], Rosekeila Simões Nomelini[1]*

SUMMARY

OBJECTIVES: The aim of this study was to evaluate CD56 immunostaining in the stroma of benign and malignant ovarian epithelial neoplasms and associate the CD56 immunostaining with prognostic factors and survival in ovarian cancer.

METHODS: Patients with ovarian epithelial neoplasia (n=77) were studied with a prospective cohort. The CD56 immunostaining was evaluated in the peritumoral stroma. Two groups were evaluated: benign ovarian neoplasms (n=40) and malignant ovarian neoplasms (n=37). Data were recorded for histological type and grade, International Federation of Gynecology and Obstetrics staging, molecular subtype, and lymph node metastases. Fisher's exact test and Kaplan-Meier survival curves were used, with a significance level of ≤0.05.

RESULTS: We found greater CD56 stromal immunostaining in malignant neoplasms when compared to the group of benign neoplasms (p=0.00001). There was no significant difference in relation to the prognostic factors and survival.

CONCLUSION: Malignant ovarian neoplasms showed higher stromal CD56 immunostaining. As the prognostic value of natural killer in ovarian cancer is controversial, knowing the specific function of each cell present both in the tumor tissue and systemically may help guide successful immunotherapies in the near future.

KEYWORDS: CD56 antigen. Killer cells, natural. Ovarian neoplasms. Prognosis.

INTRODUCTION

In 2020, 313,959 new cases of ovarian cancer were detected, and approximately 207,252 deaths from the disease occurred worldwide[1]. In Brazil, approximately 6,650 cases of ovarian cancer were registered each year of the 2020–2022 triennium, with 4,123 deaths. The estimate for new cases in 2023 is 7,310 cases, with about 3,921 deaths from the disease[2]. In the USA, there are an estimated 19,710 new cases with about 13,270 deaths in the year 2023[3].

Epithelial ovarian cancer (EOC) develops an inflammatory environment with the presence of immune cells that can promote its growth via the release of cellular signalers and cytokines. However, no consensus on this understanding of the disease has been reached[4-6]. The immune cells present in EOC comprise mainly tumor-infiltrating lymphocytes (TILs): T CD4+, T CD8+, natural killer (NK) cells (CD56), and CD3+ and CD20+ T lymphocytes[7,8]. Several theories have been proposed to describe the influence of the immune system on tumor cells and their signaling molecules. Interleukin (IL) levels in ovarian tissue and serum from patients with ovarian cancer have recently been linked to prognostic factors[6,9,10]. The immune system plays a multifaceted role, promoting and inhibiting tumor growth in different contexts. The role of the immune response against EOC has not been described clearly, given the different actions of immune cells, such as T lymphocytes, which can lead to proliferation or the inhibition of tumor growth[9].

The objectives of this study were to evaluate CD56 expression in the stroma of benign and malignant ovarian epithelial neoplasms and examine associations of CD56 immunostaining with prognostic factors and survival in patients with ovarian cancer.

METHODS

This study was conducted with a prospective cohort of 77 patients with ovarian epithelial neoplasms seen at the Pelvic Mass Outpatient Clinic of the Department of Gynecology and Obstetrics, Federal University of Triângulo Mineiro. CD56 immune expression in the peritumoral stroma of the ovarian epithelial neoplasms was evaluated. The patients were divided

[1]Universidade Federal do Triângulo Mineiro, Department of Gynecology and Obstetrics – Uberaba (MG), Brazil.
[2]Universidade Federal do Triângulo Mineiro, Surgical Pathology Service – Uberaba (MG), Brazil.
*Corresponding author: rosekeila@terra.com.br, rosekeila.nomelini@pesquisador.cnpq.br

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into two groups based on anatomopathological confirmation of diagnoses: those with benign (n=40) and primary malignant (n=37) epithelial ovarian neoplasms. Borderline cases were included in the malignancy group. The Research Ethics Committee of the Federal University of Triângulo Mineiro approved this study (protocol no. 34770014.4.0000.5154, October 30, 2014). Free and informed written consent was obtained from each patient or a family member.

The inclusion criterion was the postoperative diagnosis of primary ovarian epithelial neoplasia (benign or malignant) by the anatomopathological paraffin analysis. The exclusion criteria included secondary ovarian malignancy (metastasis) or primary nonepithelial ovarian tumor, torsion of the adnexal pedicle, receipt of treatment prior to surgery, neoplasm recurrence, and immunosuppressive disease or treatment with immunosuppressive drugs.

The data recorded were patient age, parity, ages at menarche and menopause, hormonal status, histological type and grade of EOC, International Federation of Gynaecology and Obstetrics (FIGO) stage, molecular subtype, lymph node metastasis, disease-free survival (DFS), and overall survival (OS).

DFS was calculated from the date of diagnosis to the date of the first recurrence. OS was calculated from the diagnosis to the date of death.

An experienced pathologist at the Surgical Pathology Service of the Federal University of Triângulo Mineiro performed an anatomopathological analysis of the cuts embedded in paraffin.

For the immunohistochemical analysis, specimens obtained by surgical resection were processed in paraffin and reviewed by an experienced pathologist. The selected cases were submitted to new cuts (4 μm) in silanized sheets (ATPS - Silane, Sigma® A3648). The technique was performed according to the manufacturer's instructions. The percentage of immunostained cells with these antibodies in 10 random stroma fields adjacent to the epithelium was determined by two observers (0, ≤25%; 1, 26–50%; 2, 51–75%; 3, ≥76%) at 200/400× magnification (Figure 1).

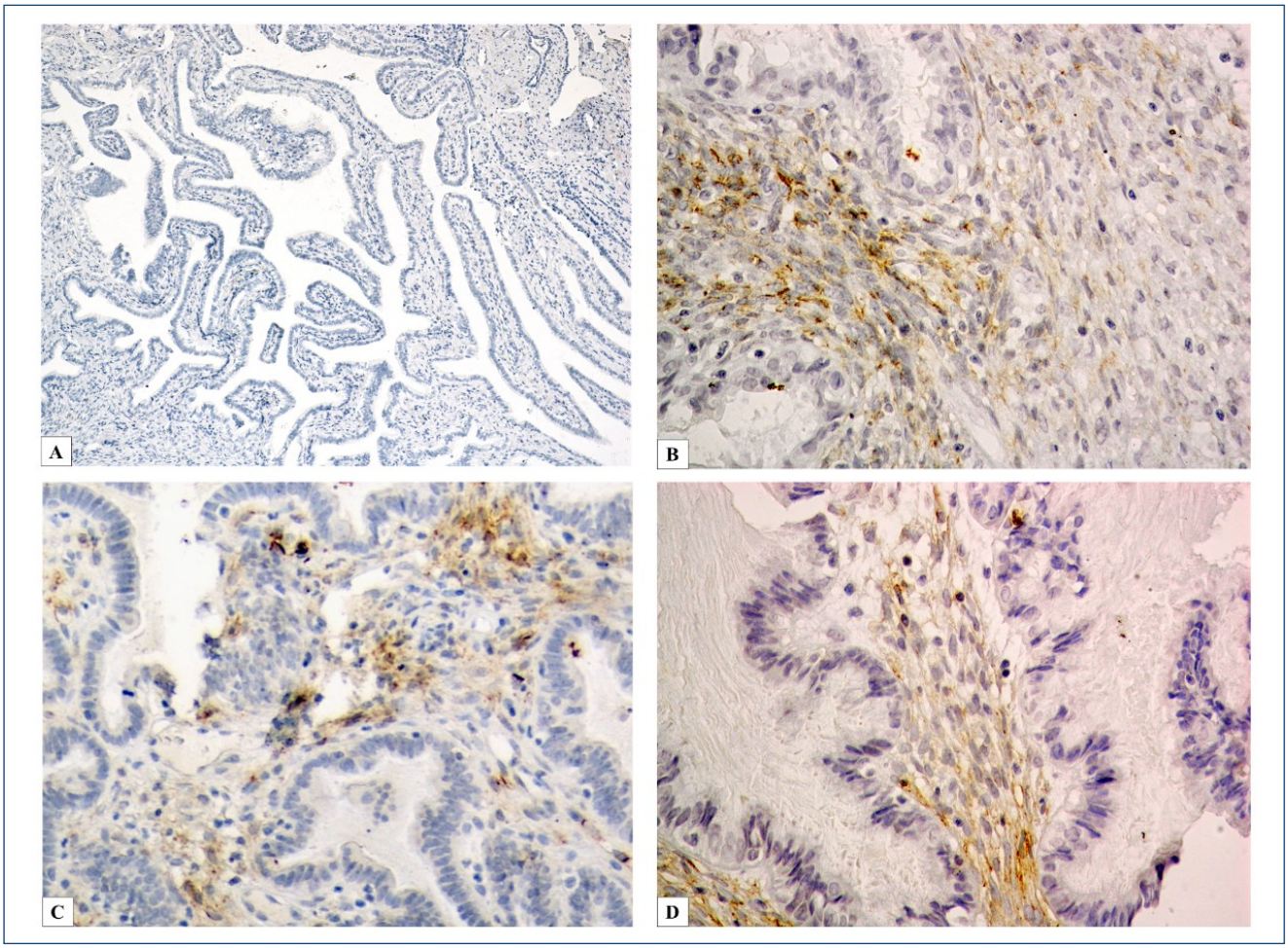

Figure 1. Immunohistochemical . of CD56. Histological sections of ovarian epithelial neoplasia. (A) Weak stromal CD56 immunostaining in serous cystadenoma (200×); (B) strong stromal CD56 immunostaining in serous borderline ovarian tumor (400×); (C) strong stromal CD56 immunostaining in serous borderline ovarian tumor (400×); (D): strong stromal CD56 immunostaining in serous borderline ovarian tumor (400×).

The GraphPad InStat and SPSS software were used for the statistical analysis. According to the data distribution (determined using the Kolmogorov-Smirnov test), the results are expressed as means and standard deviation or medians with percentiles, and Fisher's exact test was used. Kaplan-Meier curves were used to evaluate DFS and OS, in addition to the log-rank test. The significance level was 0.05. The agreement on immunohistochemical findings between the two observers was assessed using the kappa coefficient ($\kappa<0.4$, weak; $0.4\leq\kappa<0.8$, moderate; $0.8\leq\kappa<1.0$, strong; $\kappa=1.0$, perfect). Cases of disagreement were reviewed until consensus was reached.

RESULTS

The study sample comprised 77 patients, of whom 40 had benign and 37 had malignant neoplasms. For the malignant neoplasm group, the median age was 50 (range, 25–73) years, the median parity was 2 (range, 0–7) births, the median age at menarche was 13 (range, 9–16) years, and the median age at menopause was 50 (range, 38–57) years. In all, 22 (59.5%) of these patients were in menacme and 15 (40.5%) were menopausal, and 13 (35.1%) patients in this group died. For the benign neoplasm group, the median age was 48 (range, 18–69) years, the median parity was 2.5 (range, 0–9) births, the median age at menarche was 13 (range, 10–17) years, and the median age at menopause was 49 (range, 29–55) years. Of note, 23 (57.5%) patients were in menacme, and 17 (42.5%) were menopausal.

The benign ovarian neoplasm subtypes determined by the analysis of histological sections were 21 (52.5%) serous cystadenomas, 16 (40.0%) mucinous cystadenomas, 1 (2.5%) seromucinous cystadenoma, 1 (2.5%) Brenner tumor with mucinous cystadenoma, and 1 (2.5%) Brenner tumor with serous cystadenoma. The malignant neoplasm subtypes were 14 (37.9%) serous high-grade carcinoma, 12 (32.4%) mucinous borderline ovarian tumor, 3 (8.1%) serous low-grade carcinoma, 3 (8.1%) serous borderline ovarian tumor, 2 (5.4%) mucinous carcinoma, 1 (2.7%) endometrioid carcinoma, 1 (2.7%) clear cell carcinoma, and 1 (2.7%) endometrioid borderline ovarian tumor.

The FIGO stages of the malignant neoplasms were IA [n=14 (37.83%)], IB [n=2 (5.41%)], IC2 [n=2 (5.41%)], IIA [n=1 (2.70%)], IIB [n=2 (5.41%)], IIIA1 (ii) [n=1 (2.70%)], IIIA2 [n=1 (2.70%)], IIIB [n=1 (2.70%)], IIIC [n=10 (27.03%)], and IVB [n=3 (8.11%)]. The histological grades of these tumors were 1 [n=16 (43.2%)], 2 [n=14 (37.8%)], and 3 [n=7 (18.9%)]. Overall, 20 (54.05%) malignant neoplasms were of molecular subtype I and 17 (45.95%) were of molecular subtype II.

We observed greater CD56 stromal immunostaining in malignant than in benign neoplasms (p=0.00001; Table 1). No significant difference in immunostaining related to any prognostic factor was found (Table 2). The distribution of CD56

Table 1. Differences in stromal CD56 immunostaining between malignant and benign ovarian neoplasms.

		0	1/2/3	p-value
CD56	Benign neoplasms	39/40 (97.5%)	1/40 (2.5%)	0.00001*
	Malignant neoplasms	18/37 (48.6%)	19/37 (51.4%)	

*Fisher's exact test. 0: ≤25% of labeled cells; 1: 26–50% of labeled cells; 2: 51–75% of labeled cells; 3: ≥76% of labeled cells. Benign neoplasms: n=40; malignant neoplasms: n=37.

Table 2. Stromal CD56 immunostaining and association with histological grade, staging, molecular subtype, and lymph node metastasis in ovarian cancer.

		CD56 0	CD56 1,2,3	p-value*
Histological grade (n=37)	1	8/17 (47.1%)	9/17 (52.9%)	0.7463
	2/3	8/20 (40.0%)	12/20 (60.0%)	
Staging (FIGO) (n=37)	I/II	11/21 (52.4%)	10/21 (47.6%)	0.5085
	III/IV	6/16 (37.5%)	10/16 (62.5%)	
Molecular subtype (n=37)	I	11/20 (55.0%)	9/20 (45.0%)	0.3248
	II	6/17 (35.3%)	11/17 (64.7%)	
Lymph node metastasis (n=24)	Positive	2/5 (40.0%)	3/5 (60.0%)	1.0000
	Negative	7/19 (36.8%)	12/19 (63.2%)	

*Fisher's exact test. 0: ≤25% of labeled cells; 1: 26–50% of labeled cells; 2: 51–75% of labeled cells; 3: ≥76% of labeled cells. Malignant neoplasms: n=37.

Table 3. Distribution of CD56 stromal immunostaining readings according to histological subtypes of ovarian cancer.

Histological subtypes	IH 0	IH 1	IH 2	IH 3
Endometrioid adenocarcinoma	0	0	1	0
Clear cell carcinoma	1	0	0	0
Cystoadenocarcinoma	2	0	0	1
Mucinous cystadenocarcinoma	2	0	0	0
Serous papillary cystadenocarcinoma	4	4	4	2
Borderline atypical proliferative endometrioid tumor	1	0	0	0
Borderline mucinous tumor	7	1	2	2
Borderline serous tumor	0	0	0	3

IH: immunostaining.

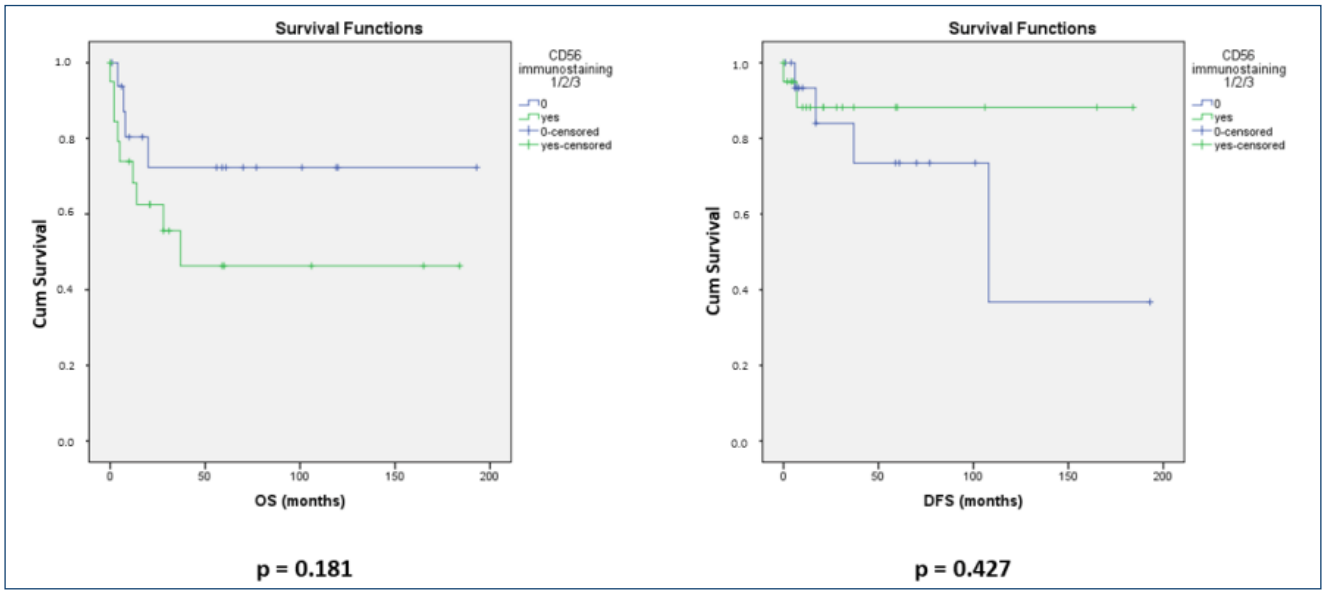

Figure 2. Evaluation of overall survival and disease-free survival in relation to stromal CD56 immunostaining.

stromal immunostaining readings according to the histological subtype of ovarian cancer is shown in Table 3. There was no statistical significance in the evaluation of OS or DFS (p=0.181 and p=427, respectively) (Figure 2).

DISCUSSION

Experimental data have shown that the inflammatory microenvironment of the EOC prevents the maturation of myeloid cells, favors the development of regulatory cells, and suppresses the cytotoxic activity of effector lymphocytes, allowing the tumor to escape the immune system and triggering the progression of cancer[11]. The immune system acts directly on tumor tissue with the expression of cytokines and their release into the serum, peritoneal fluid, and intracystic fluid of patients with cancer. This process makes evident the roles of defense cells in the tumor microenvironment, namely the promotion or inhibition of neoplastic cell growth[6,8-10,12,13].

The mechanisms by which TILs enter a tumor, crossing the vessel wall and migrating into the stroma, occur after the recruitment of T lymphocytes to the site. The complex stromal microenvironment is composed of noncancerous cells together with the extracellular matrix, and TIL migration results in interaction with tumor cells[14]. Activation of the stromal microenvironment has been identified as an important factor in the progression of cancer[15]. The rearrangement of the extracellular matrix and distinct cell clusters in the stroma create a specific microenvironment that promotes carcinogenesis, leading to

cancer cell proliferation, invasion, and survival. These events are based on activities orchestrated by cell-cell interaction[16].

We found greater stromal NK CD56 immunostaining in malignant than in benign neoplasms, but no association of this staining with any prognostic factor or survival was found. We attribute these findings to the heterogeneity of tumors evaluated. Despite their common cellular origin, ovarian neoplasms have heterogeneous, divergent, and difficult-to-understand genetic, biological, clinical, and immunological properties, especially in advanced stages[17,18].

NK are characterized phenotypically by the expression of a CD56 surface marker, although they lack CD3 expression, but they do not constitute a homogeneous population; they can be grouped into subpopulations based on maturity and functional characteristics. About 90% of NK CD56-expressing lymphocytes are cytotoxic, effectively inducing cell death. The remaining 10% have low degrees of cytotoxicity before activation, but they are the most efficient producers of cytokines with immunoregulatory properties, including interferon (IFN)-γ, tumor necrosis factor-α, granulocyte-macrophage colony stimulating factor, IL-10, and IL-13, thereby acting as regulatory T cells[5,19].

A study showed that most NK CD56 cells in patients with ovarian cancer have phenotypically regulatory and noncytotoxic characteristics, which prevent them from attacking tumor cells, thereby allowing tumors to proliferate. In the same study, however, the in vitro inhibition of certain receptors altered the activity of NK extracted from patients with ovarian tumors and healthy donors, activating them to eliminate tumor tissue[20]. Cells in the tumor microenvironment trigger the negative regulation of NK-activating receptors, thereby impairing their IFN-γ production and cytolytic functions. EOC cells' expression of the MUC-16 antigen protects them from recognition by NK, inhibiting the formation of intermembrane communication and leading to an increase in metastatic capacity[21].

On the contrary, another study revealed a larger proportion of cytotoxic NK than of those that behave as cytokine secretors in CD56+ clusters in the ascitic fluid of patients with EOC, comparing malignant and benign groups[22]. The cytotoxic functions of ascites-derived NK cells and those in peripheral blood from healthy donors are equivalent, although the former show less expression of activation markers than those in benign peritoneal fluid, which is associated with increased disease-free progression[23]. These data indicate that ascites-derived NK cells from patients with EOC and low survival have significantly less expression of activation receptors on their surfaces, an unknown variation that inhibits the cytotoxic function of these cells (in turn, this function can be activated with IL-15 stimulation)[22].

In a study by He et al., who studied the expression of CD56 in 16 normal ovaries, 17 ovarian fibromas, 11 ovarian cellular fibromas, 10 ovarian fibrothecomas, and 11 ovarian leiomyomas, the normal ovarian stromal cells were strongly positive for CD56 with the strongest immunostaining. CD56 is strongly expressed in ovarian stromal cells but not in endometrial stromal cells[24].

The frequency of these lymphocytes is much lower than that of T and B cells. The prognostic value of ovarian cancer NK is controversial, although greater NK activity in peripheral blood at the time of surgery is an indicator of better survival. Increased concentrations of NK in peritoneal and pleural exudates of metastatic tumors were associated with worse prognoses[25]. EOC-associated ascites showed a higher proportion of the subpopulation of NK $CD56^{bright}$ lymphocytes than in the blood, showing that the inflammatory profile can be different depending on the evaluated site[26]. Current experimental studies conducted with murine models have shown promise for the evaluation of the activation of NK cytolytic activity in breast and ovarian tumors. Changes in receptors obtained by the manipulation of oncological viruses associated with dendritic cell immunotherapy reduced the incidence of metastatic tumors and increased the survival of the study subjects[27].

This study has limitations. The use of immunohistochemical analysis in the present study may have limited the ability to evaluate NK activity because it does not allow the evaluation of phenotypic marking for cells that function as effectors against regulators in EOC. Another limitation of the study is the small sample of patients and the evaluation of different histological types. Future studies with a larger number of patients, enabling the stratification of histological types and NK subpopulations (CD56 dim and CD56 bright NK), are needed to clarify the role of stromal CD56 in the immune response and prognosis of ovarian cancer.

Therefore, the lymphocytes and NK cells in EOC have not been studied thoroughly, and their actions may differ at different points in the course of the disease. Knowledge of the specific functions of each cell in the tumor tissue can contribute systemically to the development of successful immunotherapies in the near future.

AUTHORS' CONTRIBUTIONS

CAL: Data curation, Methodology, Writing – original draft. **MPJ:** Investigation, Methodology, Writing – original draft. **RME:** Data curation, Methodology, Writing – original draft. **EFCM:** Conceptualization, Formal Analysis, Supervision, Validation, Writing – review & editing. **RSN:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – review & editing.

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ORIGINAL ARTICLE

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Impact of coronavirus disease pandemic on performance and satisfaction, physical activity, and quality of life of the elderly

Elif Gur Kabul[1*], Bilge Basakcı Calık[2]

SUMMARY

OBJECTIVE: The aim of this study was to examine the effects of the coronavirus disease pandemic in the elderly.

METHODS: A total of 140 elderly with a mean age of 71.30±6.00 years (69 females, 71 males) who spent the coronavirus disease pandemic period at home were included. Canadian Occupational Performance Measure, Visual Analog Scale (for pain intensity at rest and activity), International Physical Activity Questionnaire-Short Form, and EuroQol Five-Dimensional Questionnaire, Three-Level Version Health States were used in the evaluation. Two scores are obtained in Canadian Occupational Performance Measure: one for performance and one for satisfaction. EuroQol Five-Dimensional Questionnaire, Three-Level Version consists of two parts: EuroQol Five-Dimensional Questionnaire, Three-Level Version descriptive system and EuroQol Five-Dimensional Questionnaire, Three-Level Version Visual Analog Scale.

RESULTS: While female gender (p=0.006, p=0.001), using walking assistant (p=0.001, p=0.001), being single/widow (p=0.031, p=0.007), and history of falling (p=0.004, p=0.001) made difference in Visual Analog Scale (rest, activity), female gender (p=0.013) and being single/widow (p=0.020) made difference in satisfaction scores of Canadian Occupational Performance Measure. Female gender (p=0.001), using walking assistant (p=0.001), and history of falling (p=0.010) made difference in EuroQol Five-Dimensional Questionnaire, Three-Level Version descriptive system. In addition, performance scores of Canadian Occupational Performance Measure had a low correlation with Visual Analog Scale (rest r=-0.198, p=0.019; activity r=-0.188, p=0.026) and had a moderate correlation with EuroQol Five-Dimensional Questionnaire, Three-Level Version descriptive system (r=0.327, p=0.001) and EuroQol Five-Dimensional Questionnaire, Three-Level Version Visual Analog Scale (r=0.307, p=0.001). Satisfaction scores of Canadian Occupational Performance Measure had a low correlation with Visual Analog Scale (rest r=-0.247, p=0.003; activity r=-0.223, p=0.008) and had a moderate correlation with EuroQol Five-Dimensional Questionnaire, Three-Level Version descriptive system (r=0.399, p=0.001) and EuroQol Five-Dimensional Questionnaire, Three-Level Version Visual Analog Scale (r=0.306, p=0.001).

CONCLUSION: The elderly who were women, single/widowed, using walking assistant, and having a history of falling were more affected during the coronavirus disease period.

KEYWORDS: Elderly. COVID-19. Quality of life. Satisfaction.

INTRODUCTION

"Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)" is a newly discovered pathogen in humans, responsible for an infection called coronavirus disease (COVID-19)[1]. The COVID-19 pandemic has triggered a worldwide public health crisis, affecting every aspect of life, society, healthcare, and individual health outcomes[2]. The COVID-19 pandemic affects all age groups. However, the effect on the health of the elderly is greater than in other age groups[3,4].

All precautions such as physical distancing, movement restriction, and home quarantine during the COVID-19 pandemic led to negative psychological and physical effects, especially for the elderly. Despite all the relief efforts, the elderly had to endure the heavy consequences of the pandemic[5,6].

Preventing the elderly from going out can cause social isolation and a decrease in their physical levels[7]. They reduced walking activities, increased sitting, spent more time watching television, and had less social interactions with friends or families[8]. According to studies, the physical effects of the COVID-19 pandemic are sarcopenia, increased risk of falling, fragility, diabetes mellitus, hypertension, and increased risk of cardiovascular disease[9]. Armitage and Nellums reported that insufficient physical activity during the quarantine period may cause harmful effects on the mental and emotional health of the elderly. The psychological consequences of isolation are anxiety, depression, dementia, impaired cognitive functions, mental disorientation, increased suicide attempts, and post-traumatic stress disorder[10].

[1]Usak University, Institute of Health Sciences, Physiotherapy and Rehabilitation – Uşak, Turkey.
[2]Pamukkale University, School of Physical Therapy and Rehabilitation – Denizli, Turkey.
*Corresponding author: elifgur1988@hotmail.com
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Due to the fact that the elderly stay at home and cannot go out, their need for protection, surveillance, and care has increased, and they have experienced more problems in the fulfillment of daily life activities during the COVID-19 pandemic[11].

The Health-Related Quality of Life consists of various dimensions such as basic quality of life, well-being, social and psychological factors, physical function, life satisfaction, and awareness of health status[12]. The need to explore the health-related quality of life parameters in social isolation, which intensifies during the pandemic period for the already vulnerable elderly, is the focus of the literature reviews and is considered an urgent need[13]. Due to the availability of information about how the elderly self-assess their general condition during the COVID-19 period, this study was planned to examine the effects of the COVID-19 pandemic on performance and satisfaction, physical activity levels, and quality of life in the elderly.

METHODS

Participants

A total of 140 elderly (69 females, 71 males) with a mean age of 71.30±6.00 years who spent the COVID-19 pandemic period at home were included in this study. Inclusion criteria included living at home; 65 years of age and older; being a volunteer; and Hodkinson Mental Test scores of 6 and above. Exclusion criteria included elderly who cannot be contacted for reasons such as Alzheimer's disease, dementia, or psychosis; having a chronic disease that can cause pain; being blind; and having an orthopedic, neurological, or mental disability.

Approval for the study was granted by the Local Ethics Committee (decision no: 19, date: 10.19.2021). All patients were informed verbally, and informed consent forms were signed. All the procedures were in accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Evaluations

All evaluations were performed by the same investigator. After the demographic information of the participants (age, gender, marital status, educational level, using walking assistant, and history of falling) was recorded, performance and satisfaction were evaluated with the Canadian Occupational Performance Measure (COPM), pain intensity at rest and activity with Visual Analog Scale (VAS), physical activity levels with International Physical Activity Questionnaire-Short Form (IPAQ-SF), and quality of life with EuroQol Five-Dimensional Questionnaire, Three-Level Version (EQ-5D-3L) Health States. The interview was face-to-face in approximately 40 minutes. Evaluations were made in the home environment of the elderly, wearing masks and protective clothing to reduce the risk of contamination. Sterilization was achieved with disinfectants.

Canadian Occupational Performance Measure (COPM): The administration of the COPM consisted of five steps. First, they were asked to identify the problematic activities in daily life from three performance areas (self-care, work and productivity, and leisure time). Second, the importance of each problem was graded on a 10-point scale (1 is not important; 10 is very important). Then, the participant selected the five most important problems. Finally, for each of these five most important problems, the participant rated their performance (1=not able to do it at all and 10=able to do it extremely well) and satisfaction (1=not satisfied at all and 10=extremely satisfied) on a 10-point scale. Thus, two scores were obtained: one for performance and one for satisfaction[14].

Visual Analog Scale: The pain intensity of the participant at rest and activity was determined as the length of the distance from "0" to "10" (0="no pain" and 10="worst possible pain"). The mark made by the participant[15].

International Physical Activity Questionnaire-Short Form (IPAQ-SF): It was used to determine the level of physical activity. This questionnaire consisted of seven questions including the "last seven days." A score was obtained by multiplying the minute, day, and MET values[16].

EuroQol Five-Dimensional Questionnaire, Three-Level Version (EQ-5D-3L) Health States: It consisted of two parts: EQ-5D-3L descriptive system and EQ-5D-3L VAS. The score of EQ-5D-3L descriptive system ranged from -0.59 to 1. A value of 1 indicated perfect health, while negative values indicated low quality of life. EQ-5D-3L VAS was numbered from 0 to 100 (0: The worst imaginable health state and 100: The best imaginable health state)[17].

Statistical analysis

As a result of the power analysis performed by assuming that the effect size of the relationship between the variables to be examined will be moderate (r=0.3), it was calculated that 80% power could be obtained at the 95% confidence level when a minimum of 64 subjects are included in the study. The data were analyzed using the IBM SPSS Statistics vn.22 software. The Kolmogorov-Smirnov test was used to determine whether the continuous variables were normal distributions. Continuous variables were expressed as mean±SD for normal distributions and median (minimum–maximum) for non-normal

distributions. The categorical variables were expressed in numbers and percentages. The Mann-Whitney U test and independent samples test were used to compare the independent group differences. In addition, the relationships between continuous variables were examined with Pearson correlation analysis. Correlation was categorized as low (r:0.10–0.29), moderate (r:0.30–0.49), or high (r:0.50–1.00)[18]. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The study was first involved 160 elderly. The Hodkinson Mental Test score of three elderly was below 6. Two elderly had rheumatoid arthritis. Fifteen elderly did not want to participate in the study. Consequently, the study was completed with a total of 140 elderly (69 females, 71 males) with a mean age of 71.30±6.00 years. The flowchart of the study is shown in Figure 1.

Demographic data and the most challenging activities of the participants are shown in Table 1. Descriptive data by groups are given in Table 2.

Intergroup comparison results

In terms of gender, VAS at rest (p:0.006) and activity (p:0.001) scores were higher, and EQ-5D-3L descriptive system (p:0.001) and satisfaction scores of COPM (p:0.013) were lower for female than male (Table 2).

VAS at rest (p:0.001) and activity (p:0.001) scores were higher, and EQ-5D-3L descriptive system (p:0.001) scores were lower for the elderly who used a walking assistant than the elderly who did not (Table 2).

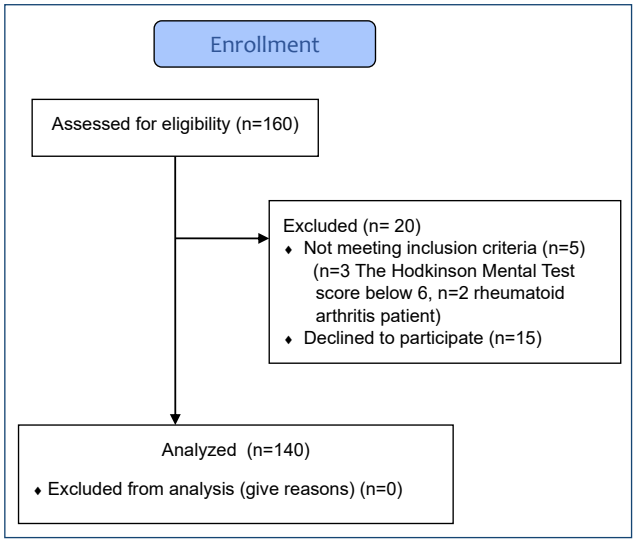

Figure 1. The flowchart of the study.

Table 1. Demographic data and the most challenging activities of the elderly participants according to Canadian Occupational Performance Measure.

Variables	Mean±SD
Age (years)	71.30±6.00
Hodkinson Mental Test	8.59±1.22
	n (%)
Gender-female	69 (49.3)
Male	71 (50.7)
Using walking assistant -Yes	33 (23.6)
No	107 (76.4)
Marital status-Married	105 (75)
Single/widow	35 (25)
History of falling-Yes	47 (33.6)
No	93 (66.4)
Educational level-Literate	26 (18.6)
Primary school	73 (52.1)
Secondary school	23 (16.4)
High school	11 (7.9)
University	7 (5)
COPM Self-care activities -Walking outside (park)	40 (28.6)
Up and down stairs	26 (18.6)
Shopping	23 (16.4)
Taking a bath	21 (15)
Take a salary	19 (13.6)
Carrying heavy bags	16 (11.4)
Paying bills	15 (10.7)
Shaving (hair, beard)	14 (10)
Sitting on the toilet	8 (5.7)
Brush hair	6 (4.3)
Cut nail	5 (3.6)
Wear shoe socks	5 (3.6)
Driving a car	5 (3.6)
Get dressed	4 (2.9)
Using technology	2 (1.4)
Get on and off the car	2 (1.4)
Carry tray	2 (1.4)
Work and productivity activities-Cook	26 (18.6)
Home cleaning	20 (14.3)
Taking things from the kitchen cabinet	10 (7.1)
Gardening	9 (6.4)
Laundry hanging/wash the clothes	4 (2.6)
Ironing	2 (1.4)
Sew	2 (1.4)
Leisure time activities-Visiting neighbors, relatives, and friends	35 (25)
Taking care of the grand children	21 (15)
Meeting with friends (such as cafes and coffee shops)	13 (9.3)
Buy a newspaper	6 (4.3)
Travel	5 (3.6)
Go to temple	2 (1.4)

Table 2. Descriptive data and intergroup comparison results.

Variables	Mean±SD Median (min/max)						
	VAS (Pain) -rest	VAS (Pain) -activity	IPAQ-SF	EQ-5D-3L descriptive system	EQ-5D-3L VAS	Performance scores of COPM	Satisfaction scores of COPM
Gender-female	2.71±2.36	5.43±2.25	4,389.60±3,347.42	0.65±0.27	64.19±21.08	4.61±1.73	3.36±1.71
	2.5 (0/10)	5 (0/10)	4,509 (49.50/16,192)	0.78 (0.09/1)	60 (0/100)	4.60 (1.40/8)	2.80 (1/7.20)
Male	1.7±1.85	3.82±2.64	5,539.72±5,176.59	0.79±0.26	70.31±18.43	5.02±2.38	4.63±2.77
	1.5 (0/6)	4 (0/10)	4,621.50 (0/29,673)	0.88 (-0.14/1)	75 (20/100)	5 (1/10)	4.40 (1/12)
p	**0.006**	**0.001**	0.404	**0.001**	0.086	0.330	**0.013**
Using walking assistant - Yes	3.45±2.55	6.03±2.32	4,474.12±2,773.81	0.54±0.30	61.69±21.26	4.35±1.96	3.25±1.82
	3.6 (0/10)	6 (1/10)	4,504 (0/10,290)	0.70 (-0.14/1)	60 (20/100)	4 (1.40/8)	3.10 (1/7)
No	1.81±1.89	4.18±2.50	5,138.52±4,796.19	0.78±0.24	69.02±19.30	4.96±2.11	4.24±2.50
	1.20 (0/10)	4 (0/10)	4,621.50 (49.50/29,673)	0.88 (0.2/1)	75 (0/100)	4.80 (1/10)	4 (1/12)
p	**0.001**	**0.001**	0.902	**0.001**	0.073	0.146*	0.053
Marital status-married	2.03±2.23	4.28±2.67	4,912.35±4,812.28	0.74±0.27	69.10±19.30	5±2.18	4.31±2.53
	1.50 (0/10)	4 (0/10)	4,032 (0/29,673)	0.80 (-0.14/1)	75 (20/100)	5 (1/10)	4.20 (1/10)
Single/widow	2.71±1.93	5.60±1.98	5,204.63±2,978.41	0.65±0.29	61.88±21.15	4.27±1.69	3.08±1.63
	3 (0/6)	5 (0/9)	5,517 (82.50/12,864)	0.70 (0.09/1)	60 (0/90)	4 (1.40/8)	2.80 (1/6.60)
p	**0.031**	**0.007**	0.173	0.071	0.084	0.074*	**0.020**
History of falling-Yes	2.88±2.20	5.60±2.30	4,575.47±3,866.13	0.61±0.32	63.14±21.81	4.52±1.50	3.73±1.74
	3 (0/10)	5.6 (0/10)	4,427 (49.50/16,192)	0.70 (-0.14/1)	60 (0/100)	4.60 (1.4/7.6)	3.75 (1/7.20)
No	1.85±2.08	4.12±2.58	5,205.19±4,686.75	0.77±0.23	69.39±18.71	4.97±2.32	4.14±2.65
	1 (0/10)	4 (0/10)	4,657.50 (0/29,673)	0.80 (0.02/1)	75 (20/100)	4.80 (1/10)	3.80 (1/10)
p	**0.004**	**0.001**	0.595	**0.010**	0.141	0.174*	0.747

Mann-Whitney U test; *Independent samples test; VAS: Visual Analog Scale; COPM: Canadian Occupational Performance Measure, IPAQ-SF: International Physical Activity Questionnaire-Short Form; EQ-5D-3L: EuroQol Five-Dimensional Questionnaire, Three-Level Version Health States. Bold values denote statistical significance at the p<0.05 level.

In terms of marital status, VAS at rest (p:0.031) and activity (p:0.007) scores were higher, and satisfaction scores of COPM (p:0.020) were lower for single/widow than married (Table 2).

VAS at rest (p:0.004) and activity (p:0.001) scores were higher, and EQ-5D-3L descriptive system (p:0.010) scores were lower for elderly with a history of falling than elderly without (Table 2).

There was no difference between groups in IPAQ-SF scores (p>0.05) (Table 2).

Pearson correlation results

Performance and satisfaction scores of COPM had a low negative correlation with VAS at rest and activity and had a moderate positive correlation with EQ-5D-3L descriptive system and EQ-5D-3L VAS (p<0.05) (Table 3).

There was no correlation between COPM and IPAQ-SF scores (p>0.05) (Table 3).

DISCUSSION

The elderly who were women, single/widow, using walking assistant, and history of falling had higher pain intensity in this study. Also, women and single/widow were less satisfied and the quality of life was lower in women, using walking assistant, and history of falling during the period of COVID-19. In addition, performance and satisfaction decreased, while pain intensity at rest and activity increased. As their performance and satisfaction decreased, their quality of life decreased.

Bezerra et al. conducted a study on perceived social isolation during the COVID-19 pandemic in Brazil and

Table 3. The relationship between performance and satisfaction scores of Canadian Occupational Performance Measure with VAS (pain), IPAQ-SF, and EQ-5D-3L.

	Performance scores of COPM		Satisfaction scores of COPM	
	r	p	r	p
Visual Analog Scale (Pain)-rest	-0.198	**0.019**	-0.247	**0.003**
Activity	-0.188	**0.026**	-0.223	**0.008**
IPAQ-SF	0.142	0.101	0.082	0.347
EQ-5D-3L descriptive system	0.327	**0.001**	0.399	**0.001**
EQ-5D-3L Visual Analog Scale	0.307	**0.001**	0.306	**0.001**

Pearson correlation analysis; COPM: Canadian Occupational Performance Measure; IPAQ-SF: International Physical Activity Questionnaire-Short Form; EQ-5D-3L: EuroQol Five-Dimensional Questionnaire, Three-Level Version Health States. Bold indicates statistically significant values.

found that social interaction was the most affected aspect[19]. Experts say being socially connected is critical to health and survival among the elderly[13,20]. The consequences of social isolation and emotional loneliness increase their vulnerability to depression, increase their stress level, and reduce their quality of life[2,21,22].

Disaggregation of COVID-19 data by age, gender, disability, and underlying health conditions is essential to accurately distinguish risks to the elderly[23]. The voices, expertise, and perspectives of elderly people in identifying problems and solutions are sometimes not adequately included in the policy-making process, particularly where elderly people are affected by such decisions. Hence, it is important to expand our partnership to make the voices heard by the elderly, benefit from their knowledge, and ensure their free, active, and meaningful participation[23].

In this study, we examined the perspectives of the elderly, who had to stay at home during the COVID-19 pandemic, on this period and how they evaluated their own situation. We found that the elderly who use a walking assistant and have a history of falling felt more pain intensity and had lower quality of life. With these results, we can say that the elderly who need one or more personal care/partially cannot be self-sufficient are more affected. The elderly who have already withdrawn from social life more than normal individuals may be more affected in terms of psychological influence with more restrictions on their movements. Thus, they may perceive their own situation as worse according to their level of activity. The elderly, who are more dependent on others, may not be able to do their personal care or perform less because they receive less help from their families during this period of restrictions. This situation may even have caused psychological pressure as it may cause further contamination because one of the rules to be considered during the pandemic period was hygiene. Therefore, as a result of our study, the elderly who use a walking assistant and have a history of falling may have higher pain intensities and lower quality of life.

The elderly living alone are at even greater risk for social isolation, which has significantly increased due to the COVID-19 pandemic. The elderly, especially who live alone and lack support, are among the groups most susceptible to discrimination[24,25]. In our results, we think that the reason why single/widow elderly have more pain intensity and less satisfaction is that they experience the effects of social isolation more intensely. Inter-American Commission on Human Rights called that "to provide the necessary balance between protection from COVID-19 and the special needs of the elderly to connect with their families, and to provide telephone or internet-based communication channels to prevent their emotional state from being adversely affected[26]."

Although the studies in the literature showed that men had higher rates than women in terms of biological exposure (passing the disease with more severe symptoms) and death rates, women are more affected in terms of psychological exposure[27]. Many studies reported that women are routinely affected more severely in mental health due to biological differences in hormone profiles compared to men[28-30]. As detailed in the policy brief on the impact of COVID-19 on women, elder women often care for elderly relatives and take care of children[23]. In our study, we think that the reason for the higher pain intensity and lower satisfaction and quality of life of the elderly women may be because they provide more intensive care during the COVID-19 period and are more affected by the psychological stress caused by this period. Women, who have a longer life expectancy and higher survival rate than men, are particularly highly represented among elderly people in the 80+ age group, and this has important implications for health policies[27].

When the average values of the physical activity levels of our sample group are examined, it is seen that they are similar. We attribute this reason why no significant difference was

observed in IPAQ-SF scores in correlation and intergroup comparisons. Physical activity provides benefits for the health of the elderly by stimulating muscle contraction and energy expenditure and reducing systemic inflammation, oxidative stress, and the prevalence of chronic diseases. The risk of functional decline is higher in older people who do not participate in regular physical activity. Physical activity is especially important for older people to maintain their level of independence, mental health, and well-being[31]. Therefore, we recommend that they can be encouraged to maintain mobility in old age.

In this study, we observed that the most challenging activities of the elderly evaluated with COPM were "self-care activities." "Walking outside" is the most challenging activity. This is followed by "visiting neighbors, relatives, and friends." This shows how much elderly individuals are affected by social isolation. Among the most challenging activities, "shopping, take a salary, and taking care of the grand children" are the activities that attract attention.

Important conclusions can be drawn from this acquired pandemic. Based on the results we obtained from this study, we think that more focus should be placed on social support for the elderly who are women, single/widow, use a walking assistant, and have a history of falls, and special methods should be developed with multidisciplinary studies in order to better manage both the physical and psychological conditions of these people within the scope of observing the rights of the elderly while making difficult decisions regarding health.

Due to the lack of a regular source of income and insufficient savings during the COVID-19 period, many individuals are facing financial crises[19]. One of the limitations of our study is that data on the source of income and its effects were not collected.

CONCLUSION

In the elderly population, female gender, using walking assistant, being single/widow, and history of falling were more affected in terms of pain intensity, satisfaction, and quality of life during the COVID-19 period. Performance and satisfaction scores of COPM had a correlation with pain intensity and quality of life.

AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

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Accuracy of intrapartum cardiotocography in identifying fetal acidemia by umbilical cord blood analysis in low-risk pregnancies

Michaela Franco Tomich[1], Renato Silva Leoni[1], Pedro Teixeira Meireles[1], Caetano Galvão Petrini[1,2], Edward Araujo Júnior[3,4*], Alberto Borges Peixoto[1,2]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the accuracy of intrapartum cardiotocography in identifying fetal acidemia by umbilical cord blood analysis in low-risk pregnancies.

METHODS: This is a retrospective cohort study of low-risk singleton pregnancies in labor after performing intrapartum cardiotocography categories I, II, and III. The presence of fetal acidemia at birth was identified by analyzing the pH of umbilical cord arterial blood (pH<7.1).

RESULTS: No significant effect of the cardiotocography category on the arterial (p=0.543) and venous (p=0.770) pH of umbilical cord blood was observed. No significant association was observed between the cardiotocography category and the presence of fetal acidemia (p=0.706), 1-min Apgar score <7 (p=0.260), hospitalization in the neonatal intensive care unit (p=0.605), newborn death within the first 48 h, need for neonatal resuscitation (p=0.637), and adverse perinatal outcomes (p=0.373). Sensitivities of 62, 31, and 6.0%; positive predictive values of 11.0, 16.0, and 10.0%; and negative predictive values of 85, 89.0, and 87.0% were observed for cardiotocography categories I, II, and III, respectively.

CONCLUSION: The three categories of intrapartum cardiotocography presented low sensitivities and high negative predictive values to identify fetal acidemia at birth in low-risk pregnancies.

KEYWORDS: Pregnancy outcomes. External cardiotocography. Fetal blood. Blood gas analyses.

INTRODUCTION

Intrapartum cardiotocography (CTG) has been employed to monitor fetal well-being during labor for about 50 years[1]. CTG is also used to monitor fetal cardiac activity, uterine contractions, and the relationship between them, thereby providing essential information about fetal oxygenation[2]. It is also widely used to predict fetal acidemia, asphyxia, neurological injuries, and cerebral palsy[3].

However, no evidence supports the use of intrapartum CTG in low-risk pregnancies, with many guidelines recommending the use of intermittent auscultation (IA) for continuous fetal well-being monitoring[4,5]. Although IA is the gold standard for monitoring low-risk women in labor, only 10.6% of these women receive it in clinical practice[6,7]. In the United States, at least 89% of pregnancies are monitored using CTG during labor[8]. Based on these data, the use of intrapartum CTG is common and widespread in tertiary centers and developed countries, even in low-risk pregnancies. Therefore, although the practice of intrapartum CTG in low-risk pregnancies meets the standard definition of medical and legal care, its continuous use is associated with an increase in the rate of cesarean sections and instrumental vaginal deliveries with no improvement in the rate of adverse perinatal outcomes[9].

The CTG category system can be utilized to help determine the ideal time for pregnancy resolution based on the fetal heart rate (FHR) pattern[10]. This decision is made easier when the CTG category is "normal" (I) or "abnormal" (III). However, the interpretation is challenging in 80% of cases in which the CTG category is "suspected" (II)[11,12].

At birth, venous cord blood reflects the maternal-placental acid–base status with a higher oxygen concentration than arterial blood rich in CO_2, with a lower pH reflecting the neonatal acid–base status[13]. Thus, retrospectively, CTG is used as the gold-standard test to assess fetal well-being during obstetric care. Due to the widespread use of intrapartum CTG in low-risk pregnancies, there is an increase in the rate of instrumentalized deliveries without significant evidence of improvement in perinatal outcomes.

[1]Universidade de Uberaba, Mário Palmério University Hospital, Gynecology and Obstetrics Service – Uberaba (MG), Brazil.
[2]Universidade Federal do Triângulo Mineiro, Department of Gynecology and Obstetrics – Uberaba (MG), Brazil.
[3]Universidade Federal de São Paulo, Paulista School of Medicine, Department of Obstetrics – São Paulo (SP), Brazil.
[4]Universidade Municipal de São Caetano do Sul, Medical Course – São Paulo (SP), Brazil.
*Corresponding author: araujojred@terra.com.br
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Therefore, the objective of this study was to evaluate the accuracy of intrapartum CTG in identifying fetal acidemia by umbilical cord blood analysis in low-risk pregnancies.

METHODS

A retrospective cohort study was conducted at the University Hospital by analyzing the medical records of women who attended during labor from November 2019 to November 2021. The study was approved by the Local Research Ethics Committee with the Certificate of Presentation for Ethical Appraisal (No. 52299421.7.0000.5145).

This study included singleton pregnancies during the first stage of labor at term, whether spontaneous or induced, with both cesarean and vaginal deliveries after performing intrapartum CTG categories I, II, or III. The exclusion criteria of this study were[1] cases in which arterial and venous blood gas analysis of the umbilical cord were not performed[2]; blood gas results in which the difference between arterial and venous pH was <0.02; and[3] high-risk pregnancies.

High-risk pregnancy was defined as a condition in which the life or health of the mother, fetus, and/or newborn is more likely to be compromised than those of the mean population considered[14]. The following examples are considered: arterial hypertension, heart diseases, severe pneumopathies, severe nephropathies, endocrinopathies, hematological diseases, neurological, psychiatric, autoimmune diseases, maternal genetic disorders, history of deep vein thrombosis/pulmonary embolism, gynecological diseases, infectious diseases, use of illicit drugs, clinical pathologies that require specialized monitoring, and factors related to reproductive life and current pregnancy[15,16].

According to the institutional protocol, the main indications for performing intrapartum CTG in low-risk pregnant women are maternal temperature >38°C, oxytocin use, misoprostol use, meconium, acute vaginal bleeding, and FRH abnormality auscultation by Doppler sonar. To perform the CTG examination, the woman was positioned either in dorsal decubitus with the head of the bed raised to 45° or in the left lateral decubitus position. The tocodynamometer was placed under the uterine fundus, and the sonar was placed close to the fetal back for continuous auscultation of the FHR for 20 min. A sensor was handed to the pregnant woman for her to signal fetal movements. Fasting of no more than 3 h was observed for the test.

CTG plots were classified according to the recommendation of the American College of Gynecologists and Obstetricians[10]: CTG category I: normal plots predictive of fetuses with normal acid–base status; category II: non-reassuring plots not included in category III and requiring further obstetric surveillance; and category III: abnormal plots, such as sinusoidal patterns, a lack of variability, and frequent decelerations, among other changes associated with abnormal acid–base status.

After clamping a 20-cm segment of the umbilical cord, 1 mL of arterial blood was collected, and 1 mL of venous blood was transferred to a 3-mL blood gas analysis syringe containing heparin (BD Luer Lok, South Hackensack, NJ, USA). Not more than 30 min after collection, blood gas analysis was performed using a Cobas b 221 gasometer (Roche Diagnostics, Switzerland), and arterial and venous pH were analyzed[13,17]. An arterial pH <7.1 was associated with fetal acidemia[17]. When the pH difference was <0.02, blood collection from the same vessel or a mixture of arterial and venous blood was suspected.

The following variables were evaluated: age, ethnicity, smoking, number of pregnancies, number of previous deliveries, pre-existing disease, obstetric risk classification (high- or habitual-risk), presence of meconium, temperature>38°C, oxytocin use, misoprostol use, FHR abnormality, maternal bleeding during the first or second stage of labor, gestational age at delivery, CTG category, type of delivery, duration between cord clamping and pH analysis, venous pH, arterial pH, presence of fetal acidemia at birth, Apgar score at 1st minute, Apgar score at 5th minute, hospitalization in neonatal intensive care unit (ICU), early neonatal death (48 h after delivery), and need for neonatal resuscitation.

The presence of fetal acidemia at birth, the Apgar score at 1st minute<7, the need for hospitalization in the neonatal ICU, early neonatal death, and the need for neonatal resuscitation were considered adverse perinatal outcomes. The presence of at least one adverse perinatal outcome was considered a composite adverse perinatal outcome.

The Gpower 3.1 program was used to calculate the sample size. To determine sensitivity, specificity, false positive rate, false negative rate, positive likelihood ratio, and negative likelihood ratio, considering an effect size of 0.17, a probability of error α of 0.05, and a power of 0.95, a total number of 113 participants would be required.

The data were transferred to an Excel 2019 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using the SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA) and Prisma GraphPad version 7.0 (GraphPad Software, San Diego, CA, USA). Quantitative variables were submitted to the normality test (D'Agostino–Pearson). Variables with a normal distribution were presented based on their means and standard deviations. Variables with a non-normal distribution were presented as medians and interquartile ranges. Categorical variables were described as absolute and percentage frequencies and

represented in tables. The chi-square test was used to assess the differences between categorical variables and their proportions, whereas analysis of variance (ANOVA) and Kruskal–Wallis tests were used among continuous variables. Dunn's *post-hoc* test was used to compare pairs. Sensitivity, specificity, false-positive and false-negative rates, and positive and negative likelihood ratios were the key outcome measures. The significance level (α) for all tests was 0.05.

RESULTS

From November 2019 to November 2021, 2,861 women in labor were admitted to the hospital. A total of 1,096 cases were excluded because they did not undergo CTG, 899 due to the absence of umbilical cord blood gas tests, 687 because they were classified as high-risk pregnancies, 29 due to inadequate blood conditions (coagulation, duration between collection, and analysis>30 min), and 20 due to differences between venous and arterial pH <0.02. For the final statistical analysis, 90 CTG category I, 30 CTG category II, and 10 CTG category III results were considered.

The clinical characteristics of the study population are presented in Table 1. Significant associations were observed between CTG category and number of pregnancies (p=0.043) and between CTG category and delivery type (p<0.001). CTG category I presented a greater mean number of pregnancies (1.9 vs. 1.1, p=0.048) than CTG category III. CTG categories II and III had higher rates of cesarean deliveries than CTG category I (70 vs. 13.3%, p<0.0001, and 80.0 vs. 13.3%, p<0.0001, respectively). CTG category I had significantly higher 1-min Apgar scores (8.5 vs. 8.0, p=0.031) and 5-min Apgar scores (9.5 vs. 9.0, p=0.022) than category III. The CTG category had no significant effect on the pH of arterial (p=0.543) and venous blood (p=0.770).

The association between CTG category and indications for fetal evaluation during labor is presented in Table 2. CTG

Table 1. Clinical characteristics of the study population.

	Category I (n=90)	Category II (n=30)	Category III (n=10)	p
Age (years)	24.0 (21.0–24.0)	22.5 (17.0–26.0)	22.5 (16.0–25.2)	0.080†
Ethnicity				
White	31.1% (28/90)	53.3% (16/30)	60.0% (6/10)	0.110§
Black	14.4% (13/90)	6.7% (2/30)	0.0% (0/10)	
Mixed	51.1% (46/90)	40.0% (12/30)	30.0% (3/10)	
Asiatic	3.3% (3/90)	0.0% (0/30)	10.0% (1/10)	
Smoking	8.9% (8/90)	13.3% (4/30)	10.0% (1/10)	0.781§
Number of pregnancies	1.9 (1.3)B	1.7 (1.0)	1.1 (0.3)	0.043ƒ
Number of deliveries				
Nulliparous	1.1% (1/90)	0.0% (0/30)	0.0% (0/10)	0.799§
Multiparous	98.9% (89/90)	100% (30/30)	100% (10/10)	
Gestational age (weeks)	40.0 (38–40)	39.5 (38–40)	39.5 (37.2–40.2)	0.808†
Type of delivery				
Vaginal	83.3% (75/90)A,B	30.0% (9/30)	20.0% (2/10)	<0.001§
Cesarean section	13.3% (12/90)A,B	70.0% (21/30)	80.0% (8/10)	
Forceps	3.3% (3/90)	0.0% (0/30)	0.0% (0/10)	
Birth weight (g)	3220.0 (474)	3137 (439)	3117 (543)	0.605ƒ
Apgar score at 1st minute	8.5 (8.0–9.0)B	8.0 (8.0–9.0)	8.0 (8.0–9.0)	0.037†
Apgar score at 5th minute	9.5 (9.0–10.0)B	9.0 (9.0–9.0)	9.0 (8.0–9.0)	0.017†
Time cord clamping and pH analysis	13.9 (3.6)	14.2 (3.3)	16.6 (4.2)	0.506ƒ
pH arterial	7.24 (7.19–7.28)	7.21 (7.17–7.28)	7.22 (7.20–7.29)	0.543†
pH venous	7.29 (7.25–7.34)	7.29 (7.21–7.33)	7.27 (7.23–7.34)	0.770†

pH: hydrogen potential; Kruskal-Wallis †: median (interquartile range); one-way ANOVA ƒ: mean (standard deviation); chi-Square §: percentage (n/N); A: category I vs. category II; B: category I vs. category III; p<0.05.

category II had higher rates of FHR abnormality in intermittent auscultation than CTG category I (30.0 vs. 12.2%, p=0.044, respectively).

There was no significant association between the CTG category and the presence of acidemia at birth (p=0.706), 1-min Apgar score <7 (p=0.260), hospitalization in the neonatal ICU (p=0.605), newborn death within the first 48 h, need for neonatal resuscitation (p=0.637), and composite adverse outcomes (p=0.373) (Table 2). There was not any case of newborn death within 48 h after delivery.

The diagnostic accuracy measures of the CTG categories for identifying acidemia at birth by analyzing cord blood are presented in Table 3. It was observed that all three CTG categories presented low sensitivity and high negative predictive value for identifying acidemia at birth. CTG category I also showed low specificity (29.0%), while categories II and III presented high specificity (78.0 and 92.0%, respectively). CTG proved to be rarely useful in improving the ability to identify truly positive (low positive likelihood ratio values) and truly negative (high negative likelihood ratio values) individuals.

DISCUSSION

This study demonstrated that, compared to CTG category I, CTG categories II and III correlate with a higher prevalence of cesarean sections in low-risk pregnancies without reducing the prevalence of acidemia and other adverse perinatal events[9,13,18].

During fetal life, oxygen supply is dependent on maternal circulatory and respiratory functions, placental perfusion, placental gas exchange capacity, and umbilical and fetal circulations. Changes in any of these values lower the circulating O_2 concentration (hypoxemia). As a result, the fetal tissue concentration of oxygen (hypoxia) decreases, leading to fetal acidemia. The severity of fetal hypoxia depends on the intensity, duration, and frequency of repetition of the event and is associated with each fetus' individual capability of adapting to the situation[19].

The lack of understanding about the individual fetal ability to adapt to hypoxia may lead to the widespread use of intrapartum CTG in low-risk pregnancies in developed countries and tertiary childbirth care centers. Intrapartum fetal surveillance aims to detect fetal hypoxia caused by acute or subacute events during labor that requires medical intervention to reduce the risk of serious complications, such as cerebral

Table 2. Association between cardiotocograph category, indications to perform the fetal evaluation during the labor assistance and adverse perinatal outcomes in low-risk pregnancies.

	Category I (n=90)	Category II (n=30)	Category III (n=10)	p
Indications of CTG				
Bleeding	8.9% (8/90)	6.7% (2/30)	20% (2/10)	0.442
FHR abnormality	12.2% (11/90)[A]	30.0% (9/30)	20.0% (2/10)	0.047
Misoprostol use	30.0% (27/90)	23.3% (7/30)	30.0% (3/10)	0.777
Oxytocin use	37.8% (34/90)	26.7% (8/30)	30.0% (3/10)	0.514
Temperature>38°C	2.2% (2/90)	0.0% (0/30)	0.0% (0/10)	0.637
Meconium	8.9% (8/90)	13.3% (4/30)	0.0% (0/10)	0.442
Adverse perinatal outcomes				
Acidemia at birth	11.1% (10/90)	16.7% (5/30)	10.0% (1/10)	0.706
Apgar score 1st minute<7	6.7% (6/90)	13.3% (4/30)	20.0% (2/10)	0.260
Admission at neonatal ICU	10.0% (9/90)	13.3% (4/30)	20.0% (2/10)	0.605
Need for neonatal resuscitation	2.2% (2/90)	0.0% (0/30)	0.0% (0/10)	0.637
Composite perinatal outcomes	21.1% (19/90)	20.0% (6/30)	40.0% (4/10)	0.373

CTG: cardiotocography; FHR: frequency of heart rate; ICU: intensive care unit. Chi-square test: percentage (n/N). A: category I vs. category II; p<0.05.

Table 3. Measurements of diagnostic accuracy of intrapartum cardiotocography categories for identification of acidemia at birth through umbilical cord blood analysis in low-risk pregnancies.

	OR (95%CI)	Sensibility	Specificity	PPV	NPV	FP	FN	LHR negative	LHR positive
Category I	0.70 (0.25–2.16)	0.62	0.29	0.11	0.85	0.71	0.38	1.31	0.87
Category II	1.61 (0.57–4.80)	0.31	0.78	0.16	0.89	0.22	0.69	0.88	1.41
Category III	0.77 (0.06–5.79)	0.06	0.92	0.10	0.87	0.08	0.94	1.02	0.75

CI: confidence interval; OR: odds ratio; PPV: positive predictive value; NPV: negative predictive value; FP: false positive; FN: false negative; LHR: likelihood ratio.

palsy, hypoxic-ischemic encephalopathy, and neonatal death. The high rate of cesarean sections found in CTG categories II and III is justified because when changes are detected in fetal intrapartum monitoring, actions such as performing maneuvers to improve maternal and fetal oxygen supply are recommended. If the monitoring continues to show alterations after these maneuvers, it is recommended to expedite delivery before the fetus progresses to metabolic acidemia and potential fetal tissue injury[19].

In the present study, although CTG category III presented lower 1- and 5-min Apgar scores than CTG category I, no significant difference was observed in the prevalence of 1-min Apgar score of <7. Apgar scores reflect the neurological, cardiovascular, and pulmonary functions of the newborn, and they are inversely proportional to the duration and intensity of hypoxia. The 1-min Apgar score is an important parameter to assist in the decision about neonatal resuscitation, but it presents a low association with hypoxia or intrapartum acidosis[20]. The 5-min Apgar score is strongly associated with the risk of neonatal death and adverse neurological outcomes, both in the short and long term[21,22]. In the present study, this finding may have corroborated the lack of need for neonatal resuscitation among patients with CTG categories II and III. Conditions such as prematurity, labor trauma, infections, meconial aspiration, preexisting lesions, and medications administered during pregnancy can cause a decrease in Apgar scores[23]. In this study, only pregnancies at term were included to reduce the bias caused by prematurity on the analyzed variables.

There is consensus that a normal FHR pattern, the presence of FHR accelerations, and the absence of decelerations are highly predictive of normal fetal oxygenation. In this case, no additional intervention is required. On the contrary, the presence of recurrent variables and late decelerations, bradycardia, and the absence of FHR variability are predictive of acidemia, determining an urgent resolution of pregnancy[24]. To facilitate the interpretation and decision-making based on the findings of intrapartum CTG and associate these results with a high risk of hypoxia, some scientific entities have created systems for categorizing CTG plots[10,20,25].

Bhatia et al.[26] demonstrated that some CTG categorization systems present similar interobserver agreement when classifying the normal and suspicious categories of hypoxia. Unfortunately, FHR classification does not improve the ability to predict acidemia. A review of the existing FHR algorithms criticized the continuous emphasis placed on describing the morphological characteristics of the decelerations instead of evaluating the fetal capability of adaptation to hypoxia[27]. Additionally, uterine contractions are independently associated with neonatal hypoxia and acidemia[28]. In this study, no difference was observed in arterial and venous pH values even after using the CTG categorization proposed by the American College of Gynecologists and Obstetricians[10]. Moreover, no significant difference was observed in the prevalence of fetal acidemia and adverse perinatal outcomes in CTG categories II and III compared to category I.

In our study, CTG categories had a low positive predictive value for identifying fetal acidemia during the first stage of labor. However, the positive predictive value of CTG category III should be reassessed in light of the duration of labor[29,30] and the presence of terminal bradycardia at the second stage of labor[31]. Our study did not evaluate the association between the duration of labor and fetal acidemia. Cavoretto et al.[29] in a retrospective case-control study on 552 low-risk pregnancies receiving continuous CTG monitoring in labor and immediate hemogas analysis at birth, demonstrated that the risk of neonatal acidemia is directly proportional to the duration of the second stage, irrespective of the presence of CTG abnormalities, increasing 12-fold (1.2–15.3%) from 30 to 180 min. The occurrence of International Federation of Gynecology and Obstetrics (FIGO) 2015 pathological CTG patterns showed a decreasing impact from bradycardia>10 min to decelerations>5 min, recurrent later or prolonged decelerations>30 min, and non-pathological CTG[19]. The risk for acidemia increased moderately across the second stage of labor with non-pathological CTG and quadrupled with pathological CTG requiring expedited delivery. Adjustment for other predictors such as meconium-stained amniotic fluid and nulliparity revealed a significant hazard increase for acidemia associated with pathologic CTG requiring expedited delivery[30]. In our study, we did not perform a multivariate approach with meconium as a covariate due to the small sample size.

As a limitation of this study, based on retrospective analysis, the smaller sample of women in labor who presented CTG category III should be highlighted. This was due to the lower prevalence of this category in obstetric practice in low-risk pregnancies. The analysis was performed with a univariate approach without including a covariate. Further studies comparing different methodologies for the classification of intrapartum cardiotocography in low-risk patients are needed to assess the ability to detect fetal acidemia and predict adverse perinatal outcomes in this population.

CONCLUSION

The three categories of intrapartum CTG presented low sensitivity and a high negative predictive value for identifying

acidemia at birth. When compared to CTG category I, CTG categories II and III showed a higher prevalence of cesarean sections without being associated with a lower prevalence of adverse perinatal outcomes.

AUTHORS' CONTRIBUTIONS

MFT: Data curation. **RSL:** Data curation. **CGP:** Methodology. **EAJ:** Writing – original draft. **PTM:** Investigation. **ABP:** Formal Analysis, Supervision.

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ORIGINAL ARTICLE

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Does telecounseling reduce anxiety and depression during pregnancy? A randomized controlled trial

Emine Koc[1*], Nazlı Baltaci[2], Sümeyye Bal[1]

SUMMARY

OBJECTIVE: This study aims to examine the effect of telecounseling in reducing the anxiety and depression experienced by pregnant women.
METHOD: This randomized control trial was conducted on 100 pregnant women (50 in each intervention and control group). The intervention group received telecounseling with regard to the mother and the fetus as needed between 08:00 h and 20:00 h for 6 weeks at home. The control group received only routine care. Anxiety and depression levels were evaluated at the beginning and end of the study using the Hospital Anxiety Depression Scale.
RESULTS: Anxiety and depression levels were found to be lower in the intervention group than in the control group ($p<0.001$). In the control group, the anxiety score increased from 5.62 to 7.16, and the depression score increased from 4.92 to 5.76 without any intervention ($p<0.001$).
CONCLUSION: This study shows that telecounseling may have an effect on reducing the level of anxiety and depression of pregnant women.
KEYWORDS: Anxiety. Depression. Pregnancy. Telemedicine.

INTRODUCTION

Pregnancy is a unique process in which physiological, social, and psychological changes occur in a woman's life. During pregnancy, most women experience anxiety and depression, both of which are important global health problems[1-3]. Worldwide, the prevalence of anxiety and depression during pregnancy ranges from 6.0 to 57.0% and 8.5 to 44.4%, respectively; however, these rates are considerably higher in underdeveloped and developing countries[3-7]. If anxiety and/or depression cannot be controlled during pregnancy, many problems such as preterm birth, prenatal infections and diseases, low birth weight, lower Apgar scores at birth, postpartum depression, and later childhood emotional difficulties may be encountered[4,7-9]. Therefore, prevention, early recognition, and controlling anxiety and/or depression during pregnancy help protect the health of the mother and fetus. Midwives and nurses can contribute to the reduction of anxiety and/or depression by fulfilling the roles of care, education, and counseling during pregnancy[7].

In the 21st century, phone-based applications have become an effective method for reducing anxiety and depression[10]. These applications are fast, flexible, and accessible[10-12]. In a systematic review, it was determined that telecounseling was effective in reducing problems such as stress, anxiety, and depression; however, no studies focusing on pregnant women were found[13]. The authors of that study recommended increasing the use of telecounseling with the advances in technology today and studies conducted on this subject[13]. The problem of having enough personnel needed to provide adequate health care in the face-to-face healthcare system can be solved by telecounseling; thus, telecounseling can indirectly help solve labor problems[10]. Concurrently, providing remote counseling has positive aspects such as increasing efficiency by reducing hospital and transportation costs, saving time, and providing access to information at any time[13]. There is no study in Turkey that examines the effect of pregnancy-specific telecounseling on anxiety and depression levels. Therefore, the results of this study will make an important contribution to the literature with data from a developing country. This study was performed to examine the effect of telecounseling provided 24/7 in reducing the anxiety and depression experienced by pregnant women before childbirth.

METHODS

Study design and location

This research was designed as a randomized controlled trial with a parallel group pre-test-post-test design. The study was

[1]Ondokuz Mayis University, Faculty of Health Sciences, Department of Midwifery – Samsun, Turkey.
[2]Ondokuz Mayıs University, Faculty of Health Sciences, Department of Nursing – Samsun, Turkey.
*Corresponding author: emine.koc@omu.edu.tr, emine_koc555@hotmail.com
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conducted in accordance with the CONSORT guidelines. The study is registered on clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT05214846). The study was conducted between January 25, 2021 and January 05, 2022, in the obstetric outpatient clinics of a public hospital in northern Turkey.

Sample size and characteristics

Sample size was determined based on a similar study in the literature[14]. Power analysis was performed with effect size d=0.81, a confidence interval of 0.95 (1-β), 0.05 alpha error rate, 0.95 power, and d=0.87 effect size. Accordingly, the minimum sample size was calculated as 68 participants (34 pregnant women in each group). Considering possible data loss, a total of 100 pregnant women, 50 in each group, were included in the study. Healthy pregnant women aged >18 years who had not been diagnosed with any psychiatric disease, had no mental and communication problems, were in their 3rd trimester (between 28th and 32nd gestational weeks), were nulliparous, and had no fetal anomalies and risky pregnancy were included in the study. Those who did not meet the inclusion criteria were excluded from the study.

Data collection tools

The introductory information form developed by the researchers in line with the relevant literature consists of 20 items[3-5,7,9]. The form contains questions related to the socio-demographic characteristics and obstetric histories of pregnant women.

Hospital anxiety depression scale (HADS): HADS was developed by Zigmond and Snaith in 1983 to determine the risk group by scanning for anxiety and depression in those with physical illness[15]. HADS is a self-assessment scale used for screening purposes but not for diagnosis. The scale can also be used to screen for anxiety and depression in the general healthy population and pregnant women[16]. The scale consists of 14 items, seven of which measure anxiety, and the other seven measure depression symptoms. A 4-item Likert scale with a scoring system between 0 and 3 is used. The minimum score obtained from the scale is 0, and the maximum score is 21[15]. Turkish validity and reliability study of HADS was conducted by Aydemir et al.[17]. Cronbach's alpha reliability coefficient of the scale was 0.8525 for the anxiety dimension and 0.7784 for the depression dimension. In this study, Cronbach's alpha reliability coefficient was 0.714 for the anxiety sub-dimension and 0.770 for the depression sub-dimension.

Randomization

Randomization was performed by the researchers with the Quickcalcs graph pad (http://www.graphpad.com/quickcalcs/, date: 18.01.2021).

Collection of data

After the consent of all pregnant women was obtained, and randomization was performed, the sociodemographic and obstetric characteristics and anxiety depression levels were determined via the pre-test. Routine care in both groups continued without any interference during the study period.

Control group: This group only received routine care in the hospital. Six weeks after the pre-test (introductory information form, HADS), participants were contacted telephonically, and the post-test (HADS) was applied.

Intervention group: The day after the pre-test, participants were contacted telephonically and encouraged to ask all questions. The intervention group received telecounseling between 08:00 h and 20:00 h for 6 weeks at home. Counseling included topics related to the mother and the fetus. In cases that required treatment or care for problems that could not be solved by phone, participants were directed to the obstetric outpatient clinic to continue the process. In total, 265 interviews were conducted with 50 pregnant women. Average time for phone calls was 13 min. Post-test was applied to the intervention group when telecounseling was terminated after 6 weeks.

Evaluation of data

To test the relationship between the categorical variables, we applied chi-square-based hypothesis tests. For nominal variables, we used chi-square independence tests and Fisher's exact tests. We carried out independent-samples t-test to compare the anxiety and depression scores between the intervention and control groups. Also, we implemented a paired-samples t-test to compare the pre-post anxiety and depression scores for each intervention and control group.

Ethics

Ethical permission (31.12.2020, decision no. 2020/737, B.30.2.ODM.0.20.08/868) was obtained from a University Clinical Research Ethics Committee, and necessary permissions were also obtained. HADS scale permission was obtained.

RESULTS

Table 1 shows that the groups are sociodemographically similar, and there is no significant difference between the groups. Participants' age, age during marriage, educational status, employment status, level of income, health insurance and family type, and smoking use are similar (p>0.05).

Table 2 shows that the groups are obstetrically similar, and there is no significant difference between the groups. Participants' gestational week, number of pregnancies, abortions, prenatal

educational status, education place, and pregnancy planning status are similar (p>0.05). All the participants (n=100) had wanted pregnancy.

Table 3 shows the comparison of the HADS scores between and within groups. Examination of inter-group differences revealed the presence of a significant difference between the anxiety pre-test scores of the intervention and control groups (p<0.001). However, no significant difference was found between the depression pre-test scores (p=0.169). Post-test anxiety and depression scores were significantly different between the intervention and the control groups (p<0.001). Accordingly, anxiety and depression levels were lower in the intervention group than in the control group.

Examination of intra-group differences revealed that the anxiety score of the intervention group before telecounseling was 7.62, while it was decreased to 5.26 after counseling (p<0.001). Similarly, although the depression score of the intervention group was 5.50 before telecounseling, it decreased to 3.52 after counseling (p<0.001). Accordingly, it was determined that the anxiety level increased by 2.36 points (p<0.001) and the depression level decreased by 1.98 points (p<0.001). In the control group, the anxiety score increased from 5.62 to 7.16 without any intervention (p<0.001). Similarly, the depression score increased from 4.92 to 5.76 without any intervention (p<0.001). Accordingly, it was determined that the anxiety level increased by 1.54 points (p<0.001) and the depression level increased by 0.84 points, but there was no significant difference (p>0.05).

DISCUSSION

According to the results of the study, anxiety and depression levels were found to be lower in the intervention group than in the control group (p<0.001). In the intervention group, the anxiety score decreased from 7.62 points to 5.26 points after telecounseling (p<0.001). Similarly, the depression score

Table 1. Sociodemographic characteristics between the groups.

Variable	Intervention group (n=50)	Control group (n=50)	p-value
Age (years)	25.50±3.86	25.46±4.72	0.963[IT]
Marriage age	24.10±3.78	24.14±6.70	0.971[IT]
Educational status			
Primary and secondary school	9 (18)	22 (44)	0.154[L]
High school	28 (56)	13 (26)	
University	13 (26)	15 (30)	
Employment status			
Employed	37 (74)	40 (80)	0.667[c]
Unemployed	8 (16)	5 (10)	
On leave	5 (10)	5 (10)	
Level of income			
Income lower than expense	20 (40)	9 (18)	0.222[L]
Income equal to expense	24 (48)	39 (78)	
Income higher than expense	6 (12)	2 (4)	
Health insurance			
Present	44 (88)	48 (96)	0.142[F]
Absent	6 (12)	2 (4)	
Family type			
Nuclear	44 (88)	43 (76)	0.88[c]
Extended	6 (12)	7 (14)	
Smoking use			
Present	4 (8)	3 (6)	1.000[F]
Absent	46 (92)	47 (94)	

Categorical variables are presented as n (%) and continuous variables as mean (SD). [IT]Independent-samples t-test; [c]Chi-square test; [F]Fisher's exact test; [L]Linear-by-linear association test.

decreased from 5.50 to 3.52 (p<0.001). This result showed that telecounseling is an effective method of reducing the level of anxiety and depression in pregnant women. Furthermore, a randomized controlled trial showed that post-traumatic stress disorder, depression, and anxiety symptoms of women experiencing traumatic childbirth after birth decreased within 72 h, and in some cases, extended up to 4–6 weeks in the intervention group that received midwife-led brief counseling; however, no immediate change was observed in the control group and anxiety, depression, and stress levels started to decrease after 3 months[18]. In a descriptive study conducted on pregnant women who did not have access to regular antenatal services, approximately 96.43% of pregnant women felt that telemedicine alleviated depression, anxiety, and stress during pregnancy. Concurrently, it was stated that the participants immediately agreed to be contacted telephonically[19]. In this study, it was observed that the participants immediately accepted to participate in the study and recommended it to their relatives.

Prenatal anxiety and depression lead to many complications in the mother and the child. Furthermore, children of mothers who experience high stress during pregnancy are more likely to have cognitive and behavioral problems and are at a higher risk for mental health problems in the future[5,20,21]. The results of this study suggest that telecounseling can be an important practice to prevent these complications, especially in countries with low economic status. In fact, the anxiety level increased from 5.62 to 7.16 points (p<0.001) and the depression level increased from 4.92 to 5.76 in the control group without any intervention; however, the difference was not significant (p>0.05). Despite the absence of intervention in the control group, the significant increase in anxiety in the 6-week period between the pre-test and the post-test may be attributable to the progression of pregnancy and approaching childbirth. The anxieties related to the approaching birth and the neonate, limitation of movement, and other physical symptoms that increase with the progression of the pregnancy reportedly decrease the quality of life and increase the anxiety levels by affecting pregnant women mentally[22]. In such circumstances, having the right information from reliable specialists at any given time relaxes the expecting mothers and keeps them informed about the birth process while reducing their anxiety. According to the results of a meta-analysis, anxiety and depression were more common in nulliparous pregnancies and in low- and middle-income

Table 3. Comparison of the Hospital Anxiety Depression Scale scores between and within groups.

Anxiety	Intervention group (n=50)	Control group (n=50)	Between groups p-value
Pre-test	7.62 (3.16)	5.62 (2.64)	<0.001[IT]
Post-test	5,26 (2.65)	7.16 (2.88)	<0.001[IT]
Within group p-value	<0.001[PST]	<0.001[PST]	
Difference	-2.36 (2.30)	1.54 (2.17)	
Depression			
Pre-test	5.50 (3.13)	4.92 (2.89)	0.169[IT]
Post-test	3.52 (2.85)	5.76 (2.78)	<0.001[IT]
Within group p-value	<0.001[PST]	0.08[PST]	
Difference	-1.98 (2.09)	0.84 (2.40)	

[IT]Independent-samples t-test; [PST]Paired-samples t-test.

Table 2. Obstetric outcomes between the groups.

Variable	Intervention group (n=50)	Control group (n=50)	p-value
Gestational week	32.34±2.17	32.32±2.14	0.963[IT]
Number of pregnancies	1.16±0.865	1.1±0.505	0.673[IT]
Number of abortions	0.16±0.865	0.6±0.313	0. 444[IT]
Participation in educational status			
Attended	22 (44)	19 (38)	0.542[c]
Did not attend	28 (56)	31 (76)	
Where she studied			
Health care personnel	4 (8)	5 (10)	0.621[F]
Internet	15 (30)	9 (18)	
Family/relative	4 (8)	4 (8)	
Pregnancy type			
Planned	47 (94)	48 (96)	1.000[F]
Not planned	3 (6)	2 (4)	

Categorical variables are presented as n (%) and continuous variables as mean (SD). [IT]Independent-samples t-test; [c]Chi-square test; [F]Fisher's exact test.

countries[4]. Therefore, telecounseling, which is a cost-effective method, can be recommended to address these issues.

CONCLUSION

The results of this study showed that telecounseling was effective in reducing the level of anxiety and depression in pregnant women. Furthermore, it was found that when no intervention was made, depression and anxiety levels of pregnant women increased as pregnancy progressed. When taking these results into account, telecounseling by health care professionals may be a viable cost-effective method, especially in low-income countries, places where access to health care is difficult.

Limitations

Owing to its single-centered nature, the results cannot be generalized to all healthy pregnant women.

ETHICS

Ethical permission was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee (31.12.2020, decision no. 2020/737, B.30.2.ODM.0.20.08/868), and necessary permissions were obtained from the institution where the study was conducted.

AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

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Comparison of hepatitis B surface antigen, anti-hepatitis B surface, and anti-hepatitis C virus prevalence in Syrian refugee pregnant women and Turkish pregnant women

Kemal Hansu[1], Ismail Gurkan Cikim[2*]

SUMMARY

OBJECTIVE: In this study, we aimed to determine and compare hepatitis B surface antigen level, anti-hepatitis B surface, and anti-hepatitis C virus positivity in Turkish pregnant women and Syrian refugee pregnant women residing in Turkey.

METHODS: The study was conducted on Syrian refugee pregnant women aged 15–45 years and Turkish pregnant women who applied to state hospital's gynecology and obstetrics outpatient clinics between April 30, 2012, and April 30, 2022. In our study, 136,376 pregnant women (104,629 Turkish and 31,747 Syrian) tested for hepatitis B surface antigen, 72,035 pregnant women (53,070 Turkish and 18,965 Syrian) tested for anti-hepatitis B surface, and 120,611 pregnant women (92,514 Turkish and 28,097 Syrian) tested for anti-hepatitis C virus were included. The patients were divided into six groups for hepatitis B surface antigen, anti-hepatitis B surface, and anti-hepatitis C virus results based on their age: <20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, and >40 years. For each age group, the results of Syrian refugee pregnant women and Turkish pregnant women were compared.

RESULTS: Hepatitis B surface antigen positivity and anti-hepatitis B surface positivity were significantly higher in Turkish pregnant women compared to Syrian refugee pregnant women. Anti-hepatitis C virus positivity was significantly higher in Syrian refugee pregnant women compared to Turkish pregnant women.

CONCLUSION: Based on the available data, we think that hepatitis B surface antigen, anti-hepatitis B surface, and anti-hepatitis C virus tests should be done routinely for pregnant women. Raising awareness among Syrian refugees about the hepatitis B virus vaccine as well as encouraging them to be vaccinated may reduce the negative impact of migration.

KEYWORDS: Hepatitis B. Hepatitis B Surface Antigens. Hepatitis C. Prevalence.

INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are one of the important public health problems worldwide. It has been reported that approximately 2 billion individuals are infected with HBV and approximately 257 million are chronic carriers[1]. In the classification of countries according to hepatitis B surface antigen (HBsAg) prevalence, regions below 2% are considered low endemic areas, those with 2–10% have moderate endemicity, and those above 10% are considered high endemic areas. Turkey falls under the category of moderate endemic areas[2]. While the prevalence of HBV is 0.1% in Ireland, it can be as high as 16.7% in the Philippines and 4.9% globally[3]. In our country, the prevalence of HBV varies between 1.2 and 19.2% depending on the region, and the overall prevalence seems to be 4%[4]. It has been reported that approximately 50 million individuals are diagnosed with HBV every year worldwide and almost half of them acquire the virus in the prenatal period[5]. Intrauterine, intrapartum, and postpartum periods are possible vertical transmission pathways for hepatitis B infection during the perinatal period. While the prevalence of HBsAg in pregnancy is reported to be 0.6–5.8% worldwide, there are studies reporting the prevalence of HBsAg in pregnant women between 1% and 4.3% in our country[6-9].

It is estimated that approximately 210 million individuals worldwide are infected with HCV and 2–3 million new cases are identified every year[10,11]. Similar to HBV infection, the prevalence of HCV infection significantly varies according to geographical regions. It has been reported that the prevalence is 0.4% in developed countries and 12.5% in Egypt[12]. Globally, the prevalence of HCV in pregnant women is 8%, and perinatal transmission in infants born to HCV-infected mothers ranges from 2.7 to 8.4%[13].

[1]Necip Fazil City Hospital, Department of Obstetrics and Gynecology – Kahramanmaraş, Turkey.
[2]Adıyaman University, Faculty of Medicine, Department of Medical Biochemistry – Adiyaman, Turkey.
*Corresponding author: drgurkanc@hotmail.com
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Owing to the civil war that started in Syria in 2011, numerous Syrians had to flee their country and many of those who left settled in Turkey. As of 2022, there have been approximately 3,652,000 Syrians in Turkey. While the estimated population of the city, Kahramanmaraş Province, in 2022 is approximately 1,180,000, it is known that there are approximately 100,000 Syrians who have registered in this city. It is inevitable that large-scale migrations of societies will lead to changes in the prevalence of infectious diseases[14]. In this study, we aimed to contribute to the existing literature by comparing the prevalence of HBsAg, anti-HBs, and anti-HCV in Turkish pregnant women and Syrian refugee pregnant women. It was aimed to know the prevalence of hepatitis B and hepatitis C in pregnant women and to reduce the diseases and deaths that can be caused by viruses by taking the necessary precautions.

METHODS

The study data were obtained and retrospectively reviewed from the information management system of obstetrics and gynecology outpatient clinics of the state hospital in Kahramanmaraş Province between April 30, 2012, and April 30, 2022. Syrian refugee pregnant women and Turkish pregnant women aged 15–45 years who applied to the obstetrics and gynecology outpatient clinics and those who were recommended for HBsAg, anti-HBs, and anti-HCV tests during these applications were included in our study.

In total, 136,376 pregnant women included in the study who were tested for HBsAg were divided into two groups: 104,629 Turkish pregnant women and 31,747 Syrian refugee pregnant women. HbsAg test results were compared according to age groups. Approximately 72,035 pregnant women tested for anti-HBs were divided into two groups: 53,070 Turkish pregnant women and 18,965 Syrian refugee pregnant women. The anti-HBs results were compared according to the age groups of Turkish pregnant women and Syrian refugee pregnant women. Some 120,611 pregnant women tested for anti-HCV were divided into two groups: 92,514 Turkish pregnant women and 28,097 Syrian pregnant women.

Patients were divided into six groups for HBsAg, anti-HBs, and anti-HCV results according to their age: <20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, and >40 years. For each age group, the results of Syrian refugee pregnant women and Turkish pregnant women were compared.

The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin, Turkey. The research was submitted to the Clinical Research Ethics Committee of the Faculty of Medicine, Kahramanmaraş Sütçü İmam University (dated 22.04.2022 and No. 2022/08-04).

The data obtained in the study were statistically analyzed using the SPSS version 22.0 software (SPSS Inc., Armonk, NY, USA). The conformity of the data to normal distribution was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics were expressed as number (n), percentage (%), and median values. For group comparisons, the Pearson chi-square test was used. A value of $p<0.05$ was considered statistically significant.

RESULTS

In total, 136,376 pregnant women included in the study who were tested for HBsAg were divided into two groups: 104,629 Turkish pregnant women and 31,747 Syrian refugee pregnant women. HBsAg test results were compared according to age groups. When all age groups were compared, HBsAg positivity was significantly higher in Turkish pregnant women compared to Syrian refugee pregnant women (1.1% vs. 0.9%, $p<0.005$) (Table 1).

Table 1. Comparison of hepatitis B surface antigen results of Syrian refugee pregnant women and Turkish pregnant women according to the age (Kemal Hansu).

Age (years)	Turkish pregnant women		Syrian refugee pregnant women		p-value
	HBsAg positive		HBsAg positive		
	n/N	Percentage	n/N	Percentage	
<20	65/8,694	0.7	13/5,144	0.3	**<0.05**
20–24	225/28,932	0.8	41/10,072	0.4	**<0.05**
25–29	309/28,036	1.1	82/6,730	1.2	0.42
30–34	314/21,790	1.4	77/4,525	1.7	0.19
35–39	172/12,533	1.3	46/4,437	1.0	0.09
>39	76/4,644	1.6	21/839	2.5	0.09
Total	1,161/104,629	1.1	280/31,747	0.9	**<0.05**

n: number of HBsAg positive patients; N: number of total patients. Bold indicates statistically significant p-values.

About 72,035 pregnant women who were tested for anti-HBs were divided into two groups: 53,070 Turkish pregnant women and 18,965 Syrian refugee pregnant women. When all age groups were compared, anti-HBs positivity was significantly higher in Turkish pregnant women compared to Syrian refugee pregnant women (31 vs. 19.4%, p<0.05) (Table 2).

About 120,611 pregnant women who were tested for anti-HCV were divided into two groups: 92,514 Turkish pregnant women and 28,097 Syrian pregnant women. When all age groups were compared, anti-HCV positivity was significantly higher in the Syrian refugee pregnant women compared to the Turkish pregnant women (0.3 vs. 0.2%, p<0.05) (Table 3).

DISCUSSION

HBV is an infectious agent that can cause fibrosis, cirrhosis, and hepatocellular carcinoma. HBV transmission from an infected mother to the baby can occur during the intrauterine, intrapartum, or postpartum periods. In infants infected perinatally, HBV can become chronic at rates of up to 90%[15]. HCV affects 8% of pregnant women worldwide, and the perinatal transmission rate in infants born to HCV-infected mothers is between 2.7 and 8.4%. In this context, it is important to identify pregnant women who are HBsAg or anti-HCV positive before their delivery. HBV and HCV seroprevalence may differ between countries, as well as in different regions within the same country. It is a well-known fact that large-scale migrations of populations will create differences in the epidemiology of infectious diseases. Accurate epidemiological assessments at the national level are important to accurately determine the current burden of diseases and the impact of existing interventions.

In our study, the prevalence of HBsAg was found to be 0.9% in the Syrian refugee pregnant women and 1.1% in Turkish pregnant women (p<0.05). In studies conducted on pregnant women in different regions of our country, HBsAg seroprevalence was reported between 0.66 and 4.3%[7-9,13,16]. Similar to our study, in the study conducted by Bahat et al., the prevalence of HBsAg was found to be 1.8% in Turkish

Table 2. Comparison of anti-hepatitis B surface results of Syrian refugee pregnant women and Turkish pregnant women according to the age (Kemal Hansu).

Age (years)	Turkish pregnant women		Syrian refugee pregnant women		p-value
	Anti-HBs positive		Anti-HBs positive		
	n/N	Percentage	n/N	Percentage	
<20	3,171/5,161	61.4	1,112/3,551	31.3	**<0.05**
20–24	7,194/15,699	45.8	1,191/7,119	16.7	**<0.05**
25–29	3,125/13,534	23.7	697/3,366	20.7	**<0.05**
30–34	1,275/10,637	11.9	352/2,914	12.0	0.90
35–39	1,115/5,843	19	245/1,519	16.1	**<0.05**
>39	622/2,196	28.3	88/496	17.7	**<0.05**
Total	16,502/53,070	31	3,685/18,965	19.4	**<0.05**

n: number of anti-HBs positive patients; N: number of total patients. Bold indicates statistically significant p-values.

Table 3. Comparison of anti-hepatitis C virus results of Syrian refugee pregnant women and Turkish pregnant women according to the age (Kemal Hansu).

Age (years)	Turkish pregnant women		Syrian refugee pregnant women		p-value
	Anti-HCV positive		Anti-HCV positive		
	n/N	Percentage	n/N	Percentage	
<20	15/7,557	0.2	17/4,852	0.4	0.1
20–24	40/25,670	0.2	16/9,552	0.2	0.8
25–29	50/24,730	0.2	16/6,355	0.3	0.44
30–34	32/19,124	0.2	10/4,249	0.2	0.34
35–39	31/11,184	0.3	8/2,297	0.3	0.56
>39	6/4,249	0.1	4/793	0.5	**<0.05**
Total	175/92,514	0.2	71/28,097	0.3	**<0.05**

n: number of anti-HCV positive patients; N: number of total patients. Bold indicates statistically significant p-values.

pregnant women and 1.1% in Syrian pregnant women[16]. In Gencer's study comparing Syrian refugees and Turkish people in Bursa province, the prevalence of HBsAg in Syrian refugees was 2.5% and that in Turkish people was calculated as 4.7%[17]. However, in both studies, the seropositivity rates in Turkish and refugee pregnant women appear to be higher than in our study. Considering the fact that studies are conducted in varied regions and refugee densities differ, such a result is expected. In a study conducted by Mutlu and Yılmaz in Düzce Province in 2019, comparing the prevalence of HBsAg in Turkish and refugee pregnant women, the prevalence of HBsAg was found to be 0.66% in Turkish pregnant women and 0.87% in the refugee pregnant women[13]. In the mentioned study, although HBsAg positivity in Syrian pregnant women was higher than in our study, it was reported that the positivity rate was not statistically significant. This outcome could have been caused by the study's small patient population, according to Mutlu and Yilmaz. In a study conducted in our province comparing foreign women of reproductive age and Turkish residents between 2014 and 2017, the prevalence of HBsAg was reported to be 1.1% in both groups[18]. Although the prevalence of HBsAg in the Turkish population was the same as in our study, the reason for the lower prevalence in foreign women may be the study's inclusion of a population other than pregnant women.

In our study, the prevalence of anti-HBs was found to be statistically significantly higher in Turkish pregnant women compared to Syrian pregnant women; this result was consistent with other studies (31 vs. 19.4%, p<0.005). According to Mutlu and Yılmaz, the prevalence of anti-HBs was reported to be 22.4 and 38.4% in Syrian and Turkish pregnant women, respectively. Conversely, in the study by Bahat et al.[13,16], the prevalence of anti-HBs was 11 and 26.3% in Syrian and Turkish pregnant women, respectively. As per data from previous studies, it is observed that the rate of vaccination of Turkish pregnant women against HBV is higher than Syrian pregnant women. In 1981, the HBV vaccine was developed; however, owing to the high cost of the vaccine and the varied health policies of countries, it was not simultaneously administered in every country. When pregnant women under 20 years of age are compared, it is noticed that the anti-HBs positivity in Turkish pregnant women is almost twice than that of Syrian pregnant women. Although this situation may reflect the difficulties experienced by the Syrian people in terms of vaccination owing to the civil war that started in Syria in 2011 or the perception that vaccination is neglected, the fact that anti-HBs positivity is lower in Syrian pregnant women in all age groups except the 30–34 age group may be the result of socio-cultural differences and vaccination policies of the Syrian government.

There are studies demonstrating that anti-HCV positivity is between 0.08 and 1.1% in different regions of our country[7,13,16,19]. In our study, anti-HCV positivity was significantly lower in Turkish pregnant women compared to Syrian refugee pregnant women (0.2 vs. 0.3%, p<0.05). In a study, similar to our study, anti-HCV positivity was found to be 0.06% in Turkish pregnant women and 0.43% in refugee pregnant women, whereas, in another study, anti-HCV positivity was reported to be 0.4% in Turkish people and 1.2% in refugees[13,17]. However, unlike our study, Bahat et al. determined in their study that anti-HCV positivity was higher in Turkish pregnant women compared to refugee pregnant women, but the difference was not statistically significant (0.2 vs. 0.1%, p=0.241)[16]. In our study, when we attempted a comparison according to age groups, we observed that the difference was significant above the age of 39 years and not statistically significant in pregnant women younger than 39 years of age.

Owing to the retrospective nature of our study, the inability to obtain the medical history of patients, the inability to differentiate between vaccination or previous infection, and the lack of access to postnatal data constitute the limitations of our study; however, to the best of our knowledge, it has the advantage of being the study with the largest patient population in our country.

CONCLUSION

Based on the current data, we suggest routine testing of pregnant women for HBsAg, anti-HBs, and anti-HCV. Raising awareness among Syrian refugees about the HBV vaccine and encouraging them to be vaccinated may reduce the negative impact caused by migration.

ETHICAL APPROVAL

The study was approved by Kahramanmaras Sutcu ImamUniversity Faculty of Medicine Clinical Researches Ethics Committee with the ethical committee decision dated April 22, 2022, and numbered 2022/08-04 and from Kahramanmaraş Provincial Health Directorate dated 03.06.2022 and numbered 20121. The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin, Turkey.

AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

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Correlation of systemic inflammation biomarkers and disease severity in pregnant women with COVID-19

Özlem Gündüz[1*], Banu Seven[1], A.Seval Ozgu-Erdınc[2], Sule Goncu Ayhan[1], Dilek Sahin[2], Ozlem Moraloglu Tekin[2], Huseyin Levent Keskin[2]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the prognostic value of whole blood parameters, systemic inflammatory indices, and systemic inflammatory markers in pregnant women with COVID-19.

METHODS: In this cross-sectional study, the demographic, clinical, and laboratory data (i.e., whole blood parameters, C-reactive protein, procalcitonin, ferritin, and D-dimer) of 464 pregnant women with COVID-19 who attended a tertiary hospital between January and April 2021 were reviewed. Systemic inflammatory indices (i.e., neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, platelet/neutrophil ratio, and systemic immune inflammation index) were calculated. Asymptomatic and mildly symptomatic pregnant women were classified as Group 1 (n=413), and those with severe disease were classified as Group 2 (n=51).

RESULTS: Lymphocyte count and lymphocyte percentage in whole blood parameters were significantly lower ($p<0.05$), and C-reactive protein, ferritin, and procalcitonin values were higher in Group 2 ($p<0.05$). Systemic inflammatory indices [neutrophil/lymphocyte ratio (4.7±2.9 (1.1–21.2) vs 7.5±4.7 (2.13–23.2)), platelet/lymphocyte ratio (191.1±104.3 (53.0–807.1) vs 269.5±118.9 (105.0–756.0)), systemic immune inflammation index (1,000±663 (209–5,231) vs 1,630±1,314 (345–7,006))] were found statistically significantly higher in severe disease group ($p<0.001$).

CONCLUSION: Evidence in this study indicates that neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic immune inflammation index at first admission are simple, rapid, and inexpensive indices in predicting the prognosis of COVID-19 in pregnant women.

KEYWORDS: COVID-19. Pregnancy. Inflammation. Neutrophil. Lymphocyte.

INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) created an unprecedented global health crisis and affected millions of people. COVID-19 infection often begins with flu-like symptoms but may progress to pneumonia, acute respiratory distress syndrome, multisystemic dysfunction, and death in some patients[1]. The elderly and those with chronic diseases are high-risk individuals for COVID-19 complications. In addition, due to physiological and immunological adaptive changes during pregnancy, the risk of severe disease is higher in pregnant women[2]. According to CDC data covering 400,000 people at reproductive age, pregnant women with COVID-19 are 3 times more likely to be admitted to the intensive care unit, 2.9 times more likely to require invasive ventilation, 2.4 times more likely to require extracorporeal membrane oxygenation, and 1.7 times more likely to die[3].

Early prediction of serious illness is critical for patient triage and management as the COVID-19 pandemic has placed unprecedented strain on the medical system worldwide[4]. Therefore, several studies have focused on available laboratory data to assess and predict clinical severity in patients with COVID-19. The most frequently used test in clinical practice is the whole blood count test. Whole blood parameters [i.e., leukocyte, neutrophil, lymphocyte hemoglobin, hematocrit, platelet, and mean platelet volume (MPV)] and inflammatory indices were used to classify COVID-19 patients. Systemic inflammatory indices [i.e., neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet/neutrophil ratio (PNR), and systemic immune inflammation index (SII:NxP/L)] are ratio indices that are accepted as effective indicators of systemic inflammation and immune balance. As COVID-19 infection is associated with a high inflammation burden, these indices play an important role in the diagnosis, prognosis, and treatment evaluation of the disease[5]. The systemic immune inflammation index is one of the most up-to-date parameters since it has been defined recently[6]. Additionally, studies on COVID-19 patients showed increased

[1]Ankara City Hospital, Ministry of Health, Department of Obstetrics and Gynecology – Ankara, Turkey.
[2]University of Health Sciences, Ankara City Hospital, Ministry of Health, Department of Obstetrics and Gynecology – Ankara, Turkey.
*Corresponding author: dr.ozlem-yasar@hotmail.com
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values of systemic inflammatory biomarkers such as C-reactive protein (CRP), ferritin, procalcitonin, and D-dimer[7].

The aim of this study was to evaluate the prognostic value of whole blood parameters, systemic inflammatory indices, and systemic inflammatory markers in SARS-CoV-2-positive pregnant women.

METHODS

This cross-sectional study included 464 pregnant COVID-19 women (confirmed by PCR test), who were admitted to the COVID-19 service of a tertiary level hospital between January and April 2021, due to obstetric or non-obstetric (presence of COVID-19 symptoms) reasons. Both the Institutional Ethics Committee (E2-21-448) and the Turkish Ministry of Health approved the study. Informed consent was obtained from all patients participating in the study.

Demographic data, symptoms related to COVID-19, oxygen saturation, and laboratory values (i.e., whole blood parameters, CRP, ferritin, D-dimer, and procalcitonin) of the pregnant women at their first admission were examined. A precise diagnosis of COVID-19 infection was arrived at following the detection of SARS-CoV-2 positivity via RT-PCR analysis of nasopharyngeal and oropharyngeal specimens. Only pregnant women with positive PCR test results were included in the study. Subjects with other acute or chronic infectious diseases, hematological disorders, malignancies, and systemic diseases were excluded from the study. Systemic inflammation indices were calculated using data from complete blood count tests.

Patients were grouped as asymptomatic, mildly symptomatic, and severe disease. Those with symptoms such as fever, cough, and sore throat but without respiratory distress were considered mildly symptomatic and those with respiratory rate>24/min and/or SatO2<93% were considered severe disease. Asymptomatic and mildly symptomatic pregnant women were classified as Group 1 (n=413) and those with severe disease were classified as Group 2 (n=51).

Statistical analyses were performed by using SPSS (version 21.0; IBM Corporation, NY, USA). As the data were distributed normally, the descriptive results were expressed as mean±SD for all subjects and each group. Chi-square test was used to compare the categorical variables, and the differences between the continuous variables were analyzed using the independent sample t-test. By performing receiver operating characteristic (ROC) analysis, the threshold value of inflammation indices for disease severity was found. As a result of statistical analysis, $p \leq 0.05$ value was considered statistically significant.

RESULTS

The results of 413 pregnant women in Group 1 (170 asymptomatic and 243 mildly symptomatic) and 51 patients in Group 2 were analyzed. In Group 2, the mean age (30.5±5.3 years vs 28.7±5.5 years) and the gestational week (23.5±10.5 vs 27.2±7.2) were higher ($p<0.05$). When examined based on the gestational periods, 22.0% (n=102) of 464 cases were in the first trimester, 40.7% (n=189) were in the second trimester, and 37.3% (n=173) were in the third trimester. While only 7.8% (4/51) of Group 2 cases were in the first trimester, 40.2% (21/51) were in the second trimester and 51.0% (26/51) were in the third trimester. Severe disease was found to be statistically significantly higher in the third trimester ($p=0.017$) (Table 1).

Of the 10 critically ill pregnant women who needed to be admitted to the intensive care unit, 3 were in the second trimester and 7 were in the third trimester. Six patients were intubated. Maternal mortality was observed in two cases, and both were in the third trimester.

Lymphocyte count and lymphocyte percentage in whole blood parameters were significantly lower in patients with severe disease ($p<0.05$). Other whole blood parameters were found similar between groups. CRP, ferritin, and procalcitonin values were higher in severe disease ($p<0.05$). Systemic inflammatory indices [NLR (4.7±2.9 (1.1–21.2) vs 7.5±4.7 (2.13–23.2)), PLR (191.1±104.3 (53.0–807.1) vs 269.5±118.9 (105.0–756.0)),

Table 1. Demographic data of the groups according to the severity of the disease.

	Group 1 (n=413) (asymptomatic/mildly symptomatic)	Group 2 (n=51) (severe disease)	p-value
Age*	28.7±5.5 (17–44)	30.5±5.3 (19–41)	**0.030**†
Gravida (n)*	2.24±1.35 (1–10)	2.45±1.39 (1–7)	0.288†
Parity (n)*	0.88±1.05 (0–9)	0.98±0.86 (0–3)	0.527†
Abortus (n)*	0.35±0.70 (0–5)	0.43±0.78 (0–3)	0.462†
Gestational week*	23.5±10.5 (5–41)	27.2±7.2 (8–38)	**0.014**†

*Mean±SD (min–max); †independent sample t-test. Statistically significant values are indicated in bold.

SII (1,000±663 (209–5,231) vs 1,630±1,314 (345–7,006))] were statistically significantly higher in pregnant women with severe disease (p<0.001) (Table 2). If the SII threshold value of COVID-19 pregnant women was calculated above 992 (AUC=0.704, 95%CI: 0.632–0.775, p<0.001), it can be accepted that the pregnant women have severe disease with 66.7% sensitivity and 66.8% specificity (Figure 1). The risk of severe COVID-19 disease was four times higher if the SII value was above 992 (OR: 3.986, 95%CI: 2.150–7.387).

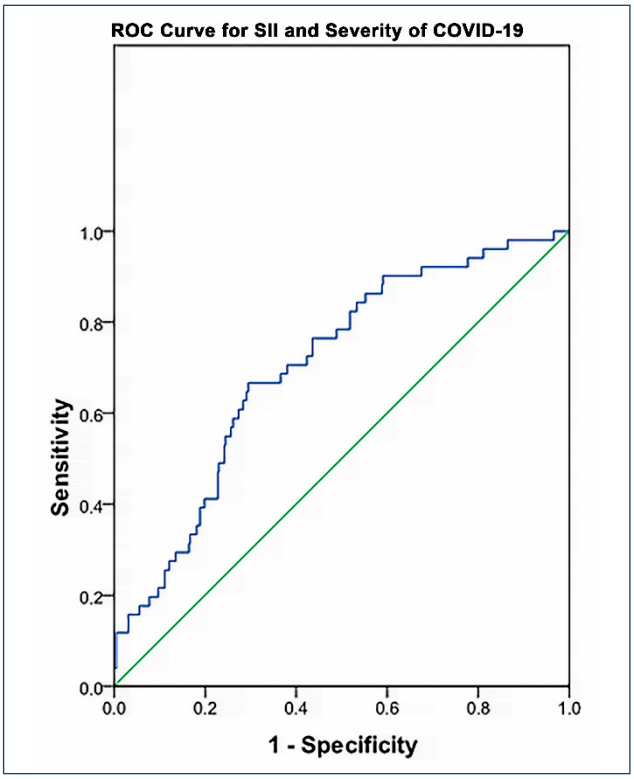

Figure 1. Receiver operating characteristic curve for systemic immune inflammation index and COVID-19 severity in pregnant women.

DISCUSSION

This study holds significance because the participants were pregnant women. In this study, 88.2% of the pregnant women were asymptomatic or mildly symptomatic, and 12.8% had severe disease. The observed rates of disease severity in pregnant women align with recent analyses[8]. Studies during the COVID-19 pandemic have shown that the vast majority of severe cases occur in the third trimester of pregnancy[9]. Similarly, in this study, severe disease was found to be statistically significantly higher in the third trimester (p=0.017).

Maternal immune response, viral clearance, and ultimately, perinatal outcomes may be affected by the timing of infection

Table 2. Laboratory data of the groups according to the severity of the disease.

	Group 1 (n =413) (Asymptomatic / mild symptomatic)	Group 2 (n =51) (Severe Disease)	p
Leukocyte (n/mm³)*	7,345±2,812 (2,680–27,000)	7,256±3,722 (2,780–25,600)	0.830†
Neutrophil (n/mm³)*	5,401±2,274 (1,500–18,400)	5,988±3,483 (1,800–23,200)	0.105†
Lymphocyte (n/mm³)*	1,330±567 (250–4,170)	873±307 (250–1,750)	**<0.001**†
Lymphocyte <800/mm³**	72 (%17.4)	23 (%45.1)	**<0.001**‡
Lymphocyte (%)*	19.0±7.1 (1.0–42.8)	13.7±5.4 (3.9–29.0)	**<0.001**†
Hemoglobin (g/dL)*	12.2±1.3 (8.0–15.6)	11.8±1.4 (8.8–15.0)	0.052†
Hemotocrit (%)*	36.9±3.7 (24.0–47.8)	35.9±4.2 (25.7–45.0)	0.061†
Thrombocyte (n/mm³)*	214,990±58,273 (79,000–419,000)	211,294±55,274 (110,000–366,000)	0.668†
MPV (fL)*	8.7±1.2 (6.4–16.2)	8.7±1.2 (6.7–13.9)	0.724†
CRP (mg/L)*	19.7±21.4 (0.5–156)	61.6±32.0 (0.075–0.142)	**<0.001**†
CRP >50 mg/L**	31 (%7.5)	33 (%64.7)	**<0.001**‡
D-Dimer (µg/L)*	1,587±1,438 (200–1,240)	1,892±1,242 (200–5,500)	0.147†
D-Dimer >1,000 µg/L**	231 (%55.9)	38 (%74.5)	0.011‡
Ferritin (ng/mL)*	35.6±42.1 (1–320)	133.1±215.3 (8–1,341)	**<0.001**†
Ferritin >500 ng/mL**	0	2 (%3.9)	**<0.001**‡
Procalcitonin (µg/L)*	0.05±0.10 (0.03–1.5)	1.47±9.30 (0.03–66.5)	**0.002**†
NLO*	4.7±2.9 (1.1–21.2)	7.5±4.7 (2.13–23.2)	**<0.001**†
PLO*	191.1±104.3 (53.0–807.1)	269.5±118.9 (105.0–756.0)	**<0.001**†
TNO*	45.4±20.0 (10.0–150.3)	42.5±18.5 (10.6–90.0)	0.322†
SII*	1,000±663 (209–5,231)	1,630±1,314 (345–7,006)	**<0.001**†

*Mean±SD (min–max); **n (%); †independent sample t-test; ‡chi-square test. Statistically significant values are indicated in bold.

during pregnancy[10]. Consisting of three stages, the immune regulation process during pregnancy is complicated. While the inflammation required for blastocyst implantation is common in the first trimester of pregnancy, the second trimester ushers the anti-inflammatory and T helper 2 (TH2)-type environment necessary for fetal growth. The immune system switches to an inflammatory and TH1-type condition in the third trimester, which is important for labor and delivery. As the first and third trimesters are proinflammatory, pregnant women infected with SARS-CoV-2 during these trimesters may be at higher risk for excessive responses to the virus (cytokine storm) and severe disease[11]. In our study, the rate of serious cases was higher in the third trimester and lower in the first trimester when compared to other trimesters.

Detecting patients with a poor prognosis seems to be one of the most important goals of medical professionals due to the limited capacity of hospitals during the pandemic. Therefore, many studies have researched clinical, radiological, and laboratory characteristics and risk factors that influence disease prognosis[12,13]. Whole blood tests are the most studied laboratory tests in COVID-19 research because they are simple, rapid, inexpensive, and informative.

SARS-CoV-2 infects T cells through angiotensin-converting enzyme 2 (ACE2) receptors and the CD147-spike protein, lowers CD3+, CD4+, and CD8+ T lymphocyte levels, and increases the number of regulatory T cells. The increase in proinflammatory cytokines during T-cell lymphopenia in severe COVID-19 patients leads to a cytokine storm that results in multiple organ failure and death[14]. As an indicator of disease severity, lymphopenia has been studied in the literature both in the general population and in pregnant women[15]. Consistent with the literature, in our study, lymphocyte count and lymphocyte percentage were found to be significantly lower in the severe group than in the non-severe group ($p<0.05$). The values of other whole blood parameters were similar between groups.

NLR, PRL, and SII are inflammatory indices considered in the diagnosis and progression of a number of inflammatory and infectious disorders, including COVID-19 infection[16]. As hyperinflammation plays an important role in COVID-19 severity, these indices are valuable in reflecting the patient's immune and inflammatory status. The role of NLR in predicting severe disease has been identified in both adults and pregnant women[6,7,17]. In a multicenter study of pregnant women with COVID-19, Lasser et al. found that lymphocyte count and NLR on presentation are extremely sensitive markers of progression to severe illness[18]. PLR on admission was reported to be higher in severe COVID-19 compared to non-severe cases in the general population[7]. Carranza et al. stated that PLR in pregnant women was significantly higher in the severe disease group[19]. Similar to recent reports, we found that NLR and PRL were statistically significantly higher in pregnant women with severe disease ($p<0.001$).

Previous studies have already pointed to SII, calculated from lymphocyte, neutrophil, and platelet counts, as a prognostic marker in patients with cancer and other inflammatory diseases. SII has also been reported as a valuable marker for predicting the clinical course of patients infected with SARS-CoV-2[20-22]. Fois et al. found that the SII value in COVID-19 patients increased mainly due to pulmonary and respiratory damage rather than other clinical comorbidities[14]. Nalbant et al. reported 70.8% sensitivity and 66.0% specificity in estimating disease severity when the cutoff value for SII was ≥813.6[20]. Similar results have been reported in studies examining the role of SII in predicting the need for intensive care and mortality[14,23]. To the best of our knowledge, very few data on the association of SII and disease severity have been reported in pregnant women with COVID-19, although it has been studied in the general population. In our results, SII values in pregnant women with severe COVID-19 were found to be statistically significantly higher than those with mild disease. Also, it is determined that SII, with a cutoff value of 992 (66.7% sensitivity, 66.8% specificity, 19.8% positive predictive value, and 94.2% negative predictive value) can be accepted as a remarkable indicator to predict severe course in pregnant women.

Many studies have suggested some serological parameters as valuable inflammation biomarkers for the diagnosis and risk estimation of severe COVID-19 infection in both the general population and pregnant women[7,24,25]. Demirkol et al. found higher levels of CRP, LDH, D-dimer, ferritin, and leukocyte in patients who deceased compared to those who survived[26]. Arslan et al. observed that NLR, LDH, AST, ALT, ferritin, and procalcitonin levels in severe pregnant COVID-19 patients were significantly higher at the time of admission compared to the mild group[27]. Likewise, Berry et al. reported increased levels of CRP, ferritin, and procalcitonin associated with COVID-19 severity in pregnant women[28]. Consistent with previous reports, we found that CRP, D-dimer, ferritin, and procalcitonin values were significantly increased in the severely infected group in our study ($p<0.05$).

There are several limitations of our study. First, this is a single-center study. Second, although obesity is associated with increased levels of inflammatory mediators[29], the patients' BMIs were not evaluated due to insufficient data in the medical records. Moreover, all pregnant women in our study were unvaccinated; therefore, it may be useful to design a similar study with vaccinated women to evaluate the role of the vaccine

in pregnancy. The final limitation is that different COVID-19 variations display distinct morbidity and death consequences. As a result, we suggest future researchers to update the information on systemic inflammatory indicators, especially for newly discovered variants.

In conclusion, it is very important to determine all clinical and laboratory parameters that will facilitate the risk stratification process in pregnant women with COVID-19 because pregnancy itself may be associated with unpredictable risks and complications. Although many studies in the literature have examined the prognostic value of systemic inflammation indices in COVID-19 patients, only few have focused on pregnant women. The evidence in this study indicates that NLR, PRL, and SII are notable systemic inflammation indices to predict COVID-19 severity in pregnant women. In addition, high CRP, ferritin, D-dimer, and procalcitonin levels were found to be associated with disease severity. These inflammatory markers on admission appear useful in rapidly identifying high-risk patients and reducing adverse maternal and perinatal outcomes.

AUTHORS' CONTRIBUTIONS

ÖG: Conceptualization, Data curation, Formal Analysis, Funding acquisition, İnvestigation, Methodology, Project administration, Resources, Software, Writing – original draft. **BS:** Conceptualization, Data curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft. **ASOE:** Resources, Supervision, Visualization. **SGA:** Formal Analysis, Investigation, Validation, Visualization. **DS:** Conceptualization, Formal Analysis, Project administration, Supervision. **OMT:** Conceptualization, Resources, Supervision, Validation. **HLK:** Conceptualization, Formal Analysis, Methodology, Project administration, Software, Visualization, Writing – original draft.

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ORIGINAL ARTICLE

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Is there an association between endometriosis and thyroid autoimmunity?

Hilal Şerifoğlu[1], Sevcan Arzu Arinkan[2*], Ozge Pasin[3], Fisun Vural[1]

SUMMARY

OBJECTIVE: It has been suggested that non-uterine endometrial implants can express thyroid-stimulating hormone receptors, thus inducing the formation of thyroid-stimulating immunoglobulin. We aimed to compare the autoantibody positivity in patients with and without endometriosis and to determine whether there is a difference in the incidence of thyroid diseases.

METHODS: This prospective observational study was conducted on 102 women who had been operated on for benign gynecological diseases. Cases enrolling in the study were divided into two groups: the study group with endometriosis (n=51) and the control group without endometriosis (n=51). The blood tests for thyroid-stimulating hormone, free thyroxine (fT4), thyroid-stimulating immunoglobulin, and anti-thyroid peroxidase antibody levels were checked.

RESULTS: The mean thyroid-stimulating immunoglobulin level was found to be higher in the endometriosis group than in the control group. However, this difference was not statistically significant. No significant difference was detected between endometriosis and control groups in terms of anti-thyroid peroxidase antibody and thyroid-stimulating hormone levels. The mean fT4 value (0.97±0.13 ng/dL) of the endometriosis patients was found to be significantly lower than the control group (1.08±0.21 ng/dL) (p=0.002; p<0.05). The mean anti-thyroid peroxidase antibody value of cases with bilateral endometrioma (82.21±252.29 IU/mL) was significantly higher than cases with unilateral endometrioma (15.81±83.13 IU/mL) (p=0.028; p<0.05). There is a positive and significant relationship between the size of endometriosis and anti-thyroid peroxidase antibody values (p=0.011; p<0.05).

CONCLUSION: This study points to an association between endometrioma diameter and anti-thyroid peroxidase antibody values which can be a stepping stone for new studies evaluating this hypothesis further.

KEYWORDS: Endometriosis. Thyroid. Autoantibodies. Autoimmunity. Hypothyroidism.

INTRODUCTION

Endometriosis is a chronic inflammatory disease affecting approximately 10% of women of reproductive age[1,2]. The etiology of endometriosis is still not clear despite some theories and many studies investigating the pathophysiology. In addition to genetic predisposition and structural abnormalities in the endometrial tissue, the impaired immune response also plays an active role in the development of endometriosis[1]. Various types of immune system cells were detected in the peritoneal fluids of women with endometriosis [3]. It is suggested that these cells increase susceptibility to disease rather than prevent disease. Endometrial cells could produce thyroid hormones in response to thyroid-stimulating hormone (TSH). Also, it has been suggested that non-uterine endometrial implants can express TSH receptors, thus inducing the formation of thyroid-stimulating immunoglobulin (TSI)[4]. Additionally, an increased risk of comorbidity of autoimmune diseases including systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, autoimmune thyroid disorder, coeliac disease, multiple sclerosis, inflammatory bowel disease, and Addison's disease was suggested[5,6]. Thyroid autoimmunity is the most common autoimmune disease in women of reproductive age and affects 5–20% of the female population[2]. In a cross-sectional study conducted in the USA, it is reported that hypothyroidism was more common in endometriosis patients[4].

In this study, we aimed to compare the thyroid autoantibody positivity in patients with and without endometriosis and to determine whether there is a difference in the incidence of thyroid diseases.

[1]University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Department of Obstetrics and Gynecology – Istanbul, Turkey.
[2]Central Hospital, Department of Obstetrics and Gynecology – Kristianstad, Sweden.
[3]Bezmialem University, Faculty of Medicine, Department of Biostatistics – Istanbul, Turkey.
*Corresponding author: sevcan.arinkan@skane.se

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METHODS

Patients

This prospective observational study was conducted at Haydarpasa Numune Training and Research Hospital between July 2019 and September 2020. The study was approved by the Local Ethics and Clinical Investigation Committee (Approval Number: HNEAH-KAEK 2019/KK/68). Informed consent was taken from all patients.

A total of 102 women who had been operated on for benign gynecological diseases were included in the study. Cases included in the study were divided into two groups: the study group with endometriosis (n=51) and the control group (n=51). The patients who did not have either endometriosis or adenomyosis were included in the control group. All patients underwent transvaginal ultrasonography by an experienced sonographer, and magnetic resonance imaging was added if needed.

The questionnaire included socio-demographic characteristics (i.e., age, education, weight, and height), medical and obstetric history including infertility and the number of spontaneous abortions, smoking habit, contraceptive methods, and other medications currently in use. It also included menstrual cycle patterns, irregularities, dysmenorrhea, and dyspareunia. Participants were also asked if they had ever been diagnosed or suspected of having hypothyroidism or hyperthyroidism, Hashimoto's thyroiditis, or Graves' disease. Patients who had malignancy and type 1 diabetes mellitus or were pregnant were excluded.

Endometriosis diagnose and stage

The endometriosis and control groups were diagnosed surgically. The diagnosis of endometriosis was approved pathologically. The stage of endometriosis was classified based on the definitions of the American Society for Reproductive Medicine[7]. The endometriotic lesions were categorized according to the number and depth of the lesions as follows: minimal stage 1 (scores 1–5), mild stage 2 (scores 6–15), moderate stage 3 (scores 16–40), and severe stage 4 (scores >40).

Laboratory analysis

The primary outcomes were TSH, free thyroxine (fT4), TSI, and anti-thyroid peroxidase antibody (anti-TPO) levels. A sample of 10 mL of venous blood was taken from each patient on an empty stomach. Blood samples were centrifuged at 4,000 rpm for 10 min and analyzed on the same day. TSH and sT4 levels were considered in the evaluation of the thyroid disease status of participants[8,9]. Serum TSH, sT4, and anti-TPO levels were measured by electrochemiluminescence immunoassay (ECLIA) method (Roche Cobas 8000/ISE). Serum TSI levels were measured by the chemiluminescence immunoassay (CLIA) method. A luminous molecule is used as the label in the immunoassay procedure known as CLIA, which is the real "indicator" of the analytical response. This is a quantitative approach for measuring antigens or antibodies based on the alteration in ECL signal or before and after immunoreaction ECLIA[10,11].

Statistical analysis

Descriptive statistics are presented as mean±standard deviation for normally distributed data and median (minimum–maximum) for non-normally distributed data. Shapiro-Wilk test was used for the assessment of the normality of data. The relationship between the categorical variables was examined using the Pearson chi-square, Fisher's exact test, and continuity Yates test. Mann-Whitney U test was used for data that were not normally distributed. Normally distributed parameters were compared among the two groups using the Student's t-test. Kruskal-Wallis test was used to compare the median of more than two independent groups. The associations between the normally distributed data were tested with Pearson correlation analysis. The results were evaluated against a confidence interval of 95% and a p-value <0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS v26, Chicago, IL, USA) was used for statistical analyses.

RESULTS

General characteristics

The general characteristics of the groups are shown in Table 1. Among the endometriosis group, 30% (n=30) had stage 3, 26% (n=26) had stage 4, 22% (n=11) had stage 2, and 22% (n=11) had stage 1 diseases. There was no statistically significant difference between the study and control groups in terms of body mass index (BMI) (p=0.095; p>0.05). Also, the mean height values of the endometriosis group (161.54±5.63 cm) were found to be significantly higher than the control group (158.63±6.78 cm) (p=0.022; p<0.05) (Table 1).

Thyroid parameters in endometriosis compared to non-endometriosis patients

Thyroid-stimulating immunoglobulin levels

There was no significant difference between endometriosis and control groups regarding TSI levels (Table 1). Among endometriosis patients, the mean TSI level was found to be

Table 1. Comparison of demographic characteristics and study variables between groups.

	Endometriosis group (n=51)	Control group (n=51)	p-value
	Mean±SD	Mean±SD	
Age (year)	40.34±9.03	45.94±8.8	[a]0.002*
Parity	1.48±1.19	2.22±1.43	[b]0.010*
Height (cm)	161.54±5.63	158.63±6.78	[a]0.022*
Body mass index (kg/m^2)	27.15±6.1	29.5±7.63	[a]0.095
TSI (U/L)	5.34±4.71	4.79±3.55	0.746
Anti-TPO (IU/mL)	37.06±158.49	38.32±112.78	0.982
TSH (μIU/mL)	1.69±0.88	1.66±1.07	[a]0.564
freeT4 (ng/dL)	0.97±0.13	1.09±0.21	0.002*
	n (%)	n (%)	
Educational status			
Primary	20 (42.6%)	40 (80%)	[c]0.001*
High school	12 (25.5%)	6 (12%)	
University	15 (31.9%)	4 (8%)	
Diseases			
Asthma	8 (16%)	6 (11.8%)	[d]0.743
Psychiatric disorders	5 (10%)	5 (9.8%)	[e]0.617
Rheumatological disorders	2 (4%)	2 (3.9%)	[e]0.684
Constipation	7 (14%)	3 (5.9%)	[e]0.151
Thyroid disorders	6 (12%)	3 (5.9%)	[e]0.234
Migraine	11 (22%)	10 (19.6%)	[d]0.959

[a]Student's t-test; [b]Mann-Whitney U test; [c]chi square test; [d]continuity Yates; [e]Fisher's exact test; and *p<0.05. TSH: thyroid-stimulating hormone; T4: free thyroxine; TSI: thyroid-stimulant immunoglobulin; Anti-TPO: anti-thyroid peroxidase antibody.

higher in women having bilateral endometriosis (5.41±3.52 μIU/mL) compared to the unilateral group (4.57±3.73 μIU/mL). However, this difference was not statistically significant (p=0.416; p>0.05). There was no significant difference between endometriosis stages regarding TSI levels (Table 2). Also, a significant correlation was not detected between TSI level and endometriosis diameter (Table 3).

Anti-thyroid peroxidase antibody levels

No significant difference was detected between endometriosis and control groups regarding anti-TPO levels (Table 1). However, the mean anti-TPO was significantly higher in women having bilateral endometriosis (82.21±252.29 IU/mL) compared to the unilateral group (15.81±83.13 IU/mL) (p=0.028; p<0.05). The mean anti-TPO level was higher among stage 4 patients, but this difference was not statistically significant (p=0.524; p>0.05). A statistically significant correlation was found between endometrioma diameter and anti-TPO values (p=0.011; p<0.05) (Table 3).

Thyroid-stimulating hormone levels

There was no significant difference between groups regarding TSH levels (Table 2). The mean fT4 value (0.97±0.13 ng/dL) of the endometriosis group was found to be significantly lower than the control group (1.08±0.21 ng/dL) (p=0.002; p<0.05). The coexistence of endometriosis and thyroid dysfunction was detected in 6 cases (6/52). Moreover, there was no significant difference between groups in terms of thyroid dysfunction and hypothyroidism (p>0.05).

DISCUSSION

Endometriosis, a chronic, progressive, inflammatory disease, is very common in women of reproductive age. Although etiopathogenesis is still unclear, it is thought that the immune system may play a role in the pathogenesis as well as genetic and epigenetic factors. The impaired immune system might have a role in the pathophysiology of endometriosis. Alterations in humoral immunity were detected in endometriotic cells.

Table 2. Comparison of thyroid-stimulating immunoglobulin, anti-thyroid peroxidase antibody, thyroid-stimulating hormone, and free T4 levels among endometriosis patients.

	Endometrioma side	n	Mean	Median	Std. deviation	Minimum	Maximum	p-value
TSI	Unilateral	35	4.57	3.66	3.731	0.18	12.80	0.416
	Bilateral	16	5.41	3.85	3.520	0.49	11.00	
Anti-TPO	Unilateral	35	15.81	.49	83.138	0.49	486.00	0.028*
	Bilateral	16	82.21	1.18	252.290	0.49	1,000.00	
TSH	Unilateral	35	1.61	1.48	0.873	0.43	3.26	0.394
	Bilateral	16	1.82	1.69	0.899	0.74	3.99	
fT4	Unilateral	35	0.99	0.97	0.126	0.81	1.34	0.232
	Bilateral	16	0.93	0.90	0.128	0.72	1.15	
	Endometriosis stage		**Mean**	**Median**	**Std. Deviation**	**Minimum**	**Maximum**	**p-value**
TSI	Stage 1	12	5.95	6.15	3.321	0.49	11.02	0.064
	Stage 2	11	5.30	3.85	3.886	0.49	12.00	
	Stage 3	15	2.95	2.33	3.379	0.18	12.80	
	Stage 4	13	5.83	5.12	3.532	0.49	11.00	
Anti-TPO	Stage 1	12	2.01	0.49	4.600	0.49	15.87	0.524
	Stage 2	11	68.83	0.49	156.771	0.49	486.00	
	Stage 3	15	1.64	0.49	2.729	0.49	9.95	
	Stage 4	13	80.68	0.53	276.370	0.49	1,000.00	
TSH	Stage 1	12	1.56	1.74	0.779	0.64	2.88	0.498
	Stage 2	11	1.71	1.67	0.867	0.48	3.26	
	Stage 3	15	1.49	1.17	0.909	0.43	3.16	
	Stage 4	13	1.98	1.72	0.946	0.74	3.99	
fT4	Stage 1	12	0.94	0.94	0.140	0.72	1.28	0.172
	Stage 2	11	0.97	0.99	0.137	0.78	1.24	
	Stage 3	15	1.03	1.00	0.131	0.82	1.34	
	Stage 4	13	0.93	0.90	0.095	0.76	1.15	

Mann-Whitney U test and Kruskall-Wallis test, *p<0.05. TSH: thyroid-stimulating hormone; T4: free thyroxine; TSI: thyroid-stimulating immunoglobulin; Anti-TPO: anti-thyroid peroxidase antibody.

Table 3. Correlation analysis between endometrioma diameter and thyroid-stimulating immunoglobulin, anti-thyroid peroxidase antibody, thyroid-stimulating hormone, and free T4 levels.

		Endometrioma diameter (cm)
TSI (U/L)	r	-0.098
	p	0.512
Anti-TPO (IU/mL)	r	0.368
	p	0.011*
TSH (μIU/mL)	r	-0.017
	p	0.908
FreeT4 (ng/dL)	r	-0.009
	p	0.950

Pearson correlation analysis, *p<0.05. TSH: thyroid-stimulating hormone; T4: free thyroxine; TSI: thyroid-stimulating immunoglobulin; Anti-TPO: anti-thyroid peroxidase antibody.

The increased incidence of autoantibodies to histones, polynucleotides, and phospholipids was also reported in endometriosis cases[3]. Recently, Vanni et al. reported autoimmunity as a predictor of advanced-stage endometriosis[12]. In their study, Peynaeu et al. detected changes in thyroid hormone metabolism in the endometriotic cells, in a relevant study conducted on mice. In addition, they reported that thyroid hormones aggravated endometriosis focuses[13]. In a case-control study including 172 endometriosis cases and 117 healthy women, a significant association was not detected between anti-TPO levels and endometriosis. They did not find a significant association between hypothyroidism and endometriosis[14]. Similarly, we detected no significant difference between groups regarding hypothyroidism. Besides, we detected a lower mean fT4 value in the endometriosis group. In their study, Petta et al. detected the ratio of thyroid diseases at 20.9% in the control group

and 26.5% in the endometriosis group. Also, they reported that the ratio of anti-TPO positivity was 14.9% in the endometriosis group and 22.2% in the control group. They concluded that there was no increased risk in endometriosis cases in terms of thyroid diseases and they did not suggest routine thyroid disease screening in endometriosis cases[15]. In our study, we detected no significant difference between endometriosis and control groups in terms of anti-TPO levels. However, we found higher anti-TPO levels in women having bilateral endometriomas compared to the unilateral group. Additionally, we detected a statistically significant correlation between endometriosis diameter and anti-TPO values. We proposed that autoimmunity might be triggered after endometrioma is formed.

Graves' disease is an autoimmune thyroid disease characterized by binding IgG antibodies to the TSH receptor. TSI is considered pathognomonic for Graves' disease and is positive in approximately 98% of patients[16]. There are conflicting results about the association between Graves' disease and endometriosis. While a higher incidence of Graves' disease was reported in some studies, no significant association was proposed by several studies[15,17,18]. Ek et al. detected 93% TSI positivity in endometriosis cases and only 7.9% positivity in the control group. They found a significant association between TSI levels and endometriosis[14]. It was reported that endometrial tissue could be a focus for extrathyroidal hormone production in response to TSH. Also, it was suggested that non-uterine endometrial implants could express TSH receptors and induce TSI formation[4]. In our study, the mean TSI level was found to be higher in the endometriosis group. However, the difference was not significant. Studies with larger sample size are required to determine the association between endometriosis and autoimmune diseases such as Graves having a low incidence in the population (4.6/1,000)[19].

It was reported that autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, hypothyroidism, systemic lupus, and Sjogren's disease were more common in endometriosis patients[20,21]. Recently, Porpora et al. reported a high prevalence of autoimmune diseases in endometriosis patients[6].

There may be a potential link between autoimmune disease and endometriosis. Research has been done on this subject in the past 20 years, but the available data are contradictory. Some of the studies on this subject have only a questionnaire or retrospective design, and the heterogeneity of the study populations makes it difficult to establish a cause-effect relationship.

Some potential limitations of this study should be noted. Age, parity, height, and education status show significant differences between endometriosis and control groups. In accordance with the literature, we detected higher mean height and lower mean parity values in the endometriosis group. By considering the differences in these results, multivariate analyses were performed, and corrections were made by adding factors to the model as covariates and factors. The sample size of the study is also another limitation. By increasing the sample size, the association between endometriosis and autoimmune diseases can be revealed more clearly. The time between blood samples taken and the date of surgery may make a difference in evaluating the association between active endometriosis and autoantibody positivity.

In conclusion, we detected no significant difference between endometriosis and control groups in terms of mean TSI and anti-TPO levels. There was no statistically significant difference between the patients with and without dysmenorrhea and dyspareunia in terms of mean TSI, anti-TPO, TSH, and fT4 values. The mean anti-TPO was significantly higher in women having bilateral endometrioma. A statistically significant correlation was found between endometrioma diameter and anti-TPO values. We hypothesize that autoantibody positivity can be triggered after the formation of endometrioma. This study points to an association between endometrioma diameter and anti-TPO level which can be a stepping stone for new studies evaluating this hypothesis further. Exploring alternative etiologic hypotheses can be assessed to identify alternative immunomodulator therapy and development of new diagnostic tools. If the effect of autoimmunity is evident in the etiopathogenesis of endometriosis, the coexistence of autoimmune diseases could be considered in the follow-up of endometriosis patients. In addition, we detected lower free T4 levels in endometriosis cases. This difference can be considered in endometriosis cases who receive thyroid hormone replacement therapy.

AUTHORS' CONTRIBUTIONS

HS: Data curation, Writing – original draft. **OP:** Formal Analysis. **FV:** Writing – review & editing. **SAA:** Formal Analysis, Methodology, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE

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miR-21, miR-221, and miR-222 upregulation in lung cancer promotes metastasis by reducing oxidative stress and apoptosis

Muhammet Yusuf Tepebaşı[1*], Önder Öztürk[2]

SUMMARY

OBJECTIVE: The purpose of our research was to observe the effects of miR-21, miR-221, and miR-222, as well as their target genes on oxidative stress, lung cancer formation, and metastasis.

METHODS: Positron emission tomography/computed tomography, fiberoptic bronchoscopy, and/or endobronchial ultrasonography were performed on a total of 69 lung cancer patients to detect the presence or absence of metastasis, and the patients were classified based on the types of cancer. Total RNA and miRNA were isolated from the obtained biopsy samples. The quantitative analysis of hsa-miR-21-5p, hsa-miR-222-3p, and hsa-miR-221-3p and their target genes was performed by the RT-qPCR method. In determining oxidative stress, total antioxidant status and total oxidant status in tissue and total thiol and native thiol in blood were determined spectrophotometrically. OSI and disulfide were calculated.

RESULTS: We discovered that the metastasis group had higher levels of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p ($p<0.05$). While TIMP3, PTEN, and apoptotic genes decreased in metastasis, anti-apoptotic genes increased ($p<0.05$). In addition, while oxidative stress decreased in the metastasis group, no change was found in the serum ($p>0.05$).

CONCLUSION: Our findings show that upregulation of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p effectively contributes to both proliferation and invasion by influencing oxidative stress and mitochondrial apoptosis.

KEYWORDS: Lung cancer. Metastasis. miRNA. Oxidative stress. Apoptosis.

INTRODUCTION

Cancer is defined as a disease that causes death as a result of uncontrolled cell growth, tumors, and developing metastases[1]. Tumor cells specifically have abilities such as insensitivity to growth and inhibition signals, unlimited replication potential, avoidance of apoptosis, angiogenesis, and eventually invasion and metastasis. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two types of lung cancer, with NSCLC being the most common. With an increased incidence of new cases and a survival rate of less than 18%, lung cancer is the most common cause of cancer-related death in both sexes[2,3]. The most important factor affecting treatment, prognosis, and survival time in lung cancer is the early detection of the disease[4]. For this reason, it is important to identify metastases in lung cancer at an early stage, to reveal their mechanisms, and to develop diagnostic markers that will prolong life.

In studies on the human genome, it has been determined that miRNAs are effective on genes related to cell growth, differentiation, cell migration, aging, and apoptosis. Previous studies have shown that miRNAs are useful biomarkers in diagnosing cancer, including NSCLC. According to the research, an increase in the expression of miR-21, miR-221, and miR-222 acts by downregulating the PTEN and TIMP3 genes, which play a role in tumor development and survival, as well as invasion and metastasis. Previous studies have shown that an increase in miR-21 promotes poor prognosis and tumor metastasis, especially in NSCLC patients[5]. It has also been reported that miR-221 and miR-222 have tumor suppressive effects on lung cancer and that the increase in miR-222 level worsens the course of the disease[6,7]. Apoptosis, which is defined as programmed cell death, is genetically and biochemically regulated by pro-apoptotic and anti-apoptotic mechanisms in cells. Apoptosis is activated or inhibited by extrinsic and intrinsic pathways. In the intrinsic pathway, factors such as cell stress and DNA damage increase Bax, Bid, Bak, and Bcl-xs, while inhibiting Bcl-2, Bcl-xl, and Bcl-w, thereby increasing apoptosis[8]. These pro-apoptotic and anti-apoptotic genes are located in the PTEN and TIMP 3 gene pathways[9].

[1]University of Süleyman Demirel, Department of Medical Genetics – Isparta, Turkey.
[2]University of Süleyman Demirel, Department of Chest Diseases – Isparta, Turkey.
*Corresponding author: gultepe74@windowslive.com

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An increase in reactive oxygen species (ROS) and a disruption in the balance between oxidants and antioxidants lead to oxidative stress. ROS are produced during events such as mitochondrial electron transport, phagocytic activation against natural stimuli, biosynthesis, and destruction, and they play an important role in the formation of cancer by mediating intracellular survival signaling pathways[10]. In determining oxidative stress in tissues, total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index can be measured, as well as non-enzymatic thiol-disulfide balance in determining oxidative stress in serum[11].

In our study, we aimed to investigate the effects of miR-21, miR-221, and miR-222 on lung cancer metastasis with oxidative stress and apoptosis mechanisms.

METHODS

Patient selection

In Süleyman Demirel University, Department of Chest Diseases, 69 patients were diagnosed with lung cancer using fiberoptic bronchoscopy (FOB) and/or endobronchial ultrasonography (EBUS), and metastasis was detected according to the positron emission tomography/computed tomography (PET/CT) results. Lung tissue samples were placed in Eppendorf tubes after a biopsy was performed by a pulmonologist and stored at -80°C for later use to perform genetic analysis. The blood obtained from the patients was centrifuged, and the serum obtained was stored at -80°C.

Quantitative real-time PCR

The samples were homogenized with the GeneAll RiboEx™ RNA Isolation Kit. miRNA and total RNA were isolated by the manufacturer's kit protocol. The amount and purity of RNA samples to be used in cDNA synthesis were measured with a nanodrop device (Thermo Scientific, USA). Quantitative determinations of RNA samples with purity levels between 1.7 and 2.0 were recorded for use in cDNA synthesis. In the translation of miRNAs to cDNA, a stem-loop primer and miR cDNA synthesis kit were used for each miRNA and converted to cDNA according to the manufacturer's protocol (A.B.T.™ miRcDNA synthesis kit, Turkey). For PTEN, TIMP3, caspase 9, BAD, Bcl-XL, MDM2, and p53 gene cDNA synthesis, cDNAs were synthesized with a cDNA synthesis kit using a random hexamer primer (Atlas Biotechnology, Turkey). Sequences of the U6 gene region were used to normalize miR-21, miR-221, and miR-222. The primer design of the PTEN, TIMP3, caspase-9, BAD, Bcl-XL, MDM2, and p53 genes used in the study was determined using NCBI primer-BLAST, and the actin B (AKTB) gene was used as a reference gene. The obtained cDNAs were studied with the Biorad CFX96 (California, USA) instrument using the A.B.T.™ 2X qPCR SYBR-Green MasterMix (Atlas Biotechnology, Turkey) and the primers mentioned above. The obtained Cq values were normalized and calculated using the formula $2^{-\Delta\Delta Cq}$.

Biochemical analyses

After homogenization, the samples were centrifuged at 10,000 rpm for 10 min to determine the oxidative stress in the lung tissue. The TAS and TOS levels were determined using Erel's colorimetric method on supernatants collected after homogenization using an automated analyzer (Beckman Coulter, USA). Then, the OSI value was determined by calculating OSI=[(TOS, µmol/L)/(TAS, mmol Trolox eq/L)x100][12].

According to the procedure described by Erel et al., thiol and native thiol levels were assessed spectrophotometrically using the Real Assay Diagnostics Commercial Kit and the Beckman Coulter AU5800 autoanalyzer. (Total Thiol-Native Thiol/2) was used to calculate the levels of disulfide (-S-S-).

Statistical analysis

G-Power analysis was performed for all tests, and the effect power was determined to be >90 with the number of patients studied. The results of the expression levels of the normalized miRNAs and genes were analyzed with the Kolmogorov-Smirnov test. A t-test was performed on the values that had a normal distribution. The Mann-Whitney U test was used to analyze those that did not exhibit a normal distribution. AUC values were determined by performing a receiver operating characteristic (ROC) analysis. The IBM SPSS (version 20) program was used to conduct all statistical analyses. Statistics were considered significant at $p<0.05$.

RESULTS

As a result of the evaluations made of the 69 lung cancer patients in the study, it was determined that 32 patients had non-metastasis and 37 patients had metastasis. In addition, in the evaluation made according to the type of lung cancer, it was determined that 42 patients were NSCLC and 27 patients were SSLC. While the mean age was 68.75 and 65.03 years in the non-metastasis and metastasis groups, it was 65.81 and 68.22 years in the NSCLC and SSLC groups, and there was no statistically significant difference ($p>0.05$). In our study, there was no statistical difference in terms of gender in the non-metastasis and metastasis groups ($p>0.05$).

When we compared the expression levels of miRNAs in non-metastasis and metastasis groups, we found that

hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p were significantly increased in the metastasis group (p<0.001, p=0.001, and p=0.003, respectively). There was a significant decrease in the expression levels of TIMP 3 and PTEN genes in the metastasis group (p=0.002 and p<0.001). While a significant decrease was observed in the expression levels of the pro-apoptotic genes Caspase 9, BAD, and P53 in the metastasis group, a significant increase was observed in the anti-apoptotic BCL XL and MDM2 gene expression levels (p<0.001, p=0.037, p=0.001, p<0.001, and p<0.001, respectively) (Table 1).

When the oxidative stress parameters TOS, TAS, and OSI were evaluated in tissues in the non-metastasis and metastasis groups, we determined that TOS and OSI increased in lung cancers but decreased in the metastasis group (p<0.001). There was no significant difference between the groups in TAS levels (p=0.694). There was no significant difference between the groups in serum oxidative stress parameters such as total thiol, native thiol, and disulfide (p>0.05) (Table 2).

In the ROC analysis we performed on non-metastasis and metastasis groups, we found that hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p also had a statistically significant discriminating power with varying sensitivity and specificity values (p<0.001, p=0.001, and p=0.003, respectively) (Table 3).

Table 1. Statistical analysis of hsa-miR-21-5p, hsa-miR-221-3p, hsa-miR-222-3p, and genes in non-metastasis and metastasis groups.

	Non-metastasis (n=32) Mean±SD [CI]	Metastasis (n=37) Mean±SD [CI]	p-value
hsa-miR-21-5p	1.17±0.65 [0.94–1.41]	3.80±1.57 [3.27–4.32]	<0.001**
hsa-miR-221-3p	1.37±1.36 [0.88–1.85]	2.83±2.47 [2.00–3.65]	0.001**
hsa-miR-222-3p	1.28±1.04 [0.90–1.65]	2.34±1.64 [1.81–2.90]	0.003*
TIMP3	1.43±1.11 [1.03–1.83]	0.66±0.50 [0.50–0.83]	0.002*
PTEN	1.24±0.81 [0.96–1.54]	0.49±0.28 [0.39–0.58]	<0.001**
Caspase 9	1.40±1.15 [0.98–1.81]	0.34±0.29 [0.24–0.44]	<0.001**
BAD	1.68±1.22 [1.24–2.12]	0.89±0.69 [0.66–1.12]	0.001*
BCL XL	1.52±1.31 [1.04–2.0]	4.49±2.44 [3.67–5.30]	<0.001**
P53	1.62±1.36 [1.13–2.11]	0.90±0.76 [0.64–1.15]	0.015*
MDM2	1.26±1.03 [0.89–1.63]	3.75±3.08 [2.73–4.78]	<0.001**

SD: standard deviation; CI: confidence interval; TIMP3: metalloproteinase inhibitor 3; PTEN: phosphatase and tensin homolog; Caspase 9: cysteine-aspartic acid protease 9; BAD: BCL2 associated agonist of cell death; BCL XL: B-cell lymphoma-extra large; MDM2: Mouse double minute 2 homolog. **p<0.001, *p<0.05.

Table 2. Statistical analysis table of oxidative stress markers in tissue and blood.

		Non-metastasis (n=32) Mean±SD [CI]	Metastasis (n=37) Mean±SD [CI]	p-value
TOS	Tissue	12.59±3.47 [11.34–13.84]	6.89±3.25 [5.8–7.9]	<0.001**
TAS		1.63±1.67 [1.45–1.81]	1.67±0.36 [1.55–1.79]	0.694
OSI		0.84±0.36 [0.72–0.97]	0.42±0.21 [0.35–0.49]	<0.001**
Total thiol	Serum	256.3±26.5 [247–266]	264.4±28.9 [258–278]	0.08
Native thiol		216.8±21.7 [209–225]	227.5±26.1 [219–236]	0.07
Disulfide		19.8±10.7 [15.9–23.6]	17.7±6.74 [15.4–19.9]	0.32

TOS: total oxidant stress; TAS: total antioxidant stress; OSI: oxidative stress index; SD: standard deviation; CI: confidence interval. **p<0.001.

Table 3. ROC analysis of miRNAs in non-metastasis and metastasis groups.

Non-metastasis and metastasis groups						
	AUC	Cutoff	95%CI	Sensitivity %	Specificity %	p-value
hsa-miR-21-5p	0.979	>2.05	0.95–1.00	94.59	90.63	<0.001
hsa-miR-221-3p	0.733	>1.271	0.611–0.856	70.27	71.88	<0.001
hsa-miR-222-3p	0.707	>1.533	0.584–0.830	56.76	81.25	0.003

DISCUSSION

Previous studies have revealed that worsening prognosis in lung cancer is closely related to tumor formation and metastasis and that early diagnosis affects survival[13]. Therefore, we tried to determine the relationships of miR-21-5p, miR-221-3p, and miR-222-3p, which are known to be effective in tumor formation and metastasis in both NSCLC and SSLC types of lung cancer. We also aimed to reveal the mechanisms of action of these miRNAs and their target genes in oxidative stress and mitochondrial apoptotic processes.

Previous studies have also indicated that miR-21 upregulation contributes to tumor growth and invasion by downregulating the tumor suppressor PTEN gene[14,15]. Li et al. reported that miR-21 inhibited apoptosis and caused invasion through the AKT/cleaved caspase 3/MMP-2/MMP-9 pathway in NSCLC cell lines[16]. Chen et al. reported that miR-21 plays a role in the apoptotic process by downregulating the PTEN and TIMP3 genes[17]. In our study, we found that hsa-miR21-5p was upregulated in the metastasizing group in lung cancer, causing inhibition of the PTEN gene and a decrease in the expression of caspase-9, BAD, and P53 genes. In addition, we determined that anti-apoptotic genes also contribute to cell proliferation and invasion by causing an increase in BCL-XL and MDM2.

In a study conducted on NSCLC cancer cells and published in 2015, Yamashita et al. stated that the effects of miR221 and miR222 occur in the cell cycle or through apoptosis[18]. Zhang C et al. reported that the downregulation of miR-221/222 affects cell proliferation and mitochondrial-mediated apoptosis in human epithelial cancer cells through PUMA, a member of the BCL2 family[19]. Garofalo et al. reported that miR-221 and 222 increased tumor formation in NSCLC by causing downregulation in the PTEN and TIMP3 genes[20]. Guo Y et al. reported that miR-221/222 has an increasing effect on tumor formation and proliferation in lung cancer cells[21]. In our study, we found that while hsa-miR-221-3p and hsa-miR-222-3p were upregulated in patients with metastasis, there was downregulation in the PTEN and TIMP3 genes, as well as a decrease in pro-apoptotic genes (caspase 9, BAD, and P53) and a significant increase in anti-apoptotic genes (BCL-XL and MDM2).

The resulting cellular stress activates the intrinsic apoptotic pathways, which causes pro-apoptotic Bax, Bid, Bak, and Bcl-xs activation and a decrease in anti-apoptotic Bcl-2, Bcl-xl, and Bcl-w[8]. Yuan et al. reported that the upregulation of miR-21-5p prevents oxidative stress-induced apoptosis[22]. Jiang et al., in their study investigating the TGF-β1-miR-21-ROS pathway in non-small-cell lung cancer cells, determined that increased TGFB1 expression caused an increase in ROS, miR-21, and DNA damage. However, there is no information about its effects on the metastatic process[23]. Stephanie et al. reported that the regulation of miR 221 inhibits apoptosis against oxidative stress[24]. Şener et al. evaluated the balance of thiol/disulfide in lung cancer and reported that they could not find a significant difference between the metastasis and non-metastasis groups[25]. In our study, when we compared the oxidative stress parameters in the tissue metastasis and non-metastasis groups, we determined that TOS and OSI were decreased in the metastasized group, but there was no significant difference in terms of TAS levels. When we evaluated oxidative stress in serum, we could not find any difference in terms of thiol-disulfide balance.

Our study showed that it reduced apoptosis with the effect of gene pathways related to the upregulation of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p in patients with lung cancer metastasis. In addition to our findings, our study has some limitations. Our study is a single-center study, and the use of glutathione peroxidase (GPx) and superoxide dismutase (SOD) in the evaluation of oxidative stress in tissues and the TUNEL test in the evaluation of apoptosis will support the results of the study.

CONCLUSIONS

In this study, we determined that decreased oxidative stress and apoptosis in the tissue contributed to the development of metastasis as a result of upregulation of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p in patients with lung cancer. However, we suggest that more studies are needed on this subject.

CONSENT TO PARTICIPATE

Consent form was obtained from all patients participating in the study.

ETHICS APPROVAL

This study was approved by Isparta Süleyman Demirel University Medical Faculty Ethics Committee (dated: 01.04.2022, No. 110).

AUTHORS' CONTRIBUTIONS

MT: Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. **ÖÖ:** Data curation, Supervision, Validation, Writing – review & editing.

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ORIGINAL ARTICLE

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Thrombocytosis in children

Altay Babacan[1], Feray Ferda Şenol[2*]

SUMMARY

OBJECTIVE: We aimed to investigate the frequency and causes of thrombocytosis in patients admitted to the Department of Pediatric Hematology and Oncology of Elazig Fethi Sekin City Hospital, Elazig, Turkey.

METHODS: Between 2019 and 2021, the laboratory parameters of 2,500 patients admitted to the Hematology Department were studied. During this examination, 319 (12.76%) patients were found to have thrombocytosis. Demographic characteristics (age and gender), hematologic parameters (hemoglobin, white blood cells, and platelets), and ultimate diagnoses ot the cases were recorded from their files.

RESULTS: Of these 319 patients with thrombocytosis, 197 (1.8%) were male and 122 (38.2%) were female, and the mean age was 72.0±69.0 (1–216) months. The median platelet count of the patients was 590.43±280.12/μL (450,000–750,000). The most common cause of secondary thrombocytosis was infection, accounting for 37.9% of all patients. Other common causes were sickle cell anemia (21%), iron deficiency anemia (15.4%), colloid tissue disease (6.6%), hemolytic anemia (5.0%), splenectomy (4.5%), and other causes (9.7%).

CONCLUSION: In our study, infections were the most common cause of thrombocytosis. In addition to infections, sickle cell anemia and iron deficiency anemia should also be considered in the differential diagnosis of thrombocytosis.

KEYWORDS: Child. Etiology. Thrombocytosis.

INTRODUCTION

Thrombocytosis, also called thrombocythemia, is generally defined as a platelet count that is above the upper limit. The most commonly accepted cutoff value for normal is <450,000/μL. Platelet counts in the range of 450,000 to 700,000/μL are considered mild, between 700,000 and 900,000 /μL are considered moderate, between 900,000 and 1,000,000/μL are considered severe, and values above 1,000,000/μL are considered extreme thrombocytosis[1]. The main medical complications of thrombocytosis are hemorrhage and thrombotic events, but thrombocytosis often occurs without symptoms. Platelet counts greater than 1,500,000/μL carry an increased risk for bleeding. The most common cause of an increased platelet count is reactive (secondary) thrombocytosis. Secondary thrombocytosis is usually a normal physiological response to coexisting inflammation or surgery. In secondary thrombocytosis, the elevated platelet levels are the result of an extrinsic process (chronic or acute inflammation) that stimulates megakaryocytopoiesis. Bacterial infections, viral infections, iron deficiency, hemolytic anemia, tissue damage, asplenia, malignancies, autoimmune diseases, and drugs are triggers of secondary thrombocytosis[2]. Secondary thrombocytosis is commonly seen in children with a variety of clinical conditions. The most common cause of secondary thrombocytosis in children is respiratory infection[3].

Considerable differences were described in the epidemiology and the clinical presentation of thrombocytosis in children when compared to adults[4]. An elevated platelet count in pediatrics is usually a common incidental finding in hospitalized and outpatient children. Thrombocytosis in children is typically transient, occurring secondary to various underlying medical, and often inflammatory disorders as an increase in platelet count is part of the acute-phase response. Rarely, persistent thrombocytosis may be the result of inherited or acquired genetic mutations. The incidence of essential thrombocytosis is 0.6–2.5 per 100,000[5]. According to the World Health Organization guidelines, the persistent diagnosis of essential thrombocythemia requires a platelet count of ≥450,000/μL in patients with thrombocytosis, and it should be determined whether thrombocytosis is primary or secondary. The criteria of the World Health Organization are often used for diagnosis[6].

In our study, we aimed to determine the frequency of thrombocytosis in childhood and the causes of thrombocytosis among a large series of our patients who were admitted to our outpatient clinic. Thus, we aimed to review our findings

[1]Ufuk University, Faculty of Medicine, Department of Pediatric Hematology and Oncology – Ankara, Turkey.
[2]Elazig Fethi Sekin City Hospital, Department of Microbiology and Clinical Microbiology – Elazig, Turkey.
*Corresponding author: drferdasenol@yahoo.com

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and put forth our data to help create institutional, local, and international algorithms.

METHODS

The demographic characteristics and laboratory parameters of 2,500 patients aged 1–216 months who were admitted to our pediatric hematology outpatient clinic were retrospectively analyzed. In this analysis, patients with a platelet count >450,000 µL were examined. Patients' age, gender, thrombocyte counts, hemoglobin and white blood cell values, clinical findings, and ultimate diagnoses were recorded. In addition, patients were classified into three age groups, namely, 1–60 months, 61–120 months, and 121–216 months, to evaluate the frequency and factors of thrombocytosis according to age groups.

Statistical analysis

A statistical analysis of the data obtained from the study was performed using the Statistica Version 20.0 program. Descriptive statistics were used to summarize the data. Continuous variables such as age, mean, standard deviation, minimum and maximum values, platelets, white blood cells, and hemoglobin were summarized as median, 1st (Q1), and 3rd (Q3) quartile values. Categorical variables such as gender, age groups, and patient groups were summarized as numbers and percentages.

The conformity of the data to the normal distribution was determined by using the Shapiro-Wilk test. Due to the lack of conformity with the normal distribution, the medians of two independent groups were compared with the nonparametric Mann-Whitney U test and the medians of more than two independent groups with the nonparametric Kruskal-Wallis test. Dunn's test, one of the multiple comparison tests, was used to determine the groups that were found to be different as a result of the comparisons. The statistical significance level was taken as $p<0.05$ for all comparisons.

RESULTS

In the study, it was determined that 319 patients (12.76% of the total) met the inclusion criteria, of whom 197 (61.8%) were males and 122 (38.2%) were females, with a mean age of 72.0±69.0 months (min-max; 1 month–216 months) (Table 1).

The median platelet count of the patients was 510,000/µL (min-max; 450,000–750,000), the white blood cell count was 10,500/µL (min-max; 8,260–14,280), and the hemoglobin value was 11.5 g/dL (min-max; 9.0–12.0). While the median platelet value was 517,000/µL (min-max; 480,500–638,500) in female patients, this value was 516,000/µL (min-max; 478,000–634,000) in male patients, and no statistical difference was determined between these groups ($p>0.05$). All the patients had secondary thrombocytosis, and the most common cause was infection with a rate of 37.9%. Other common causes include sickle cell anemia (SCA, 21%), iron deficiency anemia (16.4%), colloid tissue diseases (6.6%), hemolytic anemias (5.0%), and patients undergoing splenectomy (4.4%) (Table 1). In addition, no clinical findings related to thrombocytosis were observed in any of the patients, and thrombocytosis treatment was not given except for hydration. When the thrombocyte values of the patients were examined according to age groups, median platelet values were detected as 506,000/µL for 1–60 months, 507,500/µL for 61–120 months, and 553,000/µL for 121–216 months. The difference between the median platelet values of the age groups 1–60 months and 121–216 months was statistically significant ($p<0.01$). The difference between the groups of 61–120 months and 121–216 months was also statistically

Table 1. Age groups, gender, and pathogenesis data of included patients.

Variables	n	Value
Age (months)	319	72.0±69.0 (average)
Age groups	n	%
1–60 months	139	43.6
61–121 months	75	23.5
121–216 months	105	32.9
Hematological parameters*	319	
Platelet count (/µL)		510,000 (450,000–750,000)
White blood cell count (/µL)		10,500 (8,260–14,280)
Hemoglobin value (g/dL)		11.5 (9–12)
Gender	n	%
Male	197	61.8
Female	122	38.2
Etiology	n	%
Infection	121	37.9
Sickle cell anemia	67	21.0
Iron deficiency anemia	49	15.4
Collagen tissue disease	21	6.6
Hemolytic anemia (OIHA, HV, etc.)	16	5.0
Splenectomy applied patients	14	4.4
Others	31	9.7

*Values are given as mean (min–max).

significant (p<0.01). Among the age groups, the highest platelet count was observed in pediatric patients aged between 121 and 216 months (Table 2).

Infections (55.4%) and iron deficiency anemia (18.7%) for children aged 1–60 months, and, similarly, infections (30.7%) and iron deficiency anemia (20.0%) for children aged 61–120 months were the most common causes of thrombocytosis. SCA (55.2%) and infections (20.0%) were the most common causes for the age group of 121–216 months (Table 3).

DISCUSSION

In our study, the frequency of thrombocytosis among patients admitted to the pediatric hematology outpatient clinic was investigated. In this study, we found that 12.76% of all patients had thrombocytosis, and we observed that all patients had secondary thrombocytosis, which is consistent with the literature. Thrombocytosis in children is often secondary and usually occurs when various underlying diseases stimulate the production of megakaryocytes. In previous studies conducted on children, the frequency of primary thrombocytosis was below 1/10,000,000 per year in children under 14 years of age, while the frequency of secondary thrombocytosis was estimated to be between 4.5 and 15.0% in hospitalized children[7,8]. Although the causes and formation mechanisms of primary thrombocytosis are not fully elucidated, infections were identified as the most common causes of secondary thrombocytosis in many studies. In a study, the most common causes of severe thrombocytosis were infections in 80 (56.8%) patients, anemia in 21 (14.9%) patients, and autoimmune diseases in 14 (9.9%) patients[9]. Clemens Stockklausner et al. reported that the most common causes were infections (49.5%), postsplenectomy (7.8%), Kawasaki disease (6.4%), tissue damage (4.5%), blood diseases (3.7%), malignancies (3.7%), renal diseases (3.2%), chronic inflammation (1.8%), essential thrombocythemia (0.5%), and other causes (3.7%)[10]. In some other studies, the frequencies of infections in secondary thrombocytosis were 39, 53, 30, and 63%, respectively[11-14]. In our study, infections (37.9%) were also the most common cause of secondary thrombocytosis in accordance with the previously published studies.

The incidence of thrombocytosis secondary to anemia was reported as 12.0, 3.7, and 8.5% in various studies[12-14]. Only iron deficiency anemia was found in 17.2 and 8.0% of the cases in two studies[8,13]. In our study, 16.4 and 5.0% of patients had iron deficiency anemia and hemolytic anemia, respectively, with a higher rate of secondary thrombocytosis when compared to previously published studies. Additionally, we observed that the frequency of iron deficiency anemia in secondary thrombocytosis was higher in younger ages. We estimate that high rates of secondary thrombocytosis due to iron deficiency may be associated with the high rates of iron deficiency anemia in childhood, which are as high as 70–80% in our study region in Turkey[7]. In addition, an important point we determined in our study is that 21% of our cases with thrombocytosis were SCA patients. SCA

Table 2. Platelet values of patients with thrombocytosis according to gender and age groups.

Variables	Median (Q1–Q3)	p-value
Gender		
Male	516,000 (478,000–634,000)	>0.05
Female	517,000 (480,500–638,500)	
Age groups (months)		
1–60	506,000 (477,000–579,000)	
61–120	507,500 (477,500–560,750)	<0.0001
121–216*	553,000 (485,000–700,000)	

*Difference making variable.

Table 3. Causes of thrombocytosis based on the age group of the patients.

Causes of thrombocytosis	Age groups						Total	
	0–60 months		61–120 months		121–216 months			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Infection	77	55.4	23	30.7	21	20,0	121	37.9
SCA	2	1.4	7	9,3	58	55.2	67	21.0
Iron deficiency anemia	26	18.7	15	20.0	8	7.6	49	15.4
Collagen tissue disease	11	7.9	5	6.7	5	4.8	21	6.6
Hemolytic anemia	7	5.0	7	9.3	2	1.9	16	5.0
Splenectomy applied patients	3	2.2	7	9.3	4	3.8	14	4.4
Others	13	9.4	11	14.7	7	6.7	31	9.7

is a congenital hemolytic anemia with inflammation. In a study, 53% of patients with thrombocytosis had homozygous SCA, which is consistent with our study[15]. The occurrence of thrombocytosis in both acute and chronic inflammation in patients with SCA and autosplenectomy is an expected situation.

CONCLUSION

The most common cause of thrombocytosis in our study was infections, while SCA and IDA were the other most common respective causes of secondary thrombocytosis. In addition to the most common cause of thrombocytosis due to infections, SCA and IDA should also be considered in the differential diagnosis of thrombocytosis in children, especially in areas where iron deficiency is prevalent.

CONSENT TO PARTICIPATE

All patients involved in this study read and signed the "In-formed volunteer consent form."

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

ETHICAL APPROVAL

Ethics approval and consent to participate: Ethics approval was obtained by the Ethics Committee of Elazig Firat University, Elazig, Turkey, with protocol number E-02.2022-6854.

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AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

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Psoriasis and associated risk factors: a cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health

Marcella Cherubin[1], William Rodrigues Tebar[2], Vandrize Meneghini[2], Isabela Martins Bensenor[2*]

SUMMARY

OBJECTIVE: This study investigated the association of psoriasis with cardiovascular risk factors and psychological aspects among participants of the Brazilian Longitudinal Study of Adult Health.

METHODS: This is a cross-sectional study from the baseline data of the Brazilian Longitudinal Study of Adult Health cohort, collected between 2008 and 2010 in six state capitals of Brazil (i.e., Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo, and Vitória). Participants were active and retired civil servants from college and research institutions, aged between 35 and 74 years. Exclusion criteria included the intention to quit working at the institution, pregnancy, severe cognitive impairment, and, if retired, residence outside of a study center's corresponding area. Psoriasis case identification was based on a previous medical diagnosis of psoriasis. Cardiovascular risk profile, psychological aspects, and sociodemographic variables were investigated.

RESULTS: Data from 15,105 participants were analyzed (mean age of 52.3 years, 51.3% women). The prevalence of psoriasis was 1.6% (n=236). Psoriasis was associated with higher education (OR 1.94 [CI 1.07–3.52]), health insurance plan (OR 1.56 [CI 1.08–2.25]), central obesity (OR 1.63 [CI 1.10–2.40]), smoking status (former OR 1.40 [CI 1.03–1.88]; current OR 1.61 [CI 1.08–2.40]), and very bad self-perception of health (OR 7.22 [CI 2.41–21.64]), remaining significant even after multivariate adjustment. Self-reported Black participants were less likely to have psoriasis (OR 0.45 [CI 0.26–0.75]).

CONCLUSION: In a sample of healthy workers, psoriasis was associated with central obesity, smoking, and a very bad self-perception of health, which may contribute to future cardiovascular disease.

KEYWORDS: Psoriasis. Cardiovascular risk factors. Central obesity. Smoking. Self-perception.

INTRODUCTION

Psoriasis is one of the most common inflammatory skin disorders, with a prevalence between 0.7 and 3.0% and great variability based on the geographical region of the world[1]. Psoriasis has been associated with frequent comorbidities such as diabetes and obesity[2].

There are conflicting data about the association of psoriasis and cardiovascular diseases, with some studies showing positive associations[3] and others reporting no association at all[4]. The presence of psoriasis considerably increased the risk of myocardial infarction and stroke[3], and a less healthy profile of cardiovascular risk factors was seen in patients with psoriasis compared to the general population[5]. On the contrary, prospective data from the Rotterdam Study described a similar cardiovascular risk in a sample with a majority of mild cases of psoriasis compared with participants without the disease[4].

Besides, psoriasis also involves a psychological burden, given the emotional and social impact on the patient's life[6]. Depression is currently a risk factor for cardiovascular diseases to be considered in patients with psoriasis[7]. Other psychosocial risk factors such as quality of life and self-perception of health may be decreased in patients with psoriasis[8,9].

Brazil is a middle-income country with great climate diversity, ethnicity, and socioeconomic status, with a higher psoriasis prevalence in the Southeast and South regions[10], probably associated with better access to health care. The prevalence of psoriasis in Brazil's state capitals ranges from 1.1 to 1.5%[10]. However, few studies investigated the association of psoriasis with traditional cardiovascular risk factors and psychological aspects in low- and middle-income countries such as Brazil[5,11], mostly with small samples.

This study aimed to investigate the association of psoriasis with cardiovascular risk factors and psychological aspects among participants of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

[1]Instituto de Medicina, Estudos e Desenvolvimento, Faculdade Meridional – Passo Fundo (RS), Brazil.
[2]Universidade de São Paulo, Hospital Universitário, Centro de Pesquisa Clínica e Epidemiológica – São Paulo (SP), Brazil.
*Corresponding author: isabensenor@gmail.com
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METHODS

The Brazilian Longitudinal Study of Adult Health is a prospective cohort study of 15,105 civil servants (aged 35–74 years), active or retired employees of higher education and research institutions from six different Brazilian cities. The exclusion criteria included the intention to quit working at the institution, pregnancy, severe cognitive impairment, and, if retired, residence outside of a study center's corresponding area. The information about the ELSA-Brasil sampling recruitment protocol is found elsewhere[12,13]. This study was a cross-sectional analysis using baseline data (2008–2010) from the entire sample of the ELSA-Brasil study. The study protocol was standardized and approved by the Ethic Board of all six centers: Federal University of Bahia (process 027/06), University Hospital from University of São Paulo (process 669/06), Oswaldo Cruz Foundation (process 343/06), Federal University of Minas Gerais (process 186/06), Porto Alegre Clinical Hospital (process 194/06), and Federal University of Espírito Santo (041/06). All participants signed an informed consent form.

Psoriasis

A previous medical diagnosis of psoriasis was informed by a specific question: "Have you been previously told by a physician that you had/have psoriasis?" If the participant responded yes to this question, the year of medical diagnosis was also recorded. This information was obtained during the 9-year follow-up visit, and based on the reported year of diagnosis, we identified prevalent cases at baseline. In addition, spontaneous report about the medical diagnosis of psoriasis at baseline data collection was also considered for case identification.

Cardiovascular profile

The Brazilian Longitudinal Study of Adult Health participants were assessed by standard examinations and questionnaires[13]. Anthropometric measurements were obtained using international standard criteria[12,14]. Body mass index (BMI) was calculated (weight (kg)/height² (m²)) and classified as obesity if BMI³30.0 kg/m². Central obesity was defined as a waist circumference (WC)³88 cm for women and WC³102 cm for men. Hypertension was defined as systolic BP³140 mmHg or diastolic BP³90 mmHg[14] or the current use of antihypertensive medication. Diabetes was defined as a fasting plasma glucose ³126 mg/dL, a 2-h plasma glucose of ³200 mg/dL (5.17 mmol/L) after an overload of 75 g of glucose, glycated hemoglobin (HbA1c)³6.5, or self-reported previous medical diagnosis or use of medication for diabetes. Dyslipidemia was identified as low-density lipoprotein (LDL) cholesterol ³130 mg/dL or self-reported use of lipid-lowering medication.

Covariates

Self-reported information about sex, age (years), race (white, brown, black, and other), education attainment (less than high school, high school, and some college or complete college or more), smoking status (never, former, or current), current alcohol consumption (yes or no), marital status (not single or single), health perception (very good, good, regular, bad, or very bad), and having a private health insurance plan (yes or no) were included as covariates. In addition, depression and anxiety were evaluated using the Revised Clinical Interview Schedule[15], and physical activity was assessed by International Physical Activity Questionnaire, being classified as physically active those participants with ³75 min/week of high intensity or ³150 min/week of moderate intensity or a combination of both.

Statistical analysis

Sample characteristics were presented in absolute and relative frequency (categorical) and in mean and standard deviation (continuous), being compared according to psoriasis diagnosis (i.e., chi-square test and independent-samples t-test, respectively). Logistic regression models were used to evaluate the association of psoriasis diagnosis with sociodemographic, cardiovascular risk, and psychological risk factors, presented as odds ratio (OR) and 95% confidence interval (95%CI). Multivariate adjusted models included age, sex, self-reported race, education attainment, marital status, having private health insurance, diagnosis of hypertension, diabetes, and dyslipidemia, BMI, central obesity, smoking, alcohol, physical activity, depression, anxiety, and the self-perception of health. The significance level adopted was 5% ($p<0.05$). IBM SPSS for Statistics v.26 was used for the statistical analysis.

RESULTS

Of the 15,105 participants, 236 had a previous medical diagnosis of psoriasis at baseline. The sociodemographic and clinical characteristics are described in Table 1. Participants with psoriasis were mostly white with a lower frequency of self-reported black and mixed races ($p<0.001$), former and current smokers ($p=0.019$), had a higher education ($p<0.001$), private health insurance plan ($p<0.001$), and central obesity ($p=0.005$). The frequency of reporting "very bad" self-perception of health was higher in participants with psoriasis than those without the disease ($p=0.03$).

Table 2 describes the association between psoriasis, sociodemographic factors, cardiovascular risk factors, and psychological aspects. Participants who reported Black race were less likely to have psoriasis when compared to those who reported

Table 1. General and clinical characteristics according to the presence of psoriasis in Brazilian Longitudinal Study of Adult Health baseline sample (n=15,105).

	Psoriasis		p-value
	No n=14,869	Yes n=236	
Age (years), mean (SD)	52.1 (9.1)	52.3 (9.2)	0.78
Women, n (%)	8,097 (54.5)	121 (51.3)	0.33
Self-reported race, n (%)			
White	7,637 (52)	154 (65.8)	<0.001
Mixed	4,147 (28.2)	55 (23.5)	
Black	2,380 (16.2)	17 (7.3)	
Other	523 (3.6)	8 (3.4)	
Education, n (%)			
Less than high school	1,907 (12.8)	15 (6.4)	<0.001
High school and some college	5,173 (34.8)	60 (25.4)	
Complete college or more	7,789 (52.4)	161 (68.2)	
Marital status, n (%)			
Not single	9,826 (66.1)	158 (66.9)	0.78
Hypertension, n (%)	5.319 (35.8)	83 (35.3)	0.88
Diabetes, n (%)	2,562 (17.2)	43 (18.2)	0.69
Dyslipidemia, n (%)	8,636 (58.1)	140 (59.3)	0.70
BMI, n (%)			
Normal weight	5,483 (36.9)	82 (34.7)	0.46
Overweight	5,983 (40.3)	92 (39.0)	
Obesity	3,397 (22.8)	62 (26.3)	
Central obesity, n (%)	5,782 (38.9)	113 (47.9)	0.005
Smoking, n (%)			
Never	8,481 (57.1)	113 (47.9)	0.019
Former	4,448 (29.9)	85 (36.0)	
Current	1,939 (13.0)	38 (16.1)	
Current alcohol consumption, n (%)			
Yes	10,251 (69.1)	178 (75.4)	0.036
Physical activity, n (%)			
Physically active	3,530 (24.1)	61 (26.2)	0.26
Depression, n (%)	626 (4.2)	11 (4.7)	0.74
Anxiety, n (%)	1,937 (13.2)	30 (12.8)	0.86
Private health insurance plan, n (%)	10,110 (68)	190 (80.9)	<0.001
Self-perception of health, n (%)			
Very good	4,162 (28)	62 (26.4)	0.03
Good	7,741 (52.1)	126 (53.6)	
Regular	2,671 (18)	39 (16.6)	
Bad	236 (1.6)	4 (1.7)	
Very bad	55 (0.4)	4 (1.7)	

SD: standard deviation; BMI: body mass index.

Table 2. Association of psoriasis diagnosis with sociodemographic factors.

	Odds ratio (95% confidence interval)	
	Unadjusted	Adjusted*
Age (years)	1.0 (0.99–1.02)	0.99 (0.98–1.01)
Sex		
Men	1.0 (Reference)	1.0 (Reference)
Women	1.14 (0.88–1.47)	1.21 (0.90–1.62)
Self-reported race		
White	1.0 (Reference)	1.0 (Reference)
Mixed	0.66 (0.48–0.90)	0.77 (0.56–1.07)
Black	0.35 (0.21–0.59)	0.45 (0.26–0.75)
Others	0.32 (0.04–1.29)	0.93 (0.45–1.92)
Education attainment		
Less than high school	1.0 (Reference)	1.0 (Reference)
High school and some college	1.48 (0.84–2.60)	1.35 (0.75–2.44)
Complete college or more	2.62 (1.54–4.47)	1.94 (1.07–3.52)
s		
Single	1.0 (Reference)	1.0 (Reference)
Not single	1.04 (0.79–1.37)	0.95 (0.71–1.28)
Private health insurance plan		
No	1.0 (Reference)	1.0 (Reference)
Yes	1.99 (1.43–2.76)	1.56 (1.08–2.25)
Hypertension		
No	1.0 (Reference)	1.0 (Reference)
Yes	0.98 (0.75–1.28)	0.98 (0.72–1.33)
Diabetes		
No	1.0 (Reference)	1.0 (Reference)
Yes	1.07 (0.77–1.49)	1.08 (0.75–1.57)
Dyslipidemia		
No	1.0 (Reference)	1.0 (Reference)
Yes	1.05 (0.81–1.37)	0.99 (0.75–1.30)
BMI, n (%)		
Normal weight	1.0 (Reference)	1.0 (Reference)
Overweight	1.03 (0.76–1.39)	0.90 (0.63–1.29)
Obesity	1.22 (0.88–1.70)	0.88 (0.54–1.45)
Central obesity		
No	1.0 (Reference)	1.0 (Reference)
Yes	1.44 (1.12–1.87)	1.63 (1.10–2.40)
Smoking		
Never	1.0 (Reference)	1.0 (Reference)
Former	1.43 (1.08–1.91)	1.40 (1.03–1.88)
Current	1.47 (1.02–2.13)	1.61 (1.08–2.40)
Current alcohol consumption		
No	1.0 (Reference)	1.0 (Reference)
Yes	1.38 (1.02–1.85)	1.10 (0.80–1.51)

Continue...

Table 2. Continuation.

	Odds ratio (95% confidence interval)	
	Unadjusted	Adjusted*
Physical activity		
Insufficiently active	1.0 (Reference)	1.0 (Reference)
Physically active	1.12 (0.83–1.50)	1.07 (0.78–1.45)
Depression		
No	1.0 (Reference)	1.0 (Reference)
Yes	1.11 (0.60–2.05)	0.91 (0.45–1.85)
Anxiety		
No	1.0 (Reference)	1.0 (Reference)
Yes	0.97 (0.66–1.42)	0.88 (0.58–1.35)
Self-perception of health		
Very good	1.0 (Reference)	1.0 (Reference)
Good	1.09 (0.80–1.48)	1.12 (0.81–1.54)
Regular	0.98 (0.66–1.47)	1.15 (0.74–1.80)
Bad	1.14 (0.41–3.15)	1.48 (0.52–4.22)
Very bad	4.88 (1.72–13.9)	7.22 (2.41–21.64)

*Multivariable adjustment by age, sex, self-reported race, education attainment, marital status, having private health insurance, diagnosis of hypertension, diabetes and dyslipidemia, BMI, central obesity, smoking, alcohol, physical activity, depression, anxiety, and the self-perception of health.

White race (OR 0.45; CI 0.26–0.75), whereas those participants who have complete college or more (OR 1.94; CI 1.07–3.52) and those with private health insurance (OR 1.56; CI 1.08–2.25) had higher odds of having psoriasis. Participants with central obesity (OR 1.63; CI 1.10–2.40) and those who were former (OR 1.40; CI 1.03–1.88) and current smokers (OR 1.61; CI 1.08–2.40) had higher odds of having psoriasis diagnosis. Current alcohol consumption was associated with psoriasis diagnosis in crude analysis (OR 1.38; CI 1.02–1.85), but this association became non-significant in multiple adjusted model. Participants who reported very bad self-perception of health were seven times more likely to have a psoriasis diagnosis when compared to those who reported having very good health (OR 7.22; CI 2.41–21.64). No association was observed between psoriasis and hypertension, diabetes, dyslipidemia, BMI, physical activity, depression, and anxiety.

DISCUSSION

Our results showed an association of psoriasis with higher education attainment, central obesity, smoking, having private health insurance, and very bad self-perception of health, even after multivariate adjustment. On the contrary, self-reported Black race was associated with lower odds of having psoriasis. Our results showed a worst profile of cardiovascular risk factors such as current smoking and central obesity in participants with psoriasis compared to participants without the disease.

Brazilian Longitudinal Study of Adult Health participants who reported to be former or current smokers were more likely to have psoriasis when compared to those that never smoked. Similar results were reported by recent meta-analyses[16]. ELSA-Brasil is a cohort with a low prevalence of current smokers (13.1%) and most of the cases of psoriasis in the cohort are mild, but even under these circumstances, an association was found between smoking and psoriasis. On the contrary, it is questioned whether smoking increases the risk of developing psoriasis or if the habit is a repercussion of the undergoing stress the patients have. Therefore, it is impossible to "rule out" reverse causality to explain our results.

Psoriasis was associated with central obesity in this study. Central obesity is a risk factor for cardiometabolic diseases, mediating 52% of the risk of systolic blood pressure, total serum cholesterol, and fasting plasma glucose[17]. However, this study showed no association of psoriasis with obesity measured by BMI, which deserves further investigation into the role of different adiposity indicators in psoriasis.

Our study observed no association of psoriasis with hypertension, diabetes, and dyslipidemia, as a previous study with the Brazilian sample[5]. Comorbidities, particularly cardiometabolic disorders, were highly prevalent in patients with psoriasis compared to healthy controls[18]. A possible reason for the negative

results of the present study could be related to the mild severity of psoriasis in ELSA-Brasil. The ELSA-Brasil is a relatively young cohort, which will need a longer follow-up to present cardiovascular and metabolic complications. In addition, the nature of sample recruitment in ELSA-Brasil was substantially different compared to the case-control studies in psoriasis, which included samples from specialized health care facilities while ELSA-Brasil identified psoriasis cases within the sample.

Regarding sociodemographic factors, psoriasis was associated with higher education and private health insurance in this study. Convergently, a previous Brazilian study[19] reported higher education, higher income, and higher rates of private insurance among people with psoriasis. DiBonaventura et al.[19] suggested that possibly these patients had better access to medical care and, therefore, were more likely to have an early diagnosis of psoriasis. It is worth mentioning that the participants of ELSA-Brasil have higher education and higher access to private health care compared to the general population, which can lead to a higher frequency of the diagnosis of psoriasis even in mild cases. On the contrary, the lower frequency of psoriasis in self-reported Black individuals is interesting. ELSA-Brasil has a highly admixed sample with higher frequencies of Mixed and Black self-reported races. Psoriasis is a more common disease in White race, with a lower prevalence in Black[20]. The under-reporting and selection bias may have affected this result in our study.

Regarding psychological aspects, psoriasis was associated with very bad self-perception of health in this study. Previous studies also reported worse results related to satisfaction with life[21] and quality of life[8] in patients with psoriasis. This was an alarming result as negative self-reported health is associated with overall health status and with higher mortality rates[22]. Psoriasis was not associated with depression or anxiety in ELSA-Brasil, as reported in other studies[6,23]. This lack of association might be compromised by the mild severity of psoriasis in the cases of the ELSA-Brasil sample.

It is important to mention that even in a large sample, the psoriasis cases were small at baseline. ELSA-Brasil participants are civil servants with more education, higher income, and higher access to health care compared to the Brazilian general population, restricting the generalizability of the results. In addition, this is an occupational cohort, and the majority of psoriasis cases were mild, in which the cardiovascular risk factors may be likely healthier when compared to more severe cases. Moreover, even though the ELSA-Brasil study is prospective, this cross-sectional analysis cannot evaluate causality.

CONCLUSION

Psoriasis was associated with sociodemographic, cardiovascular risk factors and very bad self-perception of health in ELSA-Brasil. The assessment of cardiovascular risk factors and psychological support in patients with psoriasis is a key for prevention and improvement of quality of life. We suggest future research to investigate the role of disease severity in the observed associations.

AUTHORS' CONTRIBUTIONS

MC: Conceptualization, Investigation, Writing – review & editing. **WRT:** Investigation, Writing – review & editing. **VM:** Investigation, Writing – review & editing. **IMB:** Conceptualization, Formal Analysis, Investigation, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE

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Maternal-fetal outcomes of women with hypertensive disorders of pregnancy

Ivete Matias Xavier[1], Ana Carolina Zimmermann Simões[2], Ronnier de Oliveira[2], Yasha Emerenciano Barros[3], Ayane Cristine Alves Sarmento[4], Kleyton Santos de Medeiros[3,4], Ana Paula Ferreira Costa[4,5], Henri Korkes[6], Ana Katherine Gonçalves[3,4*]

SUMMARY

OBJECTIVE: The objective of this study was to determine adverse maternal and perinatal outcomes in pregnant women with hypertensive disorders of pregnancy.

METHODS: An analytical cross-sectional study was conducted on women admitted with hypertensive disorders of pregnancies to a university maternity hospital from August 2020 to August 2022. Data were collected using a pretested structured questionnaire. Variables associated with adverse maternal and perinatal outcomes were compared using multivariable binomial regression.

RESULTS: Of 501 women with pregnancies, 2, 35, 14, and 49% had eclampsia, preeclampsia, chronic hypertension, and gestational hypertension, respectively. Women with preeclampsia/eclampsia had significantly higher risks of cesarean section (79.4 vs. 65%; adjusted RR, 2,139; 95%CI, 1,386–3,302; p=0.001) and preterm delivery at <34 weeks' gestation (20.5 vs. 6%; adjusted RR, 2.5; 95%CI, 1.19–5.25; p=0.01) than those of women with chronic/gestational hypertension. Risks of prolonged maternal hospitalization (43.9 vs. 27.1%), neonatal intensive care unit admission (30.7 vs. 19.8%), and perinatal mortality (23.5 vs. 11.2%) were higher among women with preeclampsia/eclampsia.

CONCLUSIONS: Women with preeclampsia/eclampsia had a higher risk of adverse maternal and neonatal outcomes than those with chronic or gestational hypertension. This major maternity care center requires strategies for preventing and managing preeclampsia/eclampsia to improve pregnancy outcomes.

KEYWORDS: Hypertension, pregnancy-induced. Hypertension. Preeclampsia. Eclampsia.

INTRODUCTION

Hypertension is the most common medical disorder that occurs during pregnancy and complicates 5–10% of all pregnancies. Hypertensive disorders of pregnancy (HDP) are a critical threat to maternal and child health. Chronic hypertension is defined as high blood pressure before pregnancy. Gestational hypertension is characterized by high blood pressure after the 20th week of pregnancy (usually after 37 weeks), and this type of hypertension usually settles within 6 weeks after delivery[1-3].

Preeclampsia is defined as the identification of arterial hypertension in a previously normotensive pregnant woman, from the 20th week of pregnancy, with or without proteinuria. In the absence of proteinuria, preeclampsia is accompanied by systemic involvement or end-organ dysfunction, such as thrombocytopenia, liver with or without right upper quadrant or epigastric abdominal pain, renal failure, pulmonary edema, and neurological complications, such as altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata[4,5].

Eclampsia refers to the occurrence of generalized tonic-clonic seizures or coma (eclampsia sine eclampsia) in a pregnant woman with preeclampsia, which is a serious complication of the disease[4,5]. HELLP syndrome is a form of preeclampsia in which endothelial dysfunction is manifested by the activation of coagulation and liver dysfunction, as detected through laboratory tests. Clinically, it is possible to present with normal blood pressure and without proteinuria. The latter is defined by an acronym that synthesizes the presence of hemolysis (H), the elevation of

[1]Universidade Federal do Rio Grande do Norte, Postgraduate Program in Applied Sciences to Women's Health – Natal (RN), Brazil.
[2]Universidade Federal do Rio Grande do Norte, Undergraduate Course in Medicine – Natal (RN), Brazil.
[3]Universidade Federal do Rio Grande do Norte, Department of Obstetrics and Gynecology – Natal (RN), Brazil.
[4]Universidade Federal do Rio Grande do Norte, Health Sciences Center – Natal (RN), Brazil.
[5]League Against Cancer, Institute of Teaching, Research, and Innovation – Natal (RN), Brazil.
[6]Pontifícia Universidade Católica de São Paulo – São Paulo (SP), Brazil.
*Corresponding author: anakatherineufrnet@gmail.com
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liver enzymes (elevated liver enzymes), and thrombocytopenia (low platelets). HELLP syndrome develops in 10–20% of pregnant women with preeclampsia/severe eclampsia[6-8].

Almost all maternal deaths due to hypertensive syndromes occur in developing countries. A study reported that in more developed areas, the prevalence of eclampsia was estimated at 0.2%, with a maternal death rate of 0.8%, while in less favored regions, this prevalence rose to 8.1%, with a maternal death ratio of 22.0%. Thus, HDPs represent a problem of great interest in the scientific community owing to their frequency and maternal-fetal repercussions[6-8].

Notably, while the principles of management of HDPs are the same across the world, the disproportionately high adverse pregnancy outcomes in resource-limited settings are primarily due to the challenges associated with the management and quality of care for HDPs in these settings[3,4].

Thus, even within the same countries, there are differences in pregnancy outcomes due to sociocultural differences and variations in the distribution and quality of healthcare[1]. Moreover, the latter study aimed to determine the adverse maternal and perinatal outcomes among pregnant women admitted with HDP in the emergency room and directly compare the outcomes among women with preeclampsia or eclampsia and those with chronic or gestational hypertension.

METHODS

An analytical cross-sectional study was conducted according to the STROBE statement[9]. This study was conducted between August 2020 and August 2022 at a Januário Cicco Maternity School, a university maternity hospital for high-risk pregnancies in a region of northeastern Brazil with an HDI of 0.684. The study population included pregnant women older than 18 years who were at least in their 20th week of pregnancy and were admitted to the emergency room with a diagnosis of HDP. Women with other morbidities, smokers, or drug users were excluded. Those who could not respond to the questionnaire or were admitted without complete antenatal care were also excluded.

The sample size was calculated using EpiInfoTM version 7.1.1.14, with a sample power of 80% and a confidence interval (CI) of 95%. In eclampsia/eclampsia (76.7%), like the proportions of hypertensive disorders observed by Crenstil et al., an estimated sample size of 437 was adequate to detect a 15% difference in adverse maternal or fetal outcomes between women with preeclampsia/eclampsia and those with chronic/gestational hypertension, using a 5% contingency allowance, and the estimated sample size was 459.

Data were analyzed using Stata 11.0 (Stata Corporation, Texas, USA). Categorical variables were compared using the chi-square (χ^2) or Fisher's exact tests, as appropriate, while continuous variables were compared using Student's t-tests. The risk factors associated with adverse maternal and perinatal outcomes were examined using binomial regression with a log-link function to estimate crude and adjusted relative risks (RRs) with 95%CI. The variables for the regression models were selected based on biological plausibility, literature evidence, and invariable analysis results. To directly compare the outcomes in women with preeclampsia/eclampsia and those with chronic/gestational hypertension, crude and adjusted RRs were calculated for preeclampsia/eclampsia relative to chronic/gestational hypertension. Statistical significance was set at probability values<0.05.

Ethics

The study followed the ethical and legal norms recommended by Resolution 466/12 of the National Health Council and was approved by the Research Ethics Committee (CAAE:38143320.2.0000.5537). All participants signed a consent form to participate in this study. The study was conducted in accordance with the Declaration of Helsinki and its modifications.

RESULTS

Sociodemographic and reproductive characteristics

Altogether, 501 pregnant women with HDP were included: 316 with hypertension and 185 with preeclampsia or eclampsia. The mean and standard deviation ages of the hypertensive and preeclampsia/eclampsia groups were 32.19±6.59 years and 27.57±6.72 years. Regarding educational background, 181 (57.3%) patients received primary education in the hypertension group and 99 (53.5%) in the preeclampsia/eclampsia group. Regarding marital status, the results showed that 201 (63.6%) patients were married or cohabiting in the hypertension group and 121 (65.4%) in the preeclampsia/eclampsia group. Most patients were not primiparous, 185 (58.5%) in the hypertension group and 105 (56.7%) in the preeclampsia/eclampsia group. Concerning parity, 176 (55.7%) patients in the hypertension group had 1–4 deliveries compared with 100 (54.0%) in the eclampsia/eclampsia group. The estimated gestational age at diagnosis was >27 weeks for the hypertension group 310 (98.1%) and preeclampsia/eclampsia group 176 (95.1%). There were no significant differences between all variables regarding sociodemographic and reproductive characteristics.

In the eclampsia/eclampsia group, 12(6.5%) patients developed HELLP syndrome.

No statistically significant difference was found in both groups for the number of consultations: the hypertension group (mean±standard deviation) 6.7±0.68 and the eclampsia/eclampsia group 6.5±0.73.

Comparison of adverse maternal and perinatal outcomes

Concerning the adverse maternal outcomes, women with preeclampsia/eclampsia had significantly higher risks of cesarean section (79.4 vs. 65%; adjusted RR, 2.139; 95%CI, 1.386–3.302; p<0.001). Term labor at <34 weeks of gestation (20.5 vs. 6%; adjusted RR, 2.505; 95%CI, 1.194–5.257; p=0.015) was significantly higher among women with preeclampsia/eclampsia than women with chronic/gestational hypertension (Table 1).

Regarding the adverse fetal outcomes, the neonatal intensive care unit (NICU) admission (22.7 vs. 6.0%; adjusted RR, 2.567; 95%CI, 1.296–5.088; p=0.007) and perinatal mortality (5.4 vs. 2.2%; adjusted RR, 0.423; 95%CI, 0.101–1770; p=0.239) were significantly higher among women with preeclampsia/eclampsia than women with chronic/gestational hypertension. Apgar (<7) at 1 min (15.1 vs. 8.8%, adjusted RR, 1.967; 95%CI, 1.112–3.477; p=0.020) and Apgar (<7) at 5 min (7.0 vs. 2.5%, adjusted RR, 3.683; 95%CI, 1.500–9.356; p=0.006) were significantly higher among women with preeclampsia/eclampsia (Table 2).

In the initial analysis, prolonged maternal hospital stay was associated with preeclampsia/eclampsia (p=0.04). However, after calculating the adjusted risk, this association was not confirmed (p=0.556).

DISCUSSION

Hypertension during pregnancy is a major contributor to maternal and perinatal mortality[10,11]. We found that women with preeclampsia/eclampsia had a higher risk of cesarean section. It is crucial to point out that preeclampsia is not an indication for cesarean delivery, as expected, because of the severe complications arising from this condition. However, although pregnant women with preeclampsia can undergo vaginal delivery, most women choose to undergo cesarean section [12,13].

In this sample, the prevalence of preterm labor was 20.5 and 6% in the preeclampsia/eclampsia and chronic gestational hypertension

Table 1. Adverse maternal outcomes of women with chronic hypertension compared to women with preeclampsia/eclampsia.

Maternal outcomes	Chronic gestational hypertension (n=316) n (%)	Preeclampsia/ eclampsia (n=185) n (%)	Crude RR (95%CI)	p-value	Adjusted RR (95% CI)	p-value
Term labor <34 weeks	19 (6.0)	38 (20.5)	4.041 (2.251–7.254)	<0.0001	2.505 (1.194–5.257)	0.015
Term labor >37 weeks	107 (33.9)	96 (51.9)	2.106 (1.454–3.053	<0.0001	1.152 (0.980–2.361)	0.061
Cesarean section[a]	206 (65.2)	147 (79.4)	2.065 (1.35–3.160)	0.001	2.139 (1.386–3.302)	0.001
Prolonged maternal hospital stay[b]	159 (50.3)	110 (59.4)	1.448 (1.003–2.091)	0.048	1.126 (0.757–1.677)	0.556

RR: relative risk; CI: confidence interval. [a]Adjusted for the stage of pregnancy at admission. [b]Adjusted for estimated gestational age (EGA) at diagnosis, EGA at delivery, and stage of pregnancy at admission.

Table 2. Adverse fetal outcomes of women with chronic hypertension compared to women with preeclampsia/eclampsia.

Maternal outcomes	Chronic/gestational hypertension (n=316) n (%)	Preeclampsia/ eclampsia (n=185) n (%)	Crude RR (95% CI)	p-value	Adjusted RR (95%CI)	p-value
Prematurity birth<34 weeks	19 (6.0)	38 (20.5)	4.041 (2.251–7.254)	<0.001	2.505 (1.194–5.257)	0.015
Apgar (<7) at 1 min[a]	28 (8.8)	28 (15.1)	1.835 (1.049–3.207)	0.033	1.967 (1.112–3.477)	0.020
Apgar (<7) at 5 min	8 (2.5)	13 (7.0)	2.909 (1.183–7.159)	0.020	3.683 (1.500–9.356)	0.006
NICU admission	19 (6.0)	42 (22.7)	4.591 (2.577–8.179)	<0.001	2.567 (1.296–5.088)	0.007
Perinatal mortality[b]	7 (2.2)	10 (5.4)	2.522 (0.943–6.745)	0.065	0.423 (0.101–1.770)	0.239

RR: relative risk; CI: confidence interval; NICU: neonatal intensive care unit. [a]Adjusted for EGA at diagnosis and stage of pregnancy at admission. [b]Adjusted for parity (before delivery), EGA at diagnosis; the number of antenatal visits, and stage of pregnancy at admission.

groups, respectively. Worse results were previously observed in the poorest regions such as Ethiopia, Tigray region (40.8%)[14], Nekemte (41.2%)[15], Ghana (21.7%)[16], and India (24.6%)[17]. On the other hand, better results were found in the United States (17.4%)[18] and São Paulo city (10.6%)[18]. The discrepant findings can be explained due to the quality of antenatal care service and different management guidelines used across the countries[19].

Additionally, we found that preterm delivery was more observed in the preeclampsia/eclampsia group. Approximately 75% of preterm births result from spontaneous preterm labor and may be associated with a history of pregnancy-induced hypertension[20].

The risk of prolonged maternal hospitalization was significantly higher among women with preeclampsia/eclampsia. According to Goes et al., the latter results have been associated with the incorrect use of antihypertensive drugs during pregnancy[21].

NICU admission and perinatal mortality were higher among women with preeclampsia/eclampsia. Preeclampsia, when it presents itself in a severe form or when not treated early, can complicate pregnancy, increasing the risk of death to the mother and newborn, as observed in our results[22].

Despite the importance of the number of antenatal consultants, Interestingly, we did not find a statistically significant difference in both studied groups: the hypertension group (mean±standard deviation) 6.7±0.68, and the eclampsia/eclampsia group 6.5±0.73. Although the minimum number of prenatal consultations is being reached in both groups, perhaps the quality of these consultations can be questioned, considering the high prevalence of unfavorable neonatal outcomes in this population.

Another critical point that must be considered is a postpartum follow-up of these patients. In the past, it was believed that hypertensive diseases of pregnancy were self-limiting, and the resolution of pregnancy was considered a cure. However, the literature demonstrated that HDP increase the risk of cardiovascular diseases throughout a woman's life. However, this is the most neglected moment in medical care, and a lack of adequate care during the puerperium can result in significant health problems, predisposing considerable maternal death rates. The College of Obstetricians and Gynecologists (ACOG) released guidelines proposing a longitudinal action that was not restricted to just one consultation in the sixth postpartum week. Therefore, an adequate assessment should encompass physical health, breastfeeding, contraception, mental health, social support, and any specific assessment, depending on risk factors and comorbidities[23,24].

Hypertension during the gestational period has a course of development that still needs clarification as maternal hypertension and prematurity are events of multicausal origin and behave in a complex way. The number of children, antenatal consultations, hospitalization, and high-risk antenatal care were associated with prematurity[23]. These results highlight the importance of early hospital referral for women with preeclampsia and eclampsia. A health system approach focused on the availability of qualified professionals with training in emergency obstetric and neonatal care, as well as the preparation of facilities to measure blood pressure, adequate blood pressure control, and close monitoring throughout pregnancy, with timely referrals, can contribute to the reduction of maternal (and newborn) deaths[25].

A limitation of this study was its cross-sectional nature. Therefore, despite the high number of patients, our results cannot be generalized to the entire global population. Despite this limitation, our data indicate that preeclampsia and eclampsia are public health concerns with a negative impact on perinatal outcomes.

CONCLUSION

Women with HDPS have a higher risk of adverse maternal and neonatal outcomes. Women with preeclampsia/eclampsia had an increased risk of cesarean section and preterm delivery compared to those with chronic/gestational hypertension.

Strategies for improving pregnancy outcomes among women with HDPs, especially preeclampsia/eclampsia, are needed. Including a health system approach focused on the availability of qualified professionals with training in emergency obstetric and neonatal care, as well as the preparation of facilities to measure blood pressure, adequate blood pressure control, and close monitoring throughout pregnancy, with timely referrals (minimum of six quality appointments), can contribute to the reduction of maternal (and newborn) deaths in low-income regions.

Finally, some simple objective strategies could be adopted to reduce adverse events, such as at least five good-quality prenatal consultations. The early diagnosis and management of gestational hypertension could decrease unfavorable maternal-fetal outcomes. The improvement of prenatal in primary care could impact the rates of gestational hypertension and its consequences.

AUTHORS' CONTRIBUTIONS

IMX: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft. **APFC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization. **KSM:** Conceptualization, Supervision, Validation.

YEB: Conceptualization. **AKG:** Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **ACZS:** Data curation, Formal Analysis, Investigation, Writing – original draft. **RO:** Data curation, Formal Analysis, Investigation, Software, Writing – original draft. **HK:** Validation, Writing – review & editing. **ACAS:** Methodology, Supervision, Visualization, Writing – original draft.

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ORIGINAL ARTICLE

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Perception of newly graduated physicians toward ethical education in medical schools: a Brazilian cross-sectional nationwide study

Gustavo Rosa Gameiro[1,2*], Giovana Rosa Gameiro[3], Bruno Alonso Miotto[4], Aline Gil Alves Guilloux[5], Alex Jones Flores Cassenote[5], Mario César Scheffer[5]

SUMMARY

OBJECTIVE: The objective of this study was to evaluate fresh medical graduates' perceptions regarding the general aspects of ethics teaching in Brazilian medical schools.

METHODS: A structured questionnaire was applied to 4,601 participants among the 16,323 physicians who registered in one of the 27 Regional Medical Councils of Brazil in 2015. Answers to four questions regarding general aspects of ethics education in medical school were analyzed. Sampling procedures involved two stratification variables: legal nature (public vs. private) of medical schools and monthly household income higher than 10 minimum wages.

RESULTS: A large percentage of the participants had witnessed unethical behaviors during contact with patients (62.0%), toward coworkers (51.5%), and in relationships with patients' families (34.4%) over the course of their medical training. Even though most of the responders (72.0%) totally agreed that patient-physician relationship and humanities education were part of their medical school curriculum, important topics such as conflicts of interest and end-of-life education were not satisfactorily addressed in the participants' medical training. Statistically significant differences were found between the answers of public and private school graduates.

CONCLUSION: Despite great efforts to improve medical ethics education, our findings suggest the persistence of deficits and inadequacies in the ethics training currently given in medical schools in Brazil. Further modifications in ethics training must be made to address the deficiencies shown in this study. This process should be accompanied by continuous evaluation.

KEYWORDS: Medical education. Ethics. Curriculum. Physicians. Demographics.

INTRODUCTION

The evolution of society has created an increasing demand for the development of an integrated and holistic curriculum in medical school. The main objective is to train technically skilled physicians who care for the patients considering their biopsychosocial and humanistic dimensions[1,2].

In many countries, ethics and human rights are an integral part of the medical curriculum, but this is not universal. The World Medical Association (WMA), since its 51st General Assembly in Tel Aviv, Israel, in 1999, already recommended that "medical ethics and human rights should be taught at every medical school as obligatory and examined parts of the curriculum[3]." This important resolution was posteriorly reaffirmed by the 217th WMA Council Session in Seoul, in April 2021.

In Brazil, the 2014 National Medical School Curriculum Guidelines (NCD) included ethics education, but the ethics course curriculum is not standardized. A study conducted recently found that, among the federal universities with medical courses in Brazil, 94.44% offered the discipline of bioethics. At the same time, however, 16.67% of the universities offered the subject in an elective manner, and in 67.93% of the institutions, bioethics was taught in a shared course with other subjects, with no isolated workload[1].

In Brazil, the current Code of Medical Ethics (CME) was enacted on April 30, 2019, reviewing the previous version published in 2009. It incorporates approaches relevant to the contemporary world, addressing topics such as technological innovations, mass communication, and social relationships[4].

[1]Universidade de São Paulo, Faculty of Medicine, Medical Education Development Center, Health Education – São Paulo (SP), Brazil.
[2]Universidade Federal de São Paulo, Paulista School of Medicine, Department of Ophthalmology and Visual Sciences – São Paulo (SP), Brazil.
[3]Universidade Estadual de Londrina, Faculty of Medicine – Londrina (PR), Brazil.
[4]Universidade Santo Amaro – São Paulo (SP), Brazil.
[5]Universidade de São Paulo, Department of Preventive Medicine – São Paulo (SP), Brazil.
*Corresponding author: gustavo.gameiro@fm.usp.br

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The CME is important not only because it covers scientific advances and their implications for the medical practice but most importantly because it seeks to promote medical assistance based on values, duties, and virtues that guarantee dignified and equitable assistance for all citizens, while also encouraging the prestige and union of the medical category[4]. Despite the significance of the topic, there is a lack of studies in the literature concerning the current scenario of ethics education in medical schools in Brazil and the prevalence of unethical situations observed by students during their medical training.

In that sense, this study aimed to identify fresh medical graduates' demographic profiles and their perceptions toward ethics teaching in Brazilian medical schools concerning general medical ethics topics that were supposed to be covered by the medical curriculum. Moreover, this study assessed if there is any difference in the students' perceptions regarding sociodemographic and training-related aspects.

METHODS

Primary data were obtained using a 104-structured multiple-choice question survey divided into 11 thematic blocks. This study focused on the medical ethics domain, and it extends previous reports using the same survey instrument[5,6].

Out of the 104 questions, 12 referred to the general and socioeconomic data of the participants. Four questions, one of them with six subtopics, addressed general aspects of bioethics with emphasis on whether the interviewee had witnessed any ethical infraction during their time in medical school, in addition to considering if their medical training sufficiently addressed subjects such as end-of-life care, conflicts of interest, and humanities teaching. The graduates were invited to answer whether they totally agreed, partially agreed, disagreed, or preferred not to manifest their opinion on the matter.

The survey was electronically distributed to 16,323 fresh medical school graduates previously registered in one of the 27 Regional Medical Councils (CRMs) of Brazil in 2015. Data were collected in two stages, first in São Paulo and then in other Brazilian states, at the time of registration of new physicians at the CRMs. After careful processing of data, 4,601 participants were included in this study. Distribution methods, survey development, inclusion and exclusion criteria, the survey instrument, adjustments, and validation methods have been previously described elsewhere[5,6].

Sampling procedures involved two stratification variables: legal nature (public vs. private) of medical schools and family's monthly income greater than 10 minimum wages. The participants' number varied between questions and within each stratum. Hence, a complex sample was preferred considering the strata effects (the percentage of different strata in the target population) to ensure the correct representation of each analyzed stratum. A 95% confidence interval for each answer frequency was calculated by bootstrapping with 1,000 repetitions.

RESULTS

Out of the 4.601 participants, 52.9% were women and 47.1% were men. The majority (43.4%) had recently completed their medical training in a medical school from the southeast Brazilian region; 23.0% had graduated from schools in the Northeast region; 19.2% had graduated from the South region; 9.0% had graduated from the North region; and 5.4% had graduated from the Midwest region. When considering the legal nature of the medical school, 45.0% of the participants graduated from public medical schools whereas 55.0% studied in private schools. A more detailed analysis of the sociodemographic characteristics of the studied population has already been reported[6].

Table 1 shows the percentage and confidence intervals for each of the four questions and subtopics concerning general medical ethics. Table 2 explores the differences in the frequency of answers when analyzing responses from private vs. public schools for each answer. Finally, Table 3 depicts significant differences in the results divided by familiar income.

Regarding whether the following statement was true: "humanities and doctor-patient relationship training were part of my medical school curriculum," 72.0% of the subjects who answered completely agreed with the statement, 25.8% partially agreed, and 2.2% completely disagreed with the statement (Table 1). Statistically significant differences were also depicted comparing the legal nature (public vs. private) of the medical school: graduates from private schools tend to completely agree more with the statement ($p<0.001$; Table 2).

When asked whether their medical training appropriately taught them "how to deal with death," 24.0% completely agreed with the statement, 55.0% partially agreed, and 20.9% completely disagreed (Table 1). Graduates from private schools completely disagree more frequently (20.9%) with the statement than the ones who graduated from public universities (15.3%; Table 2). The group with familiar income greater than 10 minimum wages also had a trend to totally agree with the affirmation ($p=0.001$).

Out of the responders, only 12.3% stated that they had not witnessed unethical attitudes during their medical training; 62.0% stated that such unethical attitudes occurred during contact with patients; 51.5% witnessed inadequate attitudes toward work colleagues, multidisciplinary teams, and

Table 1. Fresh graduate physicians' opinions about general medical ethics themes.

	Completely agreed			Partially agreed			Completely disagreed		
	Freq. %	95%CI	n	Freq. %	95%CI	n	Freq. %	95%CI	n
My medical school training appropriately covered the topic "how to deal with death"	24.0	22.9–32.2	884	55.0	54.6–56.1	2023	20.9	13.3–22.4	770
My medical school training sufficiently addressed the topic of conflicts of interest, particularly between physicians and the pharmaceutical and medical device industry	23.1	21.2–29.4	826	48.5	47.1–49.7	1736	28.4	23–30.4	1016
Humanities and doctor-patient relationship training were part of my medical school curriculum	72.0	69.7–79.2	2662	25.8	19.7–27.4	956	2.2	1.2–3.2	80
	Yes			-			No		
Subjects answered the question that they experienced or witnessed inadequate ethical attitudes	80.1	79.1–86.1	3685				19.9	13.9–20.9	916
(A) I have experienced or witnessed inadequate ethical attitudes, especially during contact with patients (i.e., clinical visits, wards, and emergencies)	62.0	52.6–62.9	2286				38.0	37.1–47.4	1399
(B) I have experienced or witnessed inadequate ethical attitudes, especially in relationships with patients' families	34.4	25–37.1	1268				65.6	62.9–75	2417
(C) I have experienced or witnessed inadequate ethical attitudes, especially in relationships with the community and general public	16.9	12.7–17.3	624				83.1	82.7–87.3	3061
(D) I have experienced or witnessed inadequate ethical attitudes, especially toward work colleagues, multidisciplinary teams, and administrative personnel	51.5	41.4–55.1	1896				48.5	44.9–58.6	1789
(E) I have experienced or witnessed inadequate ethical attitudes, especially in decision-making in the classroom	20.2	14.4–22.2	744				79.8	77.8–85.6	2941
(F) I have not experienced or witnessed any unethical attitude	12.3	11.8–17.8	452				87.7	82.2–88.2	3233

The percentages were obtained through weighing of individuals, so the direct division of cells by the totals in this table will yield incorrect results and therefore are discouraged.

administrative personnel; 34.4% in relationships with patients' families; 20.2% in classrooms' decisions; and 16.9% in relationships with the community and general public (Table 1). The percentage of graduates who witnessed those inadequate situations was higher among the physicians who graduated from public medical schools (Table 2).

DISCUSSION

Ethics curriculum in medical school must go beyond the classroom and didactic teaching, as clinical internships present an important opportunity to enable students' discussions with faculty about practical cases and ethical challenges they will eventually face in their medical practice[3,7]. Following this line of thought, the importance of the hidden curriculum in ethics teaching becomes clear[3]. Students' experiences in clerkship rotations may shape their future attitudes and professionalism in medical practice. During their learning process, medical students' approaches to dealing with ethical issues are for the most part influenced by role models[8,9]. Therefore, observing unethical behavior in clinical settings can have very negative effects on the students' systems of values, contributing to a decline in empathy and the phenomenon of ethical erosion[8].

In this context, it is especially relevant to note that the results of this study have demonstrated a very alarming reality: a high percentage of the participants had witnessed unethical behaviors during their medical training, particularly during contact

Table 2. Fresh graduate physicians' significantly different opinions about general medical ethics themes stratified by the legal nature of the medical school.

	Legal nature of the medical school					
	Public		Private		Total	
	Freq. %	95%CI	Freq. %	95%CI	Freq. %	95%CI
[a]My medical school training appropriately covered the topic "how to deal with death"						
Completely agreed	10.5	9.8–11.4	15.5	14.6–16.5	25.5	22.9–32.2
Partially agreed	19.4	18.4–20.5	35.5	34.3–36.8	55.4	54.6–56.1
Completely disagreed	5.4	4.9–6.0	13.5	12.7–14.4	17.4	13.3–22.4
[a]My medical school training sufficiently addressed the topic of conflicts of interest, particularly between physicians and the pharmaceutical and medical device industry						
Completely agreed	4.6	1.4–14.3	20.5	12.7–31.3	25.1	21.2–29.4
Partially agreed	13.2	3.7–37.7	35.2	21.7–51.5	48.4	47.1–49.7
Completely disagreed	8.9	2.5–27	17.7	11.4–26.3	26.5	23–30.4
[a]Humanities and doctor-patient relationship training were part of my medical school curriculum						
Completely agreed	17.7	4.7–48.4	57.0	32–78.9	74.7	69.7–79.2
Partially agreed	7.8	2.3–23.5	15.5	10–23.3	23.3	19.7–27.4
Completely disagreed	0.9	0.2–3.3	1.1	0.6–1.8	1.9	1.2–3.2
[a](A) I have experienced or witnessed inadequate ethical attitudes, especially during contact with patients (i.e., clinical visits, wards, and emergencies)						
No	8.1	2.2–25.5	34.1	21–50.1	42.2	37.1–47.4
Yes	18.2	4.9–48.9	39.7	24.6–57.1	57.8	52.6–62.9
[a](B) I have experienced or witnessed inadequate ethical attitudes, especially in relationships with patients' families						
No	15.5	4.2–43.8	53.7	30.4–75.6	69.3	62.9–75
Yes	10.7	3.1–31.2	20.0	13.1–29.4	30.7	25–37.1
[a](C) I have experienced or witnessed inadequate ethical attitudes, especially in relationships with the community and general public						
No	21.2	5.5–55.7	63.9	34.6–85.5	85.1	82.7–87.3
Yes	5.0	1.5–15.5	9.9	6.6–14.5	14.9	12.7–17.3
[a](D) I have experienced or witnessed inadequate ethical attitudes, especially toward work colleagues, multidisciplinary teams, and administrative personnel						
No	10.9	3–32.3	40.9	23.8–60.4	51.8	44.9–58.6
Yes	15.3	4.2–42.9	32.9	21–47.6	48.2	41.4–55.1
[b](E) I have experienced or witnessed inadequate ethical attitudes, especially in decision-making in the classroom						
No	20.3	5.2–54	61.8	33.5–83.8	82.0	77.8–85.6
Yes	6.0	1.8–18.4	12.0	7.9–17.9	18.0	14.4–22.2
[a](F) I have not experienced or witnessed any unethical attitude						
No	24.3	6.1–61.2	61.2	34.2–82.7	85.5	82.2–88.2
Yes	1.9	0.5–6.7	12.6	8.1–19	14.5	11.8–17.8
Total	**26.2**	**6.5–64.6**	**73.8**	**35.4–93.5**	**100.0**	**100–100**
Total (n)	**1676**		**2009**		**3685**	

[a]p<0.001; [b]p=0.030.

Table 3. Fresh graduate physicians' significantly different opinions about general medical ethics themes are stratified by familiar income.

	Household income higher than 10 minimum wages					
	Yes		No		Total	
	Freq. %	95%CI	Freq. %	95%CI	Freq. %	95%CI
[a]My medical school training appropriately covered the topic "how to deal with death"						
Completely agreed	17.2	14.5–20.2	10.2	8–12.9	27.4	23–32.2
Partially agreed	30.8	29.5–32.1	24.4	22.6–26.2	55.2	54.1–56.3
Completely disagreed	9.4	7.4–11.9	8.1	5.9–10.9	17.4	13.3–22.5
[b]I have experienced or witnessed inadequate ethical attitudes, especially in relationships with patients' families						
No	39.1	35.4–43	30.1	26.5–34	69.2	62.8–74.9
Yes	18.4	15.2–22	12.4	9.8–15.6	30.8	25.1–37.2
[c]I have experienced or witnessed inadequate ethical attitudes, especially toward work colleagues, multidisciplinary teams, and administrative personnel						
No	30.9	27–35	21.0	17–25.6	51.8	44.7–58.8
Yes	26.6	22.7–31	21.6	18.5–25	48.2	41.2–55.3
Total	**57.5**	**49.7–66**	**42.5**	**35.5–50.6**	**100**	**100–100**
Total (n)	**2018**		**1592**		**3610**	

[a]p=0.001; [b]p=0.009; [c]p=0.014.

with patients (62.0%), toward coworkers (51.5%), and in relationships with patients' families (34.4%). These findings are consistent with a study conducted in the United States which found that, of the respondents, 35% of the first-year and 90% of the fourth-year medical students had been exposed to unethical conduct by residents or attending physicians[10].

On the other hand, it is heartening to note that most responders graduated from medical schools whose curriculum covered vital topics for the development of their professional and personal values, such as humanities and doctor-patient relationships[12]. These findings are supported by previously published international studies: out of the analyzed schools in a recent study by Howick et al., medical ethics was offered as part of the curriculum in all schools in Canada, in 78% of the schools in the United Kingdom (UK), and in 87.6% of the schools in the United States (US). Excluding medical ethics, a humanities course was offered by 56% of the Canadian medical schools, 73% of the schools in the UK, and 80% of the schools in the US[12]. In another study regarding the presence of humanities subjects in the medical curriculum of Italian and Spanish schools, it was found that all analyzed schools included at least one subject with humanities content[13].

The doctor-patient relationship is a powerful part of medical care and can alter the health outcomes of patients[14]. The finding that the vast majority of the new graduates agreed that the patient-physician relationship was part of their medical training is in harmony with the current focus given to "patient-centered medicine." Over the years, multiple educational strategies have been adopted in the process of medical training to improve the doctor-patient relationship[15].

Our results showed that efforts appear to be necessary to improve end-of-life training in medical education: only 24.0% of the survey participants totally agreed that they were appropriately taught in medical school about "how to deal with death." Other international studies also exposed deficiencies in the education of end-of-life care in both the formal and hidden curricula[16,17].

When comparing private medical school and public medical school graduates' answers, an interesting association was found: percentages of witnessing inadequate medical attitudes during their clinical training were lower among graduates from private medical schools. Physicians who graduated from private schools also agreed more with the statements regarding the presence of humanities and doctor-patient relationship training in their medical school curriculum and regarding the topic of conflicts of interest being addressed in their training. However, there was a lower rate of disagreement with the statement "medical training appropriately taught how to deal with death" among public school graduates, when compared with private school graduates.

There is only one study in the literature comparing medical clerkships in public and private medical schools in Brazil[18]. Access to high-complexity university hospitals was predominantly offered by public medical schools. However, the infrastructure of private schools, considering the physical space, equipment, and human resources, was considered more satisfactory. The number of patients for students was considered

adequate by 87% in private schools and 67% in public schools. It should also be taken into consideration the possibility of public-school graduates expressing a more critical opinion regarding the topics evaluated, given the fact that this study has assessed graduates' perceptions rather than the real occurrence of unethical behavior.

Overall, these results show that there is still room for change in the medical curriculum in Brazilian medical schools. Modifying the ethics course workload and methodologies of teaching, promoting bioethics education throughout the whole duration of medical school, integrating theory with clinical practice, changing the medical culture through positive role models and institutional values, and adequate assessment of the quality of clerkship rotations regarding the ethical domain are some points that might represent important steps toward the improvement of medical education and healthcare systems.

Although this is the first Brazilian study to address most of these topics, and the large sample size provides a more accurate representation of the graduates' perceptions; some limitations should be highlighted. This study did not address methodologies of ethics teaching, evaluation strategies, and different curriculum characteristics of the responders' medical schools, which could help with further investigation and explanation of our findings. Moreover, this study was based on the physicians' own perceptions about their ethical education in medical school, and no practical test to evaluate their knowledge was completed.

CONCLUSIONS

Only a small percentage of the participants stated that they had not witnessed unethical attitudes during their medical training, and the rates of witnessing unethical behavior were higher among students from public medical schools. There are still many challenges to be overcome in the ethical training currently given in medical schools in Brazil. This study can be used to guide possible changes in the medical curriculum and methodologies of teaching to improve medical students' experience and to help bridge the gap between classroom teaching and the reality of clinical ethics. Future studies should be conducted to further investigate current deficits in bioethics education with more detail.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the University of Sao Paulo Medical School's Research Ethics Committee under the number 797.424. Consent of participants was implied upon voluntary completion of the questionnaire.

AUTHORS' CONTRIBUTIONS

GuRG: Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **GiRG:** Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **BAM:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **AGAG:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **AJFC:** Conceptualization, Data curation, Project administration, Writing – review & editing. **MCS:** Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing

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ORIGINAL ARTICLE

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"Zooming" in the association between rosacea and fibromyalgia syndrome: ıs it worth mentioning?

Sevgi Kulaklı[1], Işıl Deniz Oğuz[1], Ilker Fatih Sarı[2], Ilker Sengul[3,4*], Fazıl Kulaklı[2], Burak Akşan[1], Demet Sengul[5]

SUMMARY

OBJECTIVE: We aimed to detect the frequency of fibromyalgia syndrome in patients with rosacea and determine whether this frequency was affected by the severity of rosacea and the quality of life.

METHODS: In this prospective, controlled, cross-sectional study, a total of 94 consecutive rosacea cases and 87 age- and sex-matched controls were enrolled. The severity of rosacea was assessed in light of the findings of the National Rosacea Society Ethics Committee. Dermatology Life Quality Index and Rosacea-specific Quality-of-Life instrument had been applied to the cases of rosacea. The diagnosis of fibromyalgia syndrome was established according to the 2016 revised fibromyalgia diagnostic criteria, and the Fibromyalgia Impact Questionnaire was used to determine the functional disability.

RESULTS: The frequency of fibromyalgia syndrome was higher in the rosacea group than in the control group (p=0.01), and Dermatology Life Quality Index and Rosacea-specific Quality-of-Life instrument were higher in patients with rosacea with fibromyalgia syndrome (p=0.006 and p=0.004, respectively). A statistically significant weak positive correlation was observed between Dermatology Quality-of-Life Index, Rosacea-specific Quality-of-Life instrument, and Fibromyalgia Impact Questionnaire; symptom severity scale scores; and fibromyalgia score (r=0.35, r=0.259, and r=0.32 and r=0.376, r=0.305, and r=0.312, respectively).

CONCLUSION: The patients with rosacea have higher rates and disability scores of fibromyalgia syndrome than healthy controls, independent of rosacea severity, and quality of life is correlated with fibromyalgia scores. We might point out that fibromyalgia syndrome accompanying rosacea has more restrictions in their daily routine activities than rosacea alone. As such, physicians should be aware of the possible coexistence of rosacea and fibromyalgia syndrome.

KEYWORDS: Rosacea. Fibromyalgia. Thyroid gland. Thyroidology. Pathology.

INTRODUCTION

Rosacea, *per se*, is a chronic inflammatory disease of the central facial skin characterized by flushing attacks, persistent erythema, papules, pustules, telangiectasias, less frequent phymatous changes, and eye involvement[1]. In a recent systematic review, its prevalence was predicted at 5.5% of the adult population, and both sexes are affected equally[2]. Rosacea can lead to low self-esteem, anxiety, and depression, and stigmatism frequently impairs the quality of life seriously[1]. The most common diseases accompanying rosacea were depression, anxiety disorder, hypertension, dyslipidemia, diabetes mellitus, hypothyroidism, migraine, and rheumatoid arthritis. Rosacea and thyroid disorders are also similar in accompanying metabolic status and inflammatory pathways. Augmented expression of inflammatory markers involving matrix metalloproteinases (MMP), particularly MMP-9, has been demonstrated in rosacea as well as in hypothyroid hormonal status in thyroidology[3,4].

The pathogenesis of rosacea is multifactorial, with genetic predisposition, dysregulation in innate and adaptive immunity, and neuroinflammatory mechanisms[5]. The stimulation of transient receptor potential vanilloid 1-4 (TRPV1-4) and transient receptor potential ankyrin 1 (TRPA1) receptors, localized on sensorial neurons and keratinocytes, leads to the secretion of neuromediators such as capsaicin, calcitonin-gene related peptide, and substance P, which results in neurogenic inflammation and vasodilatation[5,6]. Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by widespread and chronic musculoskeletal pain, accompanied by sleep disturbance, fatigue,

[1]Giresun University, Faculty of Medicine, Department of Dermatology and Venereology – Giresun, Turkey.
[2]Giresun University, Faculty of Medicine, Department of Physical Therapy and Rehabilitation – Giresun, Turkey.
[3]Giresun University, Faculty of Medicine, Division of Endocrine Surgery – Giresun, Turkey.
[4]Giresun University, Faculty of Medicine, Department of Surgery – Giresun, Turkey.
[5]Giresun University, Faculty of Medicine, Department of Pathology – Giresun, Turkey.
*Corresponding author: ilker.sengul.52@gmail.com
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morning stiffness, and cognitive disorders, whose prevalence varies between 2 and 3%[7]. The coexistence of FMS with diseases in which emotional factors play a role in the etiology, such as dysmenorrhea; migraine; irritable bowel syndrome; psychiatric diseases such as depression, anxiety, and panic attacks; and chronic inflammatory and autoimmune diseases like lupus erythematosus, rheumatoid arthritis, coronary artery disease, and diabetes mellitus have been described[8,9]. FMS and hypothyroidism share certain clinical characteristics like musculoskeletal pain and fatigue, and thyroid autoimmunity is more common in FMS[10]. Skin findings, including hyperhidrosis and pruritus, have been reported in cases with FMS[11]. Although the pathophysiology of FMS is unclear, the disease may be associated with alterations in peripheral cutaneous nerve fibers and dysfunction. In addition, neurogenic inflammation is higher in the skin biopsies of the cases with FMS[12].

The presence of neurogenic inflammation is a common pathogenetic factor in both rosacea and FMS. Furthermore, the association of both diseases with autoimmunity, chronic inflammation, and psychological stress is clear. Hence, we purposed to investigate the frequency of FMS in patients with rosacea and the association between the FMS and rosacea duration, severity, and quality of life.

METHODS

Ethical aspects

The present study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Giresun University under the 1205.07. KAEK-116/2019 approval number.

Study design

In our setting, a total of 94 consecutive rosacea patients and 87 age- and sex-matched controls had been enrolled in this prospective, controlled, cross-sectional study. The exclusion criteria included a history of malignancy, musculoskeletal, neurological, endocrinological, rheumatic diseases, major depression, congestive heart failure, other cutaneous diseases, younger than 18 years old, pregnant women, and receiving any treatment for rosacea within the last 3 months. As such, all the patients with rosacea were examined by the same dermatologists and classified into four subtypes according to the *National Rosacea Society* classification criteria[13]. The rosacea clinical scoring system established by the *American Rosacea Society* in 2004 was used to evaluate the clinical severity of rosacea. In this scoring system, signs and symptoms are graded from 0 to 3 as absent, mild, moderate, and severe, which leads to the rosacea severity score being classified as 0–9 mild, 10–18 moderate, and ≥19 severe[14,15].

The Rosacea-specific Quality-of-Life (RosQol) scale and Dermatology Quality-of-Life Index (DQLI) were used to evaluate the effect of rosacea on quality of life. DQLI is a questionnaire consisting of 10 questions regarding symptoms and emotions, daily activities, leisure activities, work and school, personal relationships, and treatment in the previous week. The scoring is "quite a lot=3 points", "lot=2 points", "mild=1 point", "none=0 points", and "not related=0 points", and the total score of the scale, which can vary from 0 to 30, is the sum of the scores of each question[16]. RosQol consists of 21 questions and 3 sub-dimensions such as the emotions dimension (7 items), the functions dimension (3 items), and the symptoms dimension (11 items). The answer options are structured in a five-point Likert style as "never (0 points)", "rarely (1 point)", "sometimes (2 points)", "often (3 points)", and "always (4 points)", constituting a total score ranging from 0 to 84[16]. High scores in DQLI and RosQol indicate low quality of life[16,17].

The 2016 American College of Rheumatology (ACR) diagnostic criteria were used as diagnostic criteria. The scale used in the 2016 ACR diagnostic criteria consists of two parts: (i) the Widespread Pain Index (WPI) and (ii) the Symptom Severity Scale (SSS), which leads to a total fibromyalgia score (FS). FMS was diagnosed as possessing generalized pain and symptoms for 3 months, with pain in at least four of the five anatomic locations determined except for the chin, chest, and abdomen (WPI ≥7 with SSS ≥5 or WPI 4–6 with SSS ≥9) in light of the 2016 ACR diagnostic criteria[18]. To this end, the fibromyalgia impact questionnaire (FIQ), consisting of 10 self-administered scales related to physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being, was applied to all the participants in order to determine the FMS-related effect rate and functional restriction. A score between 0 and 100 is possible from the survey. The average score of a patient diagnosed with FMS is 50, and an increase in the score means that the disease is affected[19].

Statistical analysis

Statistical analyses were performed using the SPSS software, version 23. Parametric, nonparametric, and categorical parameters were presented respectively as mean±standard deviation (SD), median [interquartile range (IQR)], and numbers (%). Analysis of skewness and kurtosis was used to test the assumption of normality, and values between -1.5 and +1.5 were considered to provide the assumption of normality. Mann-Whitney U test was used when the data did not support the assumption of normality, whereas t-test was used for the opposite. The chi-square

and Fisher's exact tests were used to identify the significance of the relationships between categorical variables. The Spearman correlation coefficient was used to evaluate the relationships between quantitative variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 22 (23.4%) cases of rosacea were diagnosed with FMS, while 8 members of the healthy control group (9.2%) also had FMS. The frequency of FMS and FIQ scores were significantly higher in rosacea than in the control (p=0.01 and p=0.01, respectively) (Table 1). The papulopustular rosacea was recognized as the most frequent subtype (53.2%), while the disease severity was moderate in 55.3% of the cases. The mean rosacea severity score was detected as 12.35±4.44, and their clinical characteristics are summarized in Table 2. No difference was recognized between the cases with and without FMS in the rosacea group in age, sex, duration of rosacea, family history, subtype, and severity of rosacea. Of note, DLQI and RosQol were higher in rosacea with FMS (p=0.006 and p=0.004, respectively) (Table 2). Notably, a statistically significant weak positive correlation was detected between DQLI, RosQol, FIQ, SSS scores, and FS (r=0.35, r=0.259, and r=0.32 and r=0.376, r=0.305, and r=0.312, respectively) (Table 3).

DISCUSSION

Rosacea is a common chronic inflammatory skin disease progressing with unclear pathogenesis and associated with multiple comorbidities, including neurologic, psychiatric, and rheumatologic diseases such as migraine, anxiety, depression, hypothyroidism, rheumatoid arthritis, and lupus erythematosus[3,4]. FMS is a clinical condition with widespread pain, usually accompanied by somatic and emotional symptoms[7]. Rosacea and FMS share similar commonalities in the chronic course, pathogenesis, association with several comorbidities, and triggering factors[3,4,7]. Both rosacea and FMS can be aggravated by emotional stress and environmental factors such as heat, cold, and light[6,7]. A study, which is a cross-sectional study incorporating 100 females with rosacea and 100 female controls, has investigated the association between rosacea and FMS to date. This study used the 2010 ACR criteria for diagnosing FMS, revealing FMS was higher in the rosacea (37% in the rosacea and 21% in the control, p=0.019)[20]. Similarly, our preliminary results revealed that rosacea had FMS (23.4%) at higher rates than the healthy control (9.2%), and the frequency of FMS was higher than in the normal population, estimated at around 2–3%[7]. The authors reported a higher frequency of FMS (37%), compared to our findings,of 23.4%[20]. We estimate this high level might be due to FMS being incorporated solely in female cases and utilizing different diagnostic criteria for FMS in the aforementioned study. In addition, they reported no difference in FIQ scores between the patients and the control group[20]. Contrarily, we recognized higher FIQ scores in cases with rosacea than in controls.

Numerous factors have been reported to contribute to rosacea's molecular and histopathologic mechanisms. Of note, the innate immune system and neurovascular dysregulation have been regarded as being primarily implicated in the pathology

Table 1. The presence of fibromyalgia and assessment of widespread pain index, symptom severity scale, fibromyalgia score, and fibromyalgia impact questionnaire score in rosacea and control group.

	Rosacea (n=94)	Control (n=87)	p-value
Age (years), mean±SD	40.90±14.42	41.06±13.73	0.942
Sex			
Female	77 (81.9%)	72 (82.8%)	0.882
Male	17 (18.1%)	15 (17.1%)	
Diagnosed with FMS	22 (23.4%)	8 (9.2%)	**0.010**
Female	20 (90.9%)	8 (100%)	
Male	2 (9.1%)	0 (0%)	
WPI, median (IQR)	1.00 (0.00–6.25)	1.00 (0.00–3.00)	0.557
SSS, mean±SD	4.58±3.23	3.94±2.75	0.157
FS, median (IQR)	6.50 (3.00–12.50)	5.00 (3.00–8.00)	0.157
FIQ, mean±SD	34.25±23.09	26.09±19.21	**0.010**

FMS: fibromyalgia syndrome; WPI: widespread pain index; SSS: symptom severity scale; FS: fibromyalgia score; FIQ: fibromyalgia impact questionnaire. Bold indicates statistically significant p-values.

Table 2. Comparison of patients with and without fibromyalgia syndrome according to the demographic, clinical characteristics, dermatology life quality index, and Rosacea-specific Quality-of-Life instrument in the patient group with rosacea.

	Rosacea with FMS (n=22)	Rosacea without FMS (n=72)	Total (n=94)	p-value
Age, years, mean±SD	44.32±12.71	39.86±14.83	40.90±14.42	0.206
Sex				
Female, n (%)	20 (90.9)	57 (79.2)	77 (81.9)	0.343*
Male, n (%)	2 (9.1)	15 (20.8)	17 (18.1)	
Duration of rosacea, years, median (IQR)	3.00 (1.00–4.25)	2 (1.00–6.75)	2 (1–5.25)	0.658
Positive family history, n (%)	6 (27.3)	20 (27.8)	26 (27.7)	0.963
Rosacea subtype, n (%)				
Erythematotelengiectatic	11 (50)	31 (43.06)	42 (44.68)	0.654
Papulopustular	11 (50)	39 (54.17)	50 (53.2)	
Phymatous	0	2 (2.78)	2 (2.13)	
Ocular†	9 (40.91)	18 (25)	27 (28.72)	
Rosacea severity, n (%)				
Mild	8 (36.36)	23 (31.94)	31 (32.98)	0.874
Moderate	12 (54.54)	40 (55.56)	52 (55.32)	
Severe	2 (9.10)	9 (12.5)	11 (11.70)	
Rosacea severity score, mean±SD	12.18±4.66	12.40±4.40	12.35±4.44	0.838
DLQI, median (IQR)	7.50 (4.75–10.75)	4.00 (3.00–8.75)	5 (3–9)	**0.006**
RosQol, mean±SD	54.73±16.78	41.88±18.40	44.88±18.75	**0.004**

IQR: interquartile range; SD: standard deviation; DLQI: dermatology life quality index; RosQol: Rosacea-specific Quality-of-Life instrument; FMS: fibromyalgia syndrome. *Fisher's exact test. †Some patients had ocular rosacea accompanying other subtypes, pure ocular rosacea was absent. Bold indicates statistically significant p-value.

Table 3. Correlation of rosacea findings and fibromyalgia scores (n=94).

	FIQ	SSS	FS
Duration of rosacea, years	0.009	0.100	0.050
Rosacea severity score	0.057	0.040	–0.016
RosQol	0.376**	0.305**	0.312**
DQLI	0.350**	0.259*	0.320**

DLQI: dermatology life quality index; RosQol: Rosacea-specific Quality-of-Life instrument; SSS: symptom severity scale; FS: fibromyalgia score; FIQ: fibromyalgia impact questionnaire. **p<0.001, *p<0.05.

of rosacea. Microscopically, a mild-to-moderate perivascular lymphocytic infiltrate or granulomatous inflammation is exhibited, while occasional plasma cells resemble an important clue for diagnostic purposes. Active pustular lesions are akin to superficial folliculitis, whereas older lesions frequently resemble granulomatous perifolliculitis. In addition, increased neurogenic inflammation in histopathology, which is correlated with allodynia, sleep disturbance, fatigue, and a decrease in the pain threshold, emerges in the skin in FMS cases[21,22]. Herewith, we suggest that the increased frequency and impact rate of FMS that we have detected in patients with rosacea may be due to increased neurogenic inflammation and increased neuropeptide levels, which play a common role in the pathogenesis of both rosacea and FMS.

In the present study, rosacea with FMS was detected to possess a lower quality of life than those without FMS, though there was no difference in terms of severity, duration, and type of rosacea. We found a positive correlation between the DLQI and RosQol and the FIQ score and SSS. Of note, the SSS scale includes emotional, cognitive, and psychological components such as fatigue, sleep disturbance, and depression[18]. Some authors reported that a positive correlation was being recognized between DLQI and FIQ scores, similar to our preliminary results (r=0.39; p=0.017)[20]. Although both studies had similar results, we believe that the inclusion of rosacea patients who did not receive any treatment is the strength of our study. Various studies have revealed that psychiatric comorbidities and underlying emotional stress affect the quality of life in dermatological diseases. It is known that both rosacea and FMS are triggered by emotional stress, and psychiatric comorbidities such as anxiety and depression accompany both diseases.

Neuro-immuno-cutaneous inflammation occurs with the effect of various neuropeptides, cytokines, and neurotransmitters released by psychological stress[1,8,23,24]. We postulate that the so-called rosacea-FMS association might be related to the augmented emotional stress in cases and the underlying common pathophysiological mechanisms.

Limitations

The limitations of the present study were (i) the constitution of a single-center institute, (ii) not evaluating the levels of neuroinflammatory biomarkers, (iii) not assessing the psychological impact on a specific validated scale, and (iv) enrolling limited numeric values of the cases.

CONCLUSION

These data suggest that the FMS frequency and impact rate are augmented in cases with rosacea, independent of their disease severity. Dermatologic and disease-related quality of life is attenuated in rosacea with FMS and correlated with disability scores for FMS. To the best of our knowledge, this is the first study in English literature regarding FMS frequency in rosacea patients of both sexes and evaluating the relationship between the clinical severity of rosacea and FMS. Our preliminary findings from a single institute experience support the notion that rosacea with FMS has more restrictions in their daily routines than rosacea alone. Last but not least, physicians must be vigilant about this phenomenon, and further studies are required to reveal the mechanisms that explain the coexistence of rosacea and FMS.

AUTHORS' CONTRIBUTIONS

SK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **IDO:** Methodology, Project administration, Resources, Validation, Visualization. **IFS:** Methodology, Software, Project administration, Resources, Validation, Visualization. **FK:** Methodology, Project administration, Resources, Validation, Visualization. **IS:** Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **BA:** Methodology, Project administration, Resources, Validation, Visualization. **DS:** Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Feminization of science: female pioneering in the healthcare area

Gisele Vissoci Marquini[1*], Letícia Maria de Oliveira[1], Claudia Cristina Takano[1], Marcia Maria Dias[1], Eduarda Vilela Silva[2], Ana Beatriz Amorim Nunes[2], Zsuzsanna Ilona Katalin de Jármy-Di Bella[1], Marair Gracio Ferreira Sartori[1]

INTRODUCTION

The phenomenon of the feminization of science has been consolidated over the last few decades. The growth of female participation in science, specifically in medicine, is evident in the evolution of the number of women who graduated each year and the increase in their participation in the labor market, in Brazil and in most parts of the world[1].

Historically, the first women to remove barriers to accessing medical education deserve to be highlighted, not only because of the relevance of their contributions to society but also because they are examples of breaking paradigms. This phenomenon of greater job opportunities for women and access to social benefits, with consequent gains in productivity and competitiveness for the economies of the countries, is largely due to the legacy of the pioneering spirit of women who gave voice to their purposes, especially in the area of science and medicine[1,2].

However, society does not always witness the progressive decrease in gender differences in science. Several authors have shown that female physicians still differ from men in the choice of specializations, territorial fixation, working hours, remuneration, and the way of professional practice[1,2].

Given this scenario, the objective of this study was to collect, from a historical perspective, a brief biography and relevant data about the 10 main pioneer women in science and their contributions to society. As a secondary impact, the authors discuss the role of these women in breaking paradigms in the context of gender inequality in science, focusing on current medicine.

METHODS

For descriptive data, the Brazilian Medical Demography prepared by the Federal Council of Medicine and Regional Council of Medicine of the State of São Paulo (2011, 2013, 2015, and 2018) was used. The evaluation of articles from PubMed, the Scientific Electronic Library Online, and the National Health Library databases was also included, using the descriptors "Medicine," "Career progression," "Leadership," "Medical education," "Women," and "Gender Inequality."

As this study is a qualitative descriptive research, focusing on the history of women in science, including the demographic context of medicine, there was no date, language, and/or nationality limit for the studied articles or area of science. Relevant articles from public domain sources have been included and properly referenced. As it was not a research involving human beings, there was no need for the approval of the research by the Ethics Committee or an informed consent form.

RESULTS

Next, it follows through a historical perspective, the collection of the 10 women who historically stood out in the areas of science, especially medicine, due to their relevance, pioneering spirit, and legacy to society.

Elizabeth Blackwell

Elizabeth Blackwell was born in 1821 in England. She challenged society at the end of the 19th century by being the first woman to enter a medical school[2-6].

Gerty Cori

Gerty Cori was born in Prague, Czech Republic, in 1896. Based in the United States, Cori was the first woman to receive the Nobel Prize in Medicine in 1947 for her studies and discoveries that expanded the understanding of diabetes[2-8].

[1]Universidade Federal de São Paulo, Department of Gynecology, Urogynecology and Vaginal Surgery Sector – São Paulo (SP), Brazil.
[2]Universidade Federal de Uberlândia, Academic of the Medicine Course – Uberlândia (MG), Brazil.
*Corresponding author: giselemarquini@gmail.com
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Rita Lobato Velho Lopes

Despite prejudice, Lobato became the first Brazilian doctor, trained in Brazil in 1887, and the second in Latin America, by defending the thesis "Parallel between the methods recommended in cesarean section"[2-8]. In her clinical practice in Rio Grande do Sul, she aimed to demystify the stigma that women's modesty was more important than their health[9].

Maria Augusta Generoso Estrela

Maria was the first Brazilian to receive a scholarship abroad. Even though she was only 16 years old – too younger than allowed – the young woman managed to get into the New York Medical College and Hospital for Women[2-6].

Françoise Barré-Sinoussi

Françoise Barré-Sinoussi is a French virologist, born in 1947, who began her research at the Pasteur Institute in the early 1970s, where she devoted herself to the study of retroviruses. Her studies were instrumental in identifying HIV as the cause of AIDS. Recognition came in 2008, with the Nobel Prize in Physiology and Medicine[2-6].

Ana Néri

Considering the pioneer of nursing in Brazil, Néri provided assistance in the Paraguayan War, in 1865, after becoming a widow. In 1923, the first nursing school in Brazil was named after Ana Néri[2-6].

Florence Nightingale

Florence Nightingale settled in England and served in the Crimean War (Russia,1953), where she treated soldiers wounded during the battle[2]. The hygiene and sanitary aspects of the place were determining elements for the healthcare conditions of the people served, encouraged by her[3].

Patricia Bath

Patricia always knew she wanted to be a doctor, but she faced a lot of racial discrimination to get into medical school. She created treatments for cataracts and co-founded the American Institute for the Prevention of Blindness[4-6].

Mae Jemison

Being a astronaut, physician, entrepreneur, and Star Trek fan, Mae Jemison was the first African-American woman to reach space. "The first thing about empowerment is understanding that you have a right to be involved. The second is that you have important contributions to make, and the third is that you have to take risks to make those contributions" (Mae Jemison)[4-6].

Zilda Arns

Zilda Arns (1934–2010) was a pediatrician and public healthcare specialist, creator of the Pastoral da Criança, and mainly responsible for the historic reduction of infant mortality in Brazil and for the improvement of the living conditions of millions of children in several countries of the world[10].

DISCUSSION

Vanguard of women in medicine

In the Middle Ages, women who were involved in medicine were considered representatives of Satan (healers) and condemned to death at the stake. Their only alternative was marriage or the convent; however, the work of midwives was allowed[11,12]. In the Renaissance period, Italy was the exception. However, the woman is seen as a representation of beauty, procreation, and virtue, to the detriment of her intellect. Chronic diseases are considered "women's diseases."[11,12]

During the French Revolution, based on the thesis of the "Incurable Inferiority of the Female Gender," the philosophy of return to nature preached that the basic role of women was relegated to that of wife and mother. The greatest impact in this period was the outbreak of the Feminist Movement in Germany, where many medical faculties paved the way for 400 women to enroll in schools in 1899[11,12].

The world wars ironically contributed to the female struggle to enter the healthcare area as protagonists. During the First World War, women were inserted due to the need to replace those who were drafted. They dedicated themselves to nursing (France/Germany), and when they were doctors, they were less accepted and received less honors. Social and political movements, industrial society, and intense cultural transformation (1960–1970) drove women to public universities in search of a life project beyond domestic[11,12].

Scenario of the current feminization of medicine

In recent years, the percentage of women in the total population of physicians in Brazil follows the global trend of feminization of medicine[1]. Women are already the majority among recent graduates and among doctors under the age of 35 years. They represent about 57.4% in the group up to 29 years old and 53.7% in the group between 30 and 34 years old. Among the older ones, the participation of men continues to be higher; about 54.8% are between 40 and 44 years old and 62.5% are between 60 and 64 years old. Despite this, gender inequalities in remuneration and occupation by specialties remain[13].

The female presence is greater in the specialties of Pediatrics, Family and Community Medicine, Gynecology and Obstetrics, and Internal Medicine, and men are the majority in surgical specialties of Urology, Orthopedics, and Traumatology, among others[13]. Women, ahead of their time, who choose surgical areas such as neurosurgery, breakthrough the paradigms of prejudice and inequality[14].

Although the number of women practicing medicine is increasing, the salary is still lower than that of men who occupy the same positions. This was one of the conclusions of the fourth edition of the Medical Demography Survey in Brazil 2018[15]. When the variable length of practice was analyzed, the researchers observed salary differences in all categories, indicating that the disparity is not produced throughout the medical career.

Inequality between genders persists in terms of working hours, consultations, and shifts[15], not only in Brazil but also in developed countries, even in specialties that are more prevalent among women such as pediatrics[15]. Studies carried out in countries such as Canada and the United Kingdom, evaluating specific subgroups of physicians, revealed salary discrepancies based on sex and gender between research, academic, and clinical groups[16,17].

Even in academic medicine, no difference is noted. Men are implicitly seen more as leaders than women[18]. In a study of internal medicine residents, most felt that gender was among the top three disadvantages in directing a healthcare team[19]. According to this study, female residents described feeling stressed when violating gender behavioral norms and conducting cardiac resuscitation[19]. Likewise, female residents reported that their decisions were challenged more often than men and also perceived negative feedback in residency assessments for showing assertive leadership behaviors[18,19].

On the contrary, in the challenge of overcoming all explicit and implicit prejudices, women physicians and researchers have consolidated their leadership and excellence in ethics and scientific quality in recent decades. The role of women is recognized and there are stories of determination and overcoming in the scientific area and throughout civil society through professionals such as the doctor Rossana Pulcineli Vieira Francisco, Ph.D., President of the Association of Gynecology and Obstetrics of the State of São Paulo (SOGESP), Brazil, biennium 2020–2021, the largest federation of FEBRASGO in the country[20]. Next is the doctor Marair Gracio Ferreira Sartori, Ph.D., cited by the other authors without conflicts of interest in the result or ethical aspects, the first female head of the Department of Gynecology and Obstetrics at Paulista School of Medicine, Federal University of São Paulo[21], among others who lead, represent, and train other professionals in the field of science and healthcare in the country. Finally, Nísia Trindade Lima, Ph.D., president of the Oswaldo Cruz Foundation (Fiocruz, 2017), is the first woman to head the Ministry of Health in Brazil (2023).

In view of the above, the consolidation of women in science is aligned with ethical evolution, humanization, transparency, credibility, respect, representativeness, innovation, excellence, and commitment established in the midst of professional practice, whether in patient care or in the management of foundations, universities, medical societies, companies, and/or other entities.

CONCLUSION

Examples of intrepid women paved the way for generations of engineers, biologists, nurses, mathematicians, doctors, astronauts, physicists, and other professions that women decide to play in society. The legacy of the contributions of the female population in science goes beyond the area of healthcare and enhances the development of each woman's purposes, whether in female entrepreneurship, teaching, technology, agriculture, politics, among other diverse sectors. The dedication of women to domestic services, by free choice, and not by gender inequality, demonstrates the socioeconomic evolution of a nation.

Steps are being taken so that the representation of women in society is in accordance with personal and professional aptitudes, by free will, and never based exclusively on gender.

ETHICAL ASPECTS

The authors declare no conflict of ethical aspects in results of this article.

AUTHORS' CONTRIBUTIONS

GVM: Conceptualization, Data curation, Investigation, Validation, Writing – original draft, Writing – review & editing. **LMO:** Supervision, Validation, Visualization. **CCT:** Resources, Software, Supervision. **MMD:** Conceptualization, Data curation, Investigation. **EVS:** Conceptualization, Data curation, Investigation, Writing – original draft. **ABAN:** Conceptualization, Data curation, Investigation, Writing – original draft. **ZIKJDB:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MGFS:** Conceptualization, Data curation, Validation, Visualization, Writing – original draft.

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REVIEW ARTICLE

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Granulosa cells and follicular development: a brief review

Giovanna Santos Cavalcanti[1], Kátia Cândido Carvalho[1], Cecília da Silva Ferreira[1], Peter Andre Chedraui Alvarez[2,3], Pedro Augusto Araújo Monteleone[4], Edmund Chada Baracat[1,4], José Maria Soares Júnior[1,4*]

INTRODUCTION

The main consequence of delaying motherhood is compromising a woman's reproductive life with a decline in fertility. A critical step in assisted human reproduction is the evaluation of the quality of oocytes and embryos before embryo transfer, and age is a predominant factor in that capacity. In fact, granulosa cells (GCs) have been proposed as fundamental for the quality of oocytes due to their close biodynamic interrelationship[1,2]. Also, GCs with *theca cells* are the main steroidogenic cells of the ovary. The development of follicles in the ovaries begins with the proliferation of GCs, which change their shape from flat to cubic and from a single layer to a multilayer, depending on the follicular phase[3-5]. The aim of the present document was to perform a narrative review, focusing on the role of GCs in follicle maturation and oocyte quality, as well as in the molecular mechanisms involved in this process.

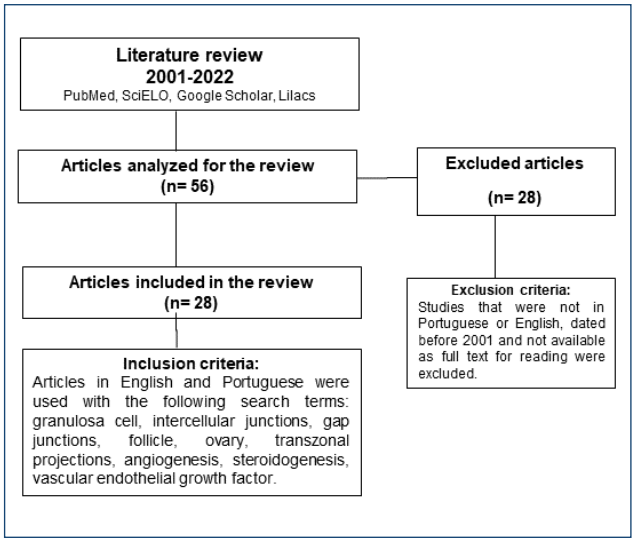

Figure 1. Algorithm of search strategy for the narrative review.

METHODS

This is a narrative review of experimental studies on the physiology of GCs.

Data sources and search strategy

To identify the relevant studies, databases, namely, PubMed, SciELO, Google Scholar, and Lilacs, were accessed from January 1997 to November 2022 with no constraint on the year of publication. Retrieval of the articles was carried out using the search strategies described in Figure 1. To supplement the search, references from retrieved articles were also examined for further data recovery (Figure 1).

Study selection and quality assessment

Study selection and assessment of titles and abstracts were conducted independently by two blinded researchers (G.S.C. and C.S.F.) with strict observation of the inclusion and exclusion criteria. In the next stage, the selected articles were critically assessed for inclusion or non-inclusion in this review. When there was disagreement between the two researchers, a third reviewer (J.M.S. Jr) was consulted.

The inclusion criteria were as follows: (a) availability of complete text; (b) articles written in Portuguese, English, Spanish, and French; and (c) in vitro and histological studies related to GCs.

[1]Universidade de São Paulo, Hospital das Clínicas, Faculty of Medicine, Department of Obstetrics and Gynecology, Discipline of Gynecology, Laboratory of Structural and Molecular Gynecology (LIM 58) – São Paulo (SP), Brazil.
[2]Universidad Católica de Santiago de Guayaquil, Instituto de Investigación e Innovación en Salud Integral – Guayaquil, Ecuador.
[3]Universidad Católica "Nuestra Señora de la Asunción", Facultad de Ciencias de La Salud – Asunción, Paraguay.
[4]Universidade de São Paulo, Hospital das Clínicas, Faculty of Medicine, Discipline of Gynecology – São Paulo (SP), Brazil.
*Corresponding author: jsoares415@hotmail.com
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RESULTS

Granulosa cells

Granulosa cells are characterized by having a squamous and cuboid shape, which gradually becomes cubic. Although GCs are sources of pro-angiogenic factors for the developing follicle, these cells make up an avascular layer that surrounds the oocytes in the cortical region of the ovary and are separated from the theca cells (which are vascularized) by a basal lamina[6-13].

During puberty, with the production and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary gland, the development and maturation of primordial follicles begin in the peripheral region of the ovarian cortex, a process called folliculogenesis[8,12,13]. The first stage of follicular development is marked by egg enlargement (the diameter increases from two to three times the original size), proliferation, and morphological alteration of the GCs, which change from epithelial to cuboid cells. Studies show that this change in GC morphology is closely linked to the regulation of steroidogenesis and cell proliferation in follicles[8,12-16].

The process of follicular development proceeds with a succession of mitoses and the formation of other cell layers composed of GCs. The primary follicle is then called a secondary follicle. Subsequently, spindle cells cluster around GCs, giving rise to a second cluster of cells called the theca. This cell layer, unlike the one composed of GCs, is divided into two layers (internal and external). In the theca interna, cells are responsible for the production of androgenic steroids, namely, androstenedione and testosterone, in response to LH[8,17].

The GCs produce a follicular fluid that has multiple functions, including oocyte maturation regulation and follicle growth control. This follicular fluid is composed of estrogen, progesterone, egg maturation inhibitor (EMI), melatonin, and inhibin[8,17]. The accumulation of this liquid inside the follicle induces the formation of an antrum. At this stage, the growing follicle becomes an antral follicle (Figure 2), also called a tertiary or pre-ovulatory follicle[8,17].

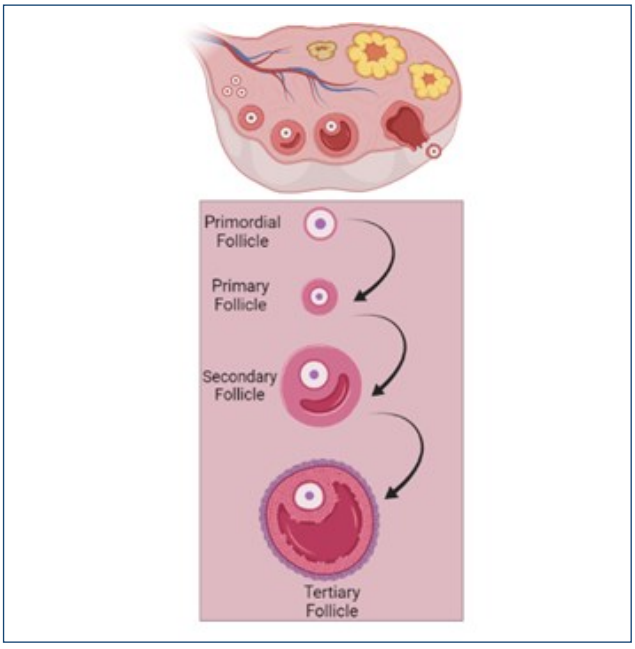

Figure 2. Schematic representation of follicular development. Source: Biorender (https://app.biorender.com/) developed by the authors.

The role of granulosa cells in folliculogenesis

The role of GCs in regulating the development of oocytes depends on their stage of differentiation and the communication between them. This intercellular communication can be mediated by paracrine, autocrine, or endocrine signaling and is responsible for metabolic cooperation that involves the transport of glucose, nucleotides, amino acids, and metabolites to the egg[14,15]. The communication between the developing oocyte and GCs is facilitated by membrane processes rich in microtubule structural proteins that support the active movement of organelles called transzonal projections (TZP). These extensions originate from GCs and reach the egg membrane through the zona pellucida, allowing cell signaling and the transport of substances between the two cells, such as growth factors, for example, through gap cell junctions of the GAP type (Figure 3A). Mora et al.[18] reported that during follicular growth, with the emergence of the zona pellucida, TZPs become abundant, accompanying the increase in the number of microvilli in the ovule. Also, the electrodense regions at the contact points between TZPs and microvilli may represent cell GAP junctions between GCs and oocytes, which are essential for follicle development and oocyte quality[12,13,18-20].

In antral follicles, GCs play a key role in modulating signaling for energy production during the processes of glycolysis and the tricarboxylic acid cycle. This follicular development determines the response of the egg in the emission of signals that culminate with the synthesis of adenosine triphosphate (ATP)[21,22].

The GCs participate in the formation of new blood vessels from those existing around each follicle. Endothelial and mural cells are destabilized, later migrate toward angiogenic stimuli, and proliferate, forming a new vessel, in a process called angiogenesis. This process requires the participation of the VEGF (vascular endothelial growth factor), which is responsible for stimulating endothelial cell

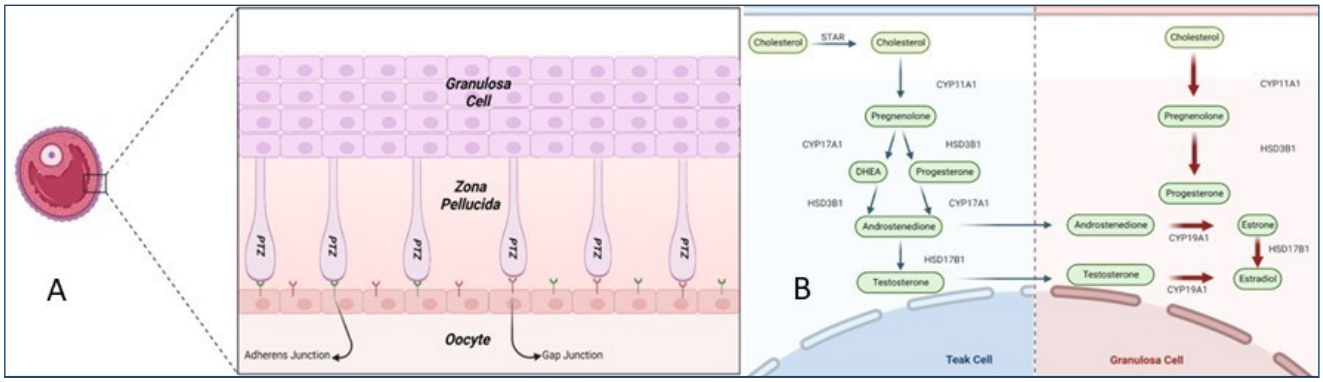

Figure 3. (A) Schematic representation of the transzonal projections between the ovule and the granulosa cells. (B) Steroidogenic pathway (theca cells and granulosa cells). Source: Biorender (https://app.biorender.com/) developed by the authors.

proliferation, endothelial cell migration, and blood vessel formation. The production of VEGF is stimulated by FSH and LH. Also, theca cells contribute to VEGF production during follicle growth[23-25,29].

Along with the continuous production of VEGF, endothelial cell proliferation occurs, and during this period of remodeling, high concentrations of VEGF support endothelial cell survival. During the development of the corpus luteum, endothelial cells reconnect and align to form tubules under the influence of VEGF. The newly formed vessels are stabilized by the recruitment of pericytes through the production of platelet-derived growth factor B (PDGFB) and the activity of the production of angiopoietin. Consequently, luteal cells are now fully vascularized, and therefore VEGF concentrations must remain elevated throughout luteal development to maintain immature vessel survival[26,29].

Granulosa cells and steroid hormones

In follicles, FSH stimulates GC proliferation and the production of steroid hormones. This process begins with the uptake of cholesterol (Figure 3B) into cells (GC and theca interna) and its conversion into pregnenolone by cytochrome P450 (CYP450) in the mitochondria. The formed pregnenolone diffuses from the mitochondria to the smooth endoplasmic reticulum, where it is processed and converted into progesterone when it undergoes the action of the 3β-hydroxysteroid dehydrogenase (HSD3B) enzyme and can also be converted into dehydroepiandrosterone sulfate (DHEA-S) by the action of the 17α-hydroxylase (CYP17A). HSD3B and CYP17A catalyze the conversion of DHEA and progesterone to androstenedione, respectively. Androstenedione can be converted to testosterone within the theca interna, by the action of 17β-hydroxysteroid dehydrogenase (HSD17B), or into estrone, testosterone, or 17-beta-estradiol (E2), within the GC, by the action of the aromatase enzyme (CYP19A1). Furthermore, in GCs, estrone can be converted into E2 through the action of HSD17B[17-19]. The synthesized estrogens in turn are also pro-proliferative factors for GCs, potentiating their action in the synthesis of steroids[23-25,27].

Angiogenesis

Ovulation and luteal development require the coordinated activity of several angiogenic factors and various cell types. VEGF regulates angiogenesis by stimulating endothelial proliferation, migration, and survival and is very necessary at all stages from a secondary follicle to a mature corpus luteum[27,28]. The accumulation of VEGF in the follicle and the consequent diffusion to the capillaries generate an angiogenic gradient that may regulate the development of a blood vessel network with the participation of the theca cell layer, located between the basal membrane and the granular layer, resulting in the potentiation of the supply of nutrients, oxygen, and hormones to the GC and oocyte[26,28].

In the preovulatory follicle, the granulosa layer remains avascular. During follicular development, VEGF and FGF (fibroblast growth factor) accumulate. Proteolytic activity increases after the LH surge, as does heparanase, which degrades the basement membrane, releasing sequestered angiogenic factors such as FGF and allowing vascular cells to migrate under the influence of VEGF. Also, the large increase in FGF levels may stimulate the disassembly of the vasculature and the dispersion of endothelial cells. The initial angiogenic step is the creation of capillaries in the thecal vasculature toward GCs that produce VEGF. Blood flow then resumes as these capillary networks start to connect with one another, create tubules, and attract pericytes. After ovulation, the process of maturation of

the vasculature continues with the corpus luteum. Also, there is extensive endothelial cell proliferation and migration in order to re-establish connections with other endothelial and luteal cells. Fibronectin participates in this process. After that, FGF concentrations decrease, and the capillary beds are rebuilt. Consequently, blood flow and progesterone production increased with this process[23,27,28].

DISCUSSION

The angiogenic process and intercellular communications of cells in the ovarian follicle are essential for follicular maturation quality as well as adequate sex steroid production. The analyzed studies report that GCs provide nutrition to the oocytes, and this action is directly related to good oocyte quality[14,15].

The communication between the GCs and follicular cells is mediated by PTZ and gap junctions, which are involved in the processes of follicular development and oocyte maturation. These projections are essential to maintain polarity and communication between cells, and the absence of those structures interrupts oocyte maturation as well as folliculogenesis. Therefore, these junctions are extremely important for the study of folliculogenesis[13].

Vascular endothelial growth factor is required for the development of the secondary follicle into the mature corpus luteum. In this process, the FGF plays a role in angiogenesis and the transformation of follicular cells into luteal ones. The increase in FGF levels stimulates the extensive tissue remodeling that accompanies the rapid angiogenesis after ovulation, which is essential for progesterone production[21-23,26-28].

Although studies evidence the importance of GCs, their knowledge regarding research is still limited since most information about this cell population has been obtained from animal models and from the primary culture of human follicular aspirate cells during *in vitro* fertilization (IVF) procedures. During this scenario, a few cells are obtained, which are usually under the influence of supraphysiological amounts of hormones, generally used for IVF.

CONCLUSION

Vascular endothelial growth factor and FGF are involved in angiogenesis, follicular growth, and steroid production. In addition, this information can be important for developing new therapies in the assisted reproduction techniques.

AUTHORS' CONTRIBUTIONS

GSC: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **KCC:** Validation, Writing – original draft, Writing – review & editing. **CSF:** Formal Analysis, Writing – original draft, Writing – review & editing. **PC:** Writing – original draft, Writing – review & editing. **PAAM:** Writing – original draft, Writing – review & editing. **ECB:** Writing – original draft, Writing – review & editing. **JMS:** Project administration, Supervision, Validation, Writing – review & editing.

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REVIEW ARTICLE

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Management of fecal incontinence: what specialists need to know?

Sthela Maria Murad-Regadas[1*], Doryane Lima dos Reis[2], Henrique Sarubbi Fillmann[3], Antonio Lacerda Filho[4]

INTRODUCTION

According to the International Urogynecology Association (IUGA) and the International Continence Society (ICS), anal incontinence is the involuntary loss of feces and/or flatus, while fecal incontinence is the involuntary loss of feces[1]. The Rome IV criteria use the definition "recurrent uncontrolled passage of fecal material for at least 3 months[2]."

Fecal incontinence is very common, but due to the associated embarrassment, the condition is underreported and its actual prevalence is difficult to determine. The prevalence of FI is estimated to be 0.4–18% in the overall population[3] and 8.3% of non-institutionalized adults in the USA. About one-quarter of women have some involuntary loss of flatus or feces (anal incontinence) in late pregnancy, and one-fifth leak flatus or feces 1 year after giving birth[4]. So, the objective of our review was to describe the challenges and limitations of fecal incontinence management and describe the current options for treatment.

A MEDLINE and PubMed search were performed over the last 6 years. Keyword combinations include "fecal incontinence"; rehabilitation/biofeedback"; "sphincteroplasty"; or "sacral nerve stimulation". Direct searches of the embedded references were performed, and the authors reviewed the evidence-based update for the management and current options for the treatment of fecal incontinence.

ETIOLOGY AND PATHOPHYSIOLOGY

Fecal control is achieved by a combination of factors, such as intact anal sphincter muscles and pelvic muscles, intact neurological function, stool consistency, and preserved rectal sensitivity and compliance[4].

Since few women seek medical care for FI, physicians should actively inquire about symptoms. Recognizing common risk factors helps identify high-risk patients and epidemiological studies have identified a number of such factors (Table 1). In women, obstetric injury is particularly relevant owing to the risk of damage to the pelvic floor, anal sphincters, and pudendal nerves during the second stage of labor. In men, iatrogenic injury to the sphincter complex secondary to anal surgery is a factor in up to 59% of those presenting for assessment[5].

Table 1. Risk factors for fecal incontinence.

Variable	Categories
Age	
Abnormal stool consistency	Diarrhea, loose stool, fecal impaction
Pregnancy, parity	
Birth trauma	Operative Vaginal delivery , high degree laceration, episiotomy
Perianal surgery or trauma	Sphincterotomy, fistulotomy, hemorrhoidectomy, anal dilation
Neurologic cause	Dementia, stroke, spina bifida, spinal cord lesions, neuropathy, multiples sclerosis, cauda equina
Inflammation	Inflammatory bowel disease, fistula, radiation
Hemorrhoids	
Prolapso	Pelvic organ prolapsed, rectal prolapse
Congenital anorectal abnormality	
obesity	
Bariatric surgery	
Limited mobility	
Urinary incontinence	

[1]Universidade Federal do Ceará, School of Medicine, Department of Surgery – Fortaleza (CE), Brazil.
[2]Gastroclínica Cascavel – Cascavel (PR), Brazil.
[3]Pontificia Universidade Católica do Rio Grande do Sul, School of Medicine, Department of Surgery – Porto Alegre (RS), Brazil.
[4]Universidade Federal de Minas Gerais, School of Medicine – Belo Horizonte (MG), Brazil.
*Corresponding author: smuradccg@gmail.com
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The etiology and pathophysiology of FI and evacuation disorders are usually multifactorial. Table 2 shows the most common causes of FI, organized by category.

ASSESSMENT

A complete medical history is necessary to rule out underlying organic pathologies. The physician should also investigate bowel habits to ensure diarrhea and overflow constipation are not the causes of the loss of feces.

Symptom severity should be graded using a scoring system (Wexner/CCF Incontinence Score, St. Marks Incontinence Score), along with the patient's QOL (Quality of Life/FIQL score, Fecal Incontinence Severity Index/FISI) and urgency. The patient should be asked about bowel movements and frequency and about stool type to help identify triggers or events potentially aggravating symptoms and determine the time to onset of symptoms, previous treatments, and outcomes[6].

To identify risk factors, additional information may be collected, such as obstetrical stretch injury, abscess formation, surgery, radiation, and systemic factors like chemotherapy and diabetes. Obstetric anal sphincter injury, a form of major permanent maternal birth trauma, is likely to be underestimated because of missed diagnoses and occult tears[7].

Table 2. Etiology and pathophysiology of fecal incontinence.

Categories	Details/Definition
Acquired structural abnormalities	Obstetric injury (vaginal delivery)
	Anorectal surgery (sphincterotomy, fistulotomy, and hemorrhoidectomy)
	Rectal intussusceptions, prolapsed
	Sphincter-sparing bowel resection
	Trauma (pelvic fracture, anal impalement)
Functional disorders	Chronic diarrhea
	Irritable bowel disease
	Inflammatory bowel disease
	Radiation proctitis
	Malabsorption
	Hypersecretory tumors
	Fecal impaction (paradoxical diarrhea)
	Physical disabilities
	Psychiatric disorder
Neurological disorders	Pudendal neuropathy (radiation, diabetes, chemotherapy)
	Spinal surgery
	Multiples sclerosis
	Dementia
	Disorders of the central neurological system: stroke, trauma , tumor , infection, spina bifida

Physical examination should include a visual inspection at rest and at the maximum strain in order to assess the anal canal, perineal body, and urogenital area. Perianal surgery, trauma, and scars should be identified. This may be followed by a digital rectal evaluation of sphincter integrity, sphincter tone, compensatory auxiliary muscle contraction, anal canal length, posterior and anterior vaginal wall prolapse, rectocele, and palpable masses.

Physiology studies have attempted to correlate complaints, symptom severity, and clinical findings. Endoanal ultrasonography is currently the first-line imaging modality for FI, allowing to distinguish between intact and damaged anal sphincters (defects, scarring, thinning, thickening, and atrophy). The scan can show if the lesion involves the internal anal sphincter (IAS) or the external anal sphincter (EAS), or both. The number of defects and their circumferential extension (radial angle in degrees or clock hours) and longitudinal extension (proximal, distal, or full length) should be registered as well. In addition, 3D technologies allow for multiplanar measurements of length, thickness, area, and volume of sphincter damage[8].

Levator ani muscle trauma affects 15–55% of women after vaginal childbirth. A transvaginal approach is employed to visualize the anatomic integrity of the muscles and measure the levator hiatus area. Scanning will detect unilateral or bilateral detachment (discontinuity) of the levator ani muscles from their insertion on the pubic ramus on each side. Studies have shown that the severity of FI symptoms is significantly associated with the score of the defect on 3D ultrasonography[9].

An anorectal manometry is a useful tool in the assessment of the neuromuscular function of the rectum and anal canal, objectively evaluating the integrity of the anal sphincter muscles (IAS and EAS) and the neuromuscular motor and sensory innervations[10]. The technology also allows for continuous and dynamic spatiotemporal mapping of anorectal pressure, with easy and detailed data interpretation[11,12].

Patients with other clinical symptoms and findings may benefit from dynamic scanning modalities like dynamic ultrasonography, dynamic pelvic MRI, proctography, and urodynamics[13].

TREATMENT

The management of FI may be conservative or surgical. Dietary and lifestyle changes, medication, pelvic floor muscle

exercises, and physical therapy/biofeedback are recommended as first-line therapies.

Some dietary factors, such as excessive coffee consumption, can increase anal seepage, often in association with pruritus ani. A simple dietary exclusion of the offending food or drink for 1–2 weeks will clarify the contribution of these foods to the seepage. Perianal skin cleanliness without excessive rubbing with tissue paper also helps decrease secondary injury to the skin from rubbing and scratching and keeps seepage at a minimum[10].

Dietary fiber has been shown to help in the treatment of FI associated with loose stool (recommendation grade A). Patients with such symptoms should also refrain from ingesting alcohol or food that could loosen the stool (recommendation grade B). Instructions in bowel habits and skin care are useful in preventing FI-associated dermatitis (recommendation grade B).

Antidiarrheals, cholestyramine, and/or fiber supplements to bulk up stools can lead to improvement in a significant portion of patients. FI episodes may be reduced by bowel management in the form of enemas or suppositories for rectal stool volume reduction[13]. More recently, an anal irrigation system (Peristeen™) used in adults with low anterior resection syndrome has been shown to improve symptoms and quality of life[14]. The device consists of a rectal balloon, a pump, a pressure control unit, and a water container. Patients are instructed to irrigate the colon with up to 1.5 L of water a few times a week.

Pelvic floor exercise (biofeedback) is a first-line therapy for FI patients, although some studies have found no significant advantage of biofeedback over advice and reeducation[15]. Biofeedback therapy can improve rectal sensation and may enhance coordination between the perception of rectal distention and external sphincter contraction in patients with reduced rectal sensation. In a study involving 124 patients, Regadas et al.[16] found a 50% reduction in FI scores in approximately 50% of the patients. Patients with CCF-FI scores≥10, previous vaginal delivery, history of anorectal and/or colorectal surgery, and inability to maintain a squeezing effort were less likely to respond to biofeedback therapy.

SURGICAL MANAGEMENT OPTIONS

Correction of anatomy

Sphincteroplasty

Surgical correction is recommended for symptomatic patients with clearly defined anal sphincter muscle defects, such as a cloaca disrupting the normal circumferential anatomy. Direct repair may be by apposition or overlapping (the latter is preferred when adequate sphincters are present). Sphincteroplasty is performed to restore sphincter integrity. The technique is associated with good-to-excellent short-term results, but the effects tend to deteriorate over time, although some authors have reported sustained improvement[17].

No specific factors, like repeat repair, are predictors of treatment failure. Thus, women developing incontinence symptoms many years after obstetric trauma (especially with incomplete sphincter defects) may benefit from alternative treatment modalities like sacral nerve stimulation.

Defective anal sphincters may be treated with dynamic graciloplasty or replaced with artificial bowel sphincters (ABS)[17].

Injection of bulking agents

The ideal bulking agent would be a biocompatible compound small enough to inject yet large enough to minimize migration. Several implant materials have been proposed (autologous fat, synthetic bovine dermal collagen, Teflon, silicone [PTQ], carbon beads, and stabilized hyaluronic acid), and different injection sites (submucosal vs. intersphincteric space) and techniques (ultrasonography-guided vs. blind) have been tested, but no consistently significant differences have been observed with regard to the number of FI episodes, symptom severity, and quality of life. Minor adverse events, such as pain at the injection site and bleeding, may occur with the use of injectable bulking agents[2], but further studies are needed to clarify the issue.

Sacral neuromodulation

Studies have shown that fecal and urinary incontinence, low anterior resection syndrome (LARS), and constipation/obstructed defecation syndromes refractive to conservative management may be treated with sacral neuromodulation (SNM). The technique is reported to improve not only symptoms but also patient satisfaction and quality of life. Less invasive than conventional surgery, SNM consists of inserting electrodes through the S3 foramen to modulate the sacral neural pathway and thereby stimulate the pelvic floor. If symptoms improve by more than 50% within 2–3 weeks, the electrode is inserted permanently. SNM is indicated to treat FI in the following scenarios: (i) unsuccessful conservative treatment, (ii) sphincter defects up to 90 degrees, (iii) recovery from low anterior resection, (iv) cauda equina syndrome, and (v) congenital malformation. Relative contraindications for SNM include severe or rapidly progressive neurological disease and abnormal sacral anatomy. The proprietary SureScan™ system, a newly developed SNM technology, allows patients to have full-body MRI scans and uses a smart programmer to access all programs. Two systems

are available, namely, recharge-free (with a battery life of 6 years) and rechargeable (the neurostimulator needs recharging once a week for 30 min). SNM therapy is a safe and effective long-term treatment for patients with FI and patients with combined FI and LARS. The rate of complications is low, and if efficacy is lost, the organism usually responds to reprogramming and/or readjustment of the stimulator settings[18,19].

Stem cell injection

Most studies have focused on stem cell therapy in the treatment of anal sphincter incontinence in animal models. One recent review looked at heterogeneous techniques in which preparations are made of cells from skeletal muscle, bone marrow, and fat tissue, in that order of frequency. The characterization of the preparations was often incomplete, stemness was not always assessed, and distinct clinical situations (acute injury or healed injury with or without surgical reconstruction) were pooled. The authors acknowledged the need for further developments to establish indications, identify the ideal cell type, standardize cell preparation methods, and validate the route and number of cell delivery[20].

On the contrary, a randomized controlled study on a large sample of patients (n=288) of both sexes found a significant improvement in FI symptoms and quality of life in comparison to controls, although the physiological parameters remained unchanged. The current trend is to tailor the cell dose to individual needs for better outcomes[21].

Devices

A recent systematic review evaluated the clinical outcomes of treatment with a vaginal insert and three types of the anal inserts. The study reported improvements in continence and quality of life for patients who tolerated both anal and vaginal inserts. Adverse effects included discomfort, leakage, and slippage. Such devices appear to be useful, but the quality of the available evidence on their effectiveness is insufficient to make recommendations[22].

Fecal diversion (colostomy/ileostomy)

Fecal diversion is an effective and safe method to treat FI when all other options have failed. It is especially indicated in cases of severe neurogenic FI, a complete sphincter muscle defect refractory to surgical intervention, and severe radiation incontinence[17].

CONCLUSION

Fecal incontinence is a debilitating disorder that negatively impacts QOL. Patients are reluctant to seek care and report symptoms, and thus they feel overwhelmed. A complete assessment is needed to identify factors that might interfere with treatment. Treatment of FI can be challenging due to the multifactorial nature of the etiology. Management may be conservative or surgical. Nonsurgical management includes dietary changes and medication, while supportive measures include skin care and protective ointments. Pelvic floor rehabilitation/biofeedback is recommended as first-line therapy. Sacral neuromodulation may be considered a first-line surgical option for incontinent patients with and without sphincter defects.

AUTHORS' CONTRIBUTIONS

SMMR: Conceptualization, Data curation, Formal Analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **DLR:** Conceptualization, Data curation, Formal Analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **HSF:** Conceptualization, Data curation, Formal Analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **ALF:** Validation, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Auricular vagus nerve stimulation: a new option to treat inflammation in COVID-19?

Fernando Mendes Sant'Anna[1,2*], Rodrigo César Lima Resende[3], Lucas Bonacossa Sant'Anna[4], Sérgio Lívio Menezes Couceiro[2], Romero Bonacossa Soares Pinto[5], Mariana Bonacossa Sant'Anna[4], Liaw Wen Chao[6], Jozsef Constantin Szeles[7], Eugenijus Kaniusas[8]

INTRODUCTION

COVID-19 is an infectious disease caused by the new coronavirus (SARS-CoV-2), which invades alveolar epithelial cells through angiotensin-2 converting enzyme (ACE2) receptors[1,2]. Infection is triggered by the binding of the spike protein (S) of SARS-CoV-1 or SARS-CoV-2 to ACE2[3] and, through this binding, the virus enters the host cell, where ACE2 is later inactivated. As this enzyme is abundantly found in alveolar epithelial cells and in the myocardium, potentially serious damage can occur in the lungs and heart[2,4].

COVID-19 can cause acute respiratory distress syndrome (ARDS), leading to severe hypoxemia, and is associated with thromboembolic events. In ARDS, small-sized pulmonary blood vessels become more permeable, which leads to fluid leakage into the alveoli, impairing pulmonary gas exchange[5]. ARDS is characterized by generalized inflammation in the lungs, inflammatory cytokine storms, and an imbalance in the sympathetic-parasympathetic activity of the autonomic nervous system (ANS)[6].

Several treatments have been tried for ARDS from COVID-19, based on its pathophysiology using ACE-2 receptors, and some of the most feared complications such as pulmonary thromboembolism. Unfortunately, the results were not promising. The BRACE CORONA trial[7] determined whether discontinuation compared with the continuation of ACE inhibitors (ACEIs) or angiotensin-2 receptor blockers (ARBs) changed the number of days alive and out of the hospital through 30 days in 659 patients hospitalized with mild or moderate COVID-19 who were taking ACEIs or ARBs, and there was no significant difference for those assigned to discontinue vs. continue these medications. The ACTION trial[8] investigated whether patients hospitalized with mild to moderate COVID-19 and elevated D-dimer concentration benefited from therapeutic vs. prophylactic anticoagulation, and results at day 30 have shown that therapeutic anticoagulation did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation.

All that said and based on its preclinical effects and some initial clinical studies, auricular vagus nerve stimulation (aVNS) emerges as a promising therapy for the treatment of inflammation in COVID-19, especially its pulmonary manifestations, due to its positive effect on autonomic balance, as discussed in the following sections.

VAGUS NERVE, INFLAMMATORY RESPONSE, AND AUTONOMIC BALANCE

The vagus nerve (10th cranial pair) is the largest and most important nerve in the parasympathetic nervous system and modulates the immune response to inflammatory processes that occur in our body[9,10]. It is composed of sensory (»80%) and motor fibers[11].

Inflammatory mediators released due to any aggression (e.g., pro-inflammatory cytokines) activate vagal afferent fibers that

[1]Universidade Federal do Rio de Janeiro – Macaé (RJ), Brazil.
[2]Hospital Santa Izabel – Cabo Frio (RJ), Brazil.
[3]Hospital Nossa Senhora de Fátima – Patos de Minas (MG), Brazil.
[4]Fundação Técnico-Educacional Souza Marques – Rio de Janeiro (RJ), Brazil.
[5]Multivix Cachoeiro – Cachoeiro de Itapemirim (ES), Brazil.
[6]Universidade de São Paulo, Hospital das Clínicas – São Paulo (SP), Brazil.
[7]Medical University of Vienna, Department of Surgery, Division of Vascular Surgery – Vienna, Austria.
[8]Vienna University of Technology, Institute of Biomedical Electronics, Faculty of Electrical Engineering and Information Technology – Vienna, Austria.
*Corresponding author: fmsantanna@gmail.com
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convey information to the nucleus of the solitary tract (NST)[9]. Activation of NST neurons originates the anti-inflammatory response in the following two different ways[1]. In the first, known as the hypothalamic-pituitary adrenal axis (HPAA)[12], NST efferents to the paraventricular nucleus of the hypothalamus stimulate the release of corticotropin-releasing hormone (CRH), which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH reaches the adrenal gland, stimulating the production of glucocorticoids, which act on the spleen leading to reduction of cytokine release[2]. In the second way, known as "cholinergic anti-inflammatory reflex," NST efferents activate the dorsal motor nucleus of the vagus nerve (DMNV), and its cholinergic motoneurons project to the splenic nerve in the celiac ganglion, releasing acetylcholine (ACh) in the preganglionic terminals and provoking release of norepinephrine (NE) in the spleen, which ultimately inhibits macrophages' cytokines release, decreasing inflammation. Both responses are illustrated in Figures 1 and 2.

A shift in the balance of the ANS toward sympathetic predominance can lead to (chronic) diseases associated with this system[13]. In COVID-19, hyperactivity of the sympathetic nervous system can cause excessive release of plasma epinephrine and norepinephrine, which leads to pulmonary vasoconstriction and increased capillary permeability[14].

At this point, a positive feedback system is created in favor of the sympathetic system that causes an exponential worsening of symptoms. That is, acute lung injury causes an additional imbalance with increased sympathetic tone and significant

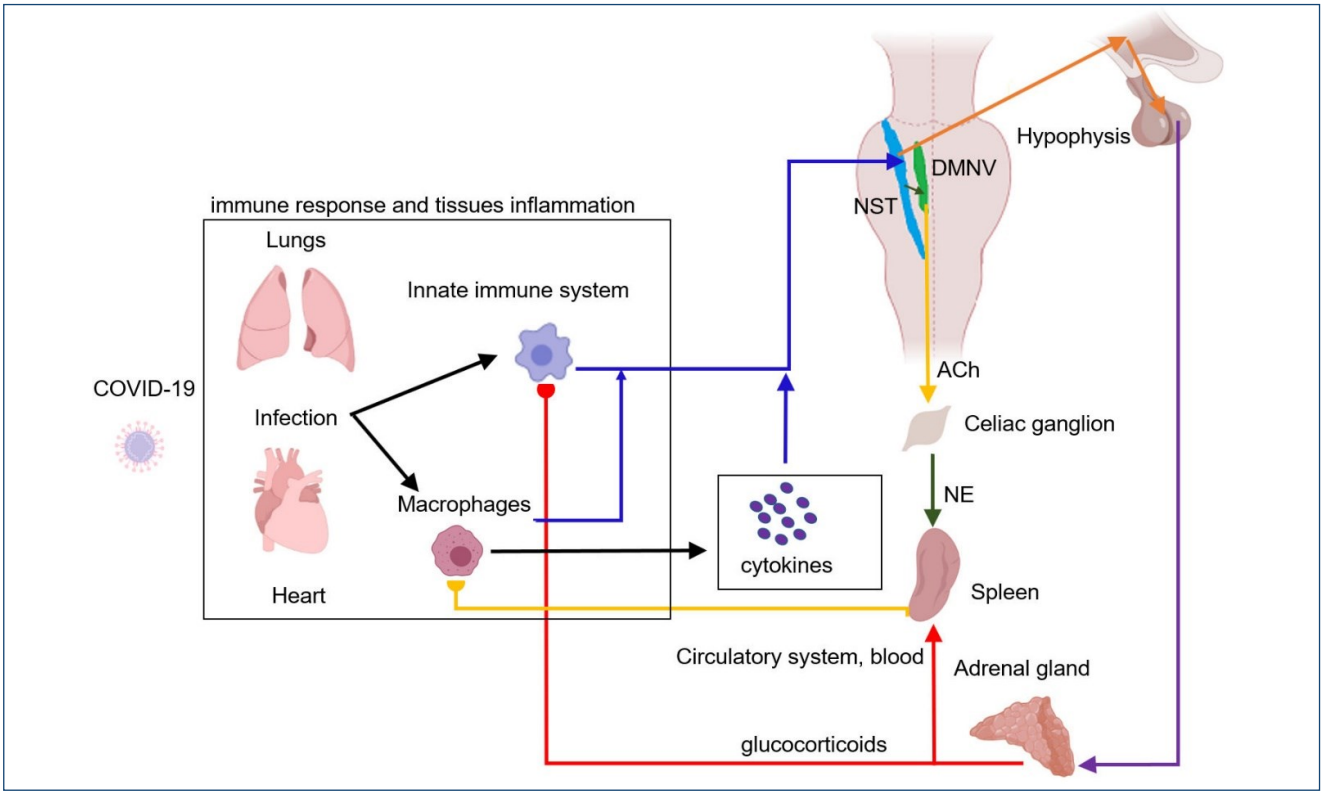

Figure 1. Diagram of the vagus nerve-mediated anti-inflammatory responses. The vagus nerve plays a key role in the neuro-endocrine-immune axis, having a dual anti-inflammatory role through its afferent and efferent fibers. In an infection, such as that caused by COVID-19, a primary immune response leads to the release of pro-inflammatory cytokines, generating an inflammatory process at the site of infection, in this case, the lungs and heart. Released cytokines are recognized by afferent fibers of the vagus nerve (blue arrows; information about inflammation from the lung, heart, and blood) that transmit such information to the nucleus of the solitary tract. The activation of nucleus of the solitary tract neurons is the origin of the anti-inflammatory response, which is generated through two different pathways. The first, known as the "hypothalamic-pituitary-adrenal axis," nucleus of the solitary tract efferents to the hypothalamus (orange arrows) stimulate the release of corticotrophin-releasing hormone, which stimulates the secretion of adrenocorticotropic hormone from the pituitary gland. adrenocorticotropic hormone reaches the adrenal glands (purple arrow), where it stimulates the production of glucocorticoids (cortisol in humans). Glucocorticoids act on the spleen (red arrow), which leads to reduced cytokine release by acting on cells of the immune system. The second, known as the "cholinergic anti-inflammatory reflex", nucleus of the solitary tract efferents to dorsal motor nucleus of the vagus nerve, the dorsal motor nucleus of the vagus nerve (black arrow, green nucleus), and stimulates the cholinergic motoneurons that project to the splenic nerve in the celiac ganglion (yellow arrow). Acetylcholine, released from the preganglionic terminals, excites celiac neurons and provokes the release of norepinephrine in the spleen (NE, green arrow). Then, the splenic response inhibits macrophages' cytokine release, decreasing inflammation. Reprinted with permission from Kaniusas et al.[24].

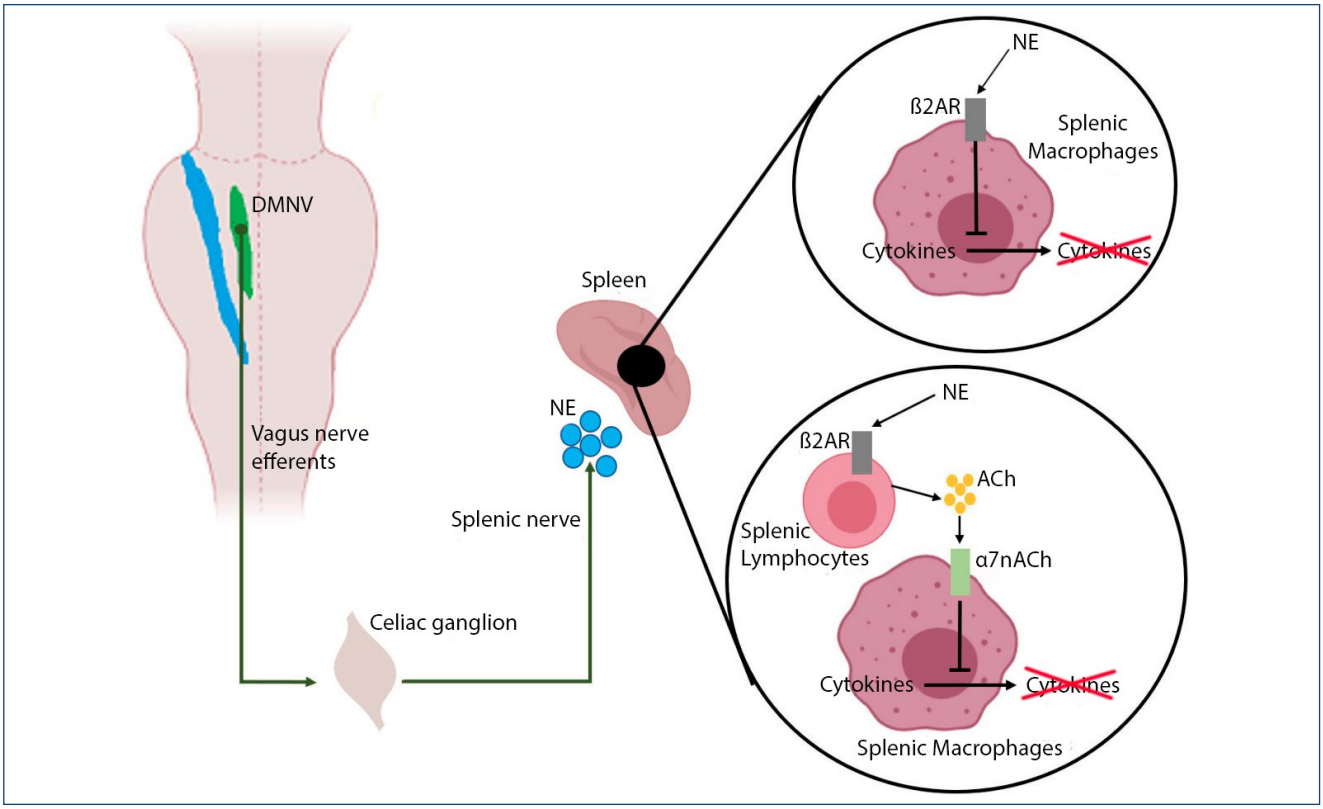

Figure 2. Scheme of the anti-inflammatory activity of the vagal efferents. Vagal efferents arise from the dorsal motor nucleus of the vagus nerve and project to the celiac ganglion, where they synapse with the splenic nerve. dorsal motor nucleus of the vagus nerve efferents activity stimulates the splenic nerve, which releases norepinephrine over the spleen. Norepinephrine binds to β2 adrenergic receptors expressed on splenic macrophages and splenic lymphocytes. Norepinephrine binding on macrophages inhibits the release of pro-inflammatory cytokines by these cells. Norepinephrine binding on lymphocytes provokes the release of acetylcholine, which is recognized by α7-acetylcholine receptors on the membrane of the macrophages. α7-Acetylcholine receptors activation provokes a disruption of the cytokine release pathway. Reprinted with permission from Kaniusas et al.[24].

elevation of plasma interleukins (IL)-6 and 10, accompanied by considerable hemorrhage, edema, consolidation, atelectasis, neutrophil infiltration, alveolar epithelial edema type I, and other deleterious effects[14].

In addition, the loss of autonomic balance worsens the inflammation caused by COVID-19 through the renin-angiotensin-aldosterone system (RAAS), a cascade of vasoactive peptides[15], which has recently been proposed as a mediator of lung injury caused by ARDS[16]. Indeed, activation of the sympathetic nervous system and RAAS seem to be intrinsically and reciprocally linked, at least in the case of patients with hypertension[17].

Finally, there is also a decreased vagal tone in some patients with COVID-19, which implies destabilized sympathetic-vagal balance, favoring the deleterious effects of the disease, as demonstrated in a recent publication[18]. To sum up, the dorsal vagal complex of the brainstem can be a target of SARS-CoV-2 because of its specifically high enrichment in ACE2 and could be reached readily by the virus through two distinct lung-to-brain routes, namely, the vagus nerve and the blood circulation.

INNERVATION OF THE EAR

To understand the effects of auricular vagus nerve stimulation, we need to know the innervation of the ear, which is rich and multiple[19]. The main nerves involved are auriculotemporal nerve (the branch of trigeminal nerve, fifth cranial pair), auricular branch of the vagus nerve (ABVN), and great auricular nerve (GAN), formed by the roots of C1-C2-C3. The ABVN innervates the central region of the auricle: the concha (upper and lower), much of the antihelix, and the internal portion of the tragus (Figure 3).

This innervation, particularly the trigeminal areas and the cervical nerves, is often mixed and its limits are variable[20]. One study, which involved dissection of 14 ears from 7 cadavers[19],

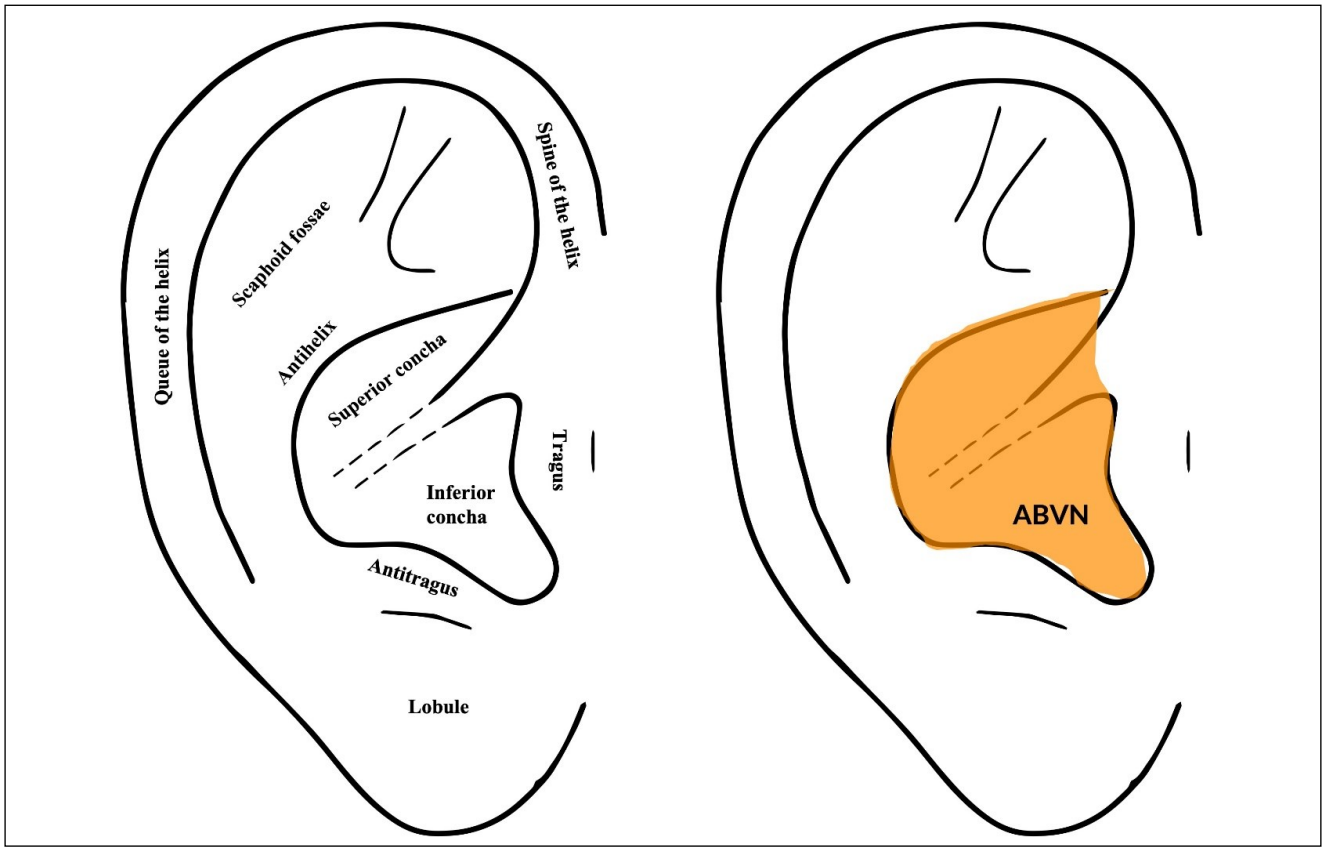

Figure 3. Diagram of the outer ear and area of innervation by the vagus nerve. ABVN: auricular branch of the vagus nerve.

showed the complete course of ear innervation. Its results are displayed in Table 1.

In a recently published review[21], the authors argue that the three main sites in the ear where the vagus nerve can be stimulated are the superior concha, the inferior concha, and the internal wall of the tragus, which covers the external auditory meatus. Evidence supporting the stimulation of these sites comes from both studies with ear dissection in cadavers[19] and functional magnetic resonance imaging (fMRI)[22,23].

It is important to remember that the ear is the only place in the body where the vagus is externalized and can be accessed in a simple and non-invasive way.

Table 1. Innervation pattern of the lateral surface of the ear.

	ABVN	GAN	ATN
Ascending branch of the helix	20%	–	80%
Knee of the helix	–	9%	91%
Queue of the helix	–	100%	–
Scaphoid fossae	–	100%	–
Anti-helix	73%	9%	18%
Antitragus	–	100%	–
Tragus	45%	46%	9%
Superior concha	100%	–	–
Inferior concha	45%	55%	–
Lobe	–	100%	–

ABVN: auricular branch of the vagus nerve; GAN: great auricular nerve; ATN: auriculotemporal nerve. Adapted from Peuker et al.[19].

AURICULAR VAGUS NERVE STIMULATION

Auricular vagus nerve stimulation (aVNS) is produced by non-invasive auricular electrical stimulation of the vagus nerve[24], through electrodes or miniature needles placed in the concha and/or in the inferior part of the tragus, and both the left and right ear can be used since the afferent information from the vagus merges when reaching the brainstem[25,26].

Invasive (surgically implanted) and non-invasive (transcutaneous or percutaneous) stimulation are the options available to stimulate the vagus nerve. Devices for non-invasive stimulation are based on the existence of a distribution of vagal afferents in the skin region, both in the external ear (the auricular branch

of the vagus nerve) and in the neck (the cervical branch of the vagus nerve). aVNS has been proposed as a new analgesic and anti-inflammatory intervention.

Both cervical vagus nerve stimulation (VNS) and aVNS have comparable physiological effects[25,27]. Brain activity patterns induced by aVNS were similar to patterns induced by cervical VNS[28], with equally favorable therapeutic results.

THERAPEUTIC EFFECTS OF VAGAL STIMULATION

The therapeutic effects of parasympathetic activity induced by aVNS are supported by a wide range of state-of-the-art clinical and experimental data: decrease in pro-inflammatory cytokines (TNF-α, IL-8, IL-1ß, and IL-6), modulation of pulmonary lesions by activating anti-inflammatory pathways, improvement of pulmonary and cardiac functions, adjusting the autonomic imbalance, and so on[14,29,30].

Imbalances in ANS activity have been linked to many clinical disorders, including heart failure[31], inflammatory bowel disease[32], and chronic pain syndromes[33]. In general, reported imbalances involve elevated sympathetic activity associated with a deficit in parasympathetic activity[34].

VNS corrects autonomic imbalance and increases parasympathetic activity[10,24]. A regularization of the autonomic balance will decrease sympathetic activity, which, in turn, will cause vasodilation and, consequently, improve oxygenation. In addition, VNS-mediated nitric oxide release[35], combined with its anti-inflammatory effects, mediates cardiovascular responses, potentially leading to further improvement in tissue oxygenation in terms of a positive feedback system[24,27]. Therefore, it is expected that the respiratory feedback provided by VNS favors the control of pulmonary inflammation.

Next, we will examine some scientific evidence for the use of taVNS.

Pre-clinical evidence

In animal models of inflammation, vagus nerve stimulation results in decreased inflammatory activity and increased anti-inflammatory activity, preventing tissue injury and increasing survival. For example, aVNS reduced the amount of pro-inflammatory cytokines[36] as well as the levels of norepinephrine[28], reinforcing its anti-inflammatory effects and counterbalancing sympathetic hyperactivity. VNS provided favorable effects on rheumatoid arthritis in rats[37], as well as reduced intestinal inflammation induced by surgery and improved intestinal transit[38]. Furthermore, it prevented the development of shock in rats by inhibiting the synthesis of tumor necrosis factor[39] and reduced inflammation in an experimentally induced model of colitis[40]. aVNS demonstrated its efficiency in rats with lethal endotoxemia or polymicrobial infection, reducing the production of tumor necrosis factor through its anti-inflammatory effects[41]. aVNS also suppressed lipopolysaccharide-induced inflammatory responses in toxemic rats by decreasing the levels of pro-inflammatory cytokines, indicating that it modulates immune functions through the cholinergic anti-inflammatory pathway[42].

Laboratory research demonstrates the protective effects of vagal stimulation on the lung[43]. Vagal stimulation protected rats against respiratory distress syndrome induced by *Mesobuthus tamulus* venom, improving respiratory parameters, hypoxemia, pulmonary edema, and histopathological changes, although it did not show the same result in rats with oleic acid-induced ARDS, which seems to indicate different mechanisms of vagal action in these cases[44]. Johnson et al.[45] showed that VNS diminishes the expression of proinflammatory cytokines TNF-α and IL-6 in the respiratory brain nuclei of developing rats, thereby reducing the inflammation caused by lipopolysaccharide instilled in the trachea, and may remain a viable alternative to antibiotics.

Clinical evidence

All the data mentioned below come from observational and interventional studies, small randomized clinical trials, and reviews. Most of the studies mentioned were observational studies, which somewhat limits the level of evidence derived from them.

VNS favorably modulates several cardiovascular parameters, resulting in a reduction in blood pressure[46,47], reduction in arrhythmias[46], and suppression of atrial fibrillation[30], the last one shown by Stavrakis et al. in a small randomized clinical trial. VNS inhibits sympathetic hyperactivity in heart failure[48] and reverses cardiac remodeling after myocardial infarction[49]. Thus, VNS could favorably modulate cardiovascular complications in patients with COVID-19, especially in those with comorbidities, and could reduce the percentage of fatal outcomes[24].

VNS attenuated ventilation-induced lung injury, reducing pro-apoptosis and pro-inflammatory reactions[36,50]. In hemorrhagic shock, vagal stimulation has prevented intestinal barrier failure and lung injury[51], relieving the latter through a decrease in cell permeability[52,53], mainly due to its anti-inflammatory properties.

Huang et al. showed, in a prospective observational trial, that VNS reduces inflammation by restoring balance to the sympathetic-parasympathetic binomial, reducing sympathetic activity, and slowing down the progression of sepsis[54].

In inflammation, respiratory dysfunction, and cardiovascular diseases, aVNS has the effect of reducing the production

of pro-inflammatory cytokines[55,56]; decreasing inflammation in chronic processes such as rheumatoid arthritis, postoperative ileus, and inflammatory bowel disease[12,57]; and systemic inflammation and attenuation of the postoperative acute inflammatory response of pulmonary lobectomy[24,37].

aVNS improves cardiac baroreflex sensitivity[58], increases venocapillary oxygenation in the deep tissues of diabetic patients[24], increases skin temperature in humans with peripheral artery dysfunctions and patients with chronic wounds caused by diabetes[59], and improves symptoms in peripheral obstructive arterial diseases[60]. Systemic effects of aVNS also include improvement of metabolic processes[61,62] (aVNS reduced 2-h glucose tolerance, systolic blood pressure, fasting plasma glucose and glycosylated hemoglobin compared to *sham*), attenuation of neurological disorders[63] (aVNS increased heart rate variability inducing a shift in autonomic nervous system function from sympathetic preponderance to parasympathetic predominance, and can be used to treat tinnitus-triggered stress), improvement of cognitive performance[64] (reducing depressive disorder symptoms without the burden of surgical intervention), and pain relief[27,35] (aVNS significantly improved low back pain, specially neuropathic pain, compared to manual acupuncture in a randomized clinical trial).

Recently, Seitz et al.[65] published a small clinical trial about aVNS and COVID-19 lung inflammation in patients admitted to the intensive care unit (ICU) but not yet ventilated. The study involved 10 patients randomized either to aVNS plus standard of care (SOC) or SOC alone (dexamethasone for at least 10 days and prophylactic anticoagulation therapy). aVNS was performed with the AuriStim device (Multisana, GmbH, Austria), stimulation frequency 1 Hz continuous, 3 h ON/3 h OFF for 24 h, until the patient died or was discharged from the ICU. The results showed decreased pro-inflammatory parameters as follows: a reduction in the C-reactive protein levels by 80%, a reduction in the TNF-α levels by 58.1%, and a reduction in the DDIMER levels by 66%, all after 7 days of treatment. Moreover, there was an increase in anti-inflammatory biomarkers such as IL (interleukin)-10 levels by 66% after 7 days, over the aVNS duration, and without collateral effects.

It seems that both cervical VNS and aVNS are promising options in the treatment of different inflammatory diseases and can help patients with COVID-19[36,66], especially those with significant sympathetic-parasympathetic imbalance. As biophysical principles and results are similar for both forms of vagal electrostimulation, aVNS is promising as it is not invasive. Czura et al.[67] published in 2022 a very complete review of all available neuromodulation strategies to reduce inflammation and improve lung complications in COVID-19 patients.

SIDE EFFECTS AND CONTRAINDICATIONS

aVNS is safe, with minor side effects such as headache, dizziness, skin irritation, or pain[68]. Surface electrodes are used in transcutaneous aVNS (taVNS), making the stimulation not as selective and precise as when using miniature needles, which can contribute to a lower effectiveness of the technique and a higher incidence of side effects. Stimulation is usually done intermittently (around 1 h, 3–4 times a day), with a total duration of stimulation of approximately 3–4 h per day.

On the contrary, percutaneous aVNS (paVNS) employs microelectrodes with needles, which favors a more precise and specific stimulation of nerve endings[25,27]. The skin impedance is much lower, which allows for a more efficient and economical stimulus with minimal side effects such as bleeding (<1%) and skin irritation (<10%)[35,69]. The stimulus is also performed intermittently (3 h ON, 3 h OFF), but remains active day and night, with a much longer stimulation time than in taVNS (12 h vs. 4–5 h), for 2–4 days, offering chronic stimulation for chronic ailments.

Very mild adverse effects of aVNS have been reported[70,71] and observed in a few cases: Arnold's cough reflex, vasovagal reflex, tearing, and bradycardia, all of which are indirect effects of afferent-efferent vagal reflexes. Furthermore, it is known that stimulation of cholinergic nerves can cause bronchial spasm and increase mucus production in the airways[72], which could attenuate the beneficial effects of aVNS in the anti-inflammatory process. Fortunately, these are all very rare side effects, occurring in less than 1% of the patients, and are widely overcome by the potential advantages of aVNS, in view of severity of comorbidities in COVID-19 patients.

aVNS is contraindicated in people with vagal hypersensitivity, hemophilia, *psoriasis vulgaris* at the application site, and patients with active implantable devices, such as pacemakers, because of their possible interference with the pacing device. There are no reports of special adverse events or contraindications for aVNS in viral infections such as COVID-19[24].

TYPES OF NERVOUS FIBERS AND STIMULATION PARAMETERS

Nerve fibers can be classified into three groups based on their diameter: groups A (Aα, Aβ, Aγ, and Aδ), B, and C. Different types of nerve fibers have different diameters and thicknesses of the myelin sheath (Table 2), which correspond to different conduction speeds, with thicker myelinated fibers typically linked to faster conduction speeds[73].

Table 2. Classification of the nerve fibers.

Type of nerve fiber	Diameter (μm)	Conduction velocity (m/s)	Afferent/Efferent	Type
Aα	13–20	80–120	Both	Sensory and motor
Aβ	6–12	33–75	Both	Sensory and motor
Aγ	5–8	4–24	Efferent	Motor
Aδ	1–5	3–30	Afferent	Sensory
B	<3	3–14	Afferent	Autonomic
C	0.2–1.5	0.5–2	Afferent	Sensory and motor

Adapted from Yap et al.[73].

At the cervical level, the vagus nerve consists mainly of small-diameter unmyelinated C fibers (65–80%), a smaller portion of intermediate-diameter myelinated B fibers, and large-diameter myelinated A fibers[74]. Kraus et al.[75] showed that, in the treatment of epilepsy, the destruction of peripheral C fibers did not influence the VNS-suppression of induced seizures, and the therapeutic effects of VNS were attributed to the maximum recruitment of thickened A and B afferent nerve fibers[76]. Other authors[77] have shown that aVNS does not cause painful sensations in participants, which suggests that afferent C axons and thin myelinated Aδ axons are not activated.

As with the stimulation of the cervical branches of the vagus nerve with low-intensity electrical currents, the ideal would be that ABVN stimulation activates only thick myelinated fibers, without activating the reduced diameter unmyelinated C fibers with their higher stimulation thresholds. ABVN is a general sensory fiber and is one of the few branches of the vagus that does not contain motor fibers. As such, the myelinated fibers found in ABVN would be expected to be sensory axons from group A rather than autonomic fibers from group B. Only one study determined the number of myelinated axons that are present in ABVN[78]. According to this study, about 50% of the measured myelinated axons had a diameter between 2.5 and 4.4 μm, suggesting that they belong to the Aδ group. Almost 20% of the axons showed a diameter >7 μm, suggesting that these fibers belong to the Aβ class. However, ABVN contains almost six times less class Aβ nerve fibers than those found in the cervical branch of the vagus nerve. This number also varied widely between individuals, which may explain why some individuals do not experience therapeutic effects after treatment with aVNS, as well as explain the anatomical basis behind the mechanism and efficacy of aVNS[21].

A tingling sensation should be targeted, as pointed out by some studies[79,80]. This is because the non-painful stimulus of ABVN would recruit more of the myelinated Aβ fibers in the ear, responsible for mechanoreception and touch sensation, and not the Aδ fibers, responsible for the sensation of pain and temperature. As already mentioned, thicker Aβ fibers are more easily recruitable than smaller Aδ fibers[25]. For this effect to be obtained, the stimulus must be performed with lower current intensities, always below the painful threshold.

Another important parameter to optimize the recruitment of Aβ fibers is the stimulation frequency[81]. Slightly higher frequencies, between 20 and 25 Hz, are better for peripheral electrical stimulation of the parasympathetic nervous system, while lower frequencies (between 0.5 and 10 Hz) are better for the sympathetic nervous system. This is because higher frequencies show a shorter duration of the depolarization period and, therefore, are only able to recruit larger and more easily excitable nerve fibers[27], such as Aβ fibers, which can indirectly modulate the parasympathetic nervous system. On the contrary, more recent studies[82,83] have shown good results in inflammatory diseases with the use of low frequencies as well, and therefore the ideal frequency has not been established yet.

Many studies have shown that stimulus efficiency has been increased by burst stimulation for 3–4 h a day[25,84]. A burst can be defined as the discharge of impulses for a short time, followed by an off interval. One or more nerve impulses triggered by vagal sensory afferences in response to single electrical stimuli are less likely to influence systemic regulation or brain activity (e.g., sympathetic-vagal balance) than a rhythmic sequence of these impulses[25,85].

Therefore, from a practical point of view, based on studies published in recent years, there is a potential role for aVNS to treat inflammation, as in COVID-19 and other conditions. However, there is still no convincing evidence from properly designed studies to endorse a formal recommendation. All we can say is that it is a very attractive experimental therapy that deserves further investigation.

Below, we propose three different types of aVNS for the treatment of COVID-19 and its inflammatory manifestations,

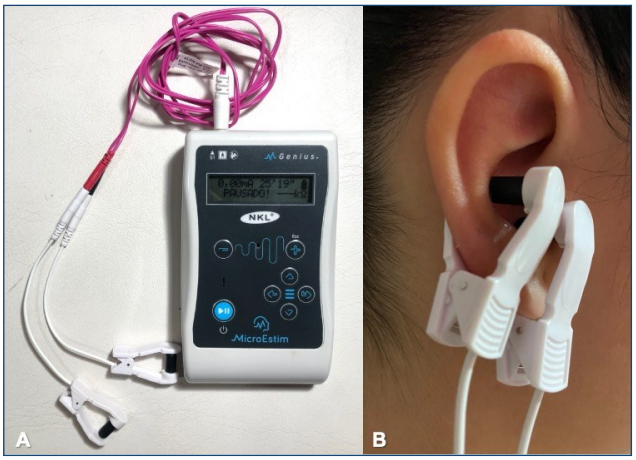

Figure 4. MicroEstim device and electrodes positioned on the ear (upper and lower concha) for stimulation. (A) MicroEstim (NKL Produtos Eletrônicos, Brusque, SC) with ear electrodes. (B) Electrodes positioned on the ear, on the upper and lower concha.

which can be implemented using a cutaneous electrical stimulation device:

1. Burst stimuli at frequency of 20–25 Hz, pulse width of 500 μs, intensity below pain threshold, 30 s ON/30 s OFF; this option is mostly used in taVNS;
2. Continuous stimuli at a frequency of 1 Hz, pulse width of 500 μs to 1 ms, intensity below pain threshold (generally <1.5 mA);
3. In this third option, we propose a new concept of vagal stimulation based on very recent studies[85,86]. Stimulus frequency of 1 Hz, pulse width of 1 ms, maximum intensity of 1.5–2 mA (only required to feel a tingling sensation), train of 100 biphasic pulses every 200 ms (0.2 s), remaining without any stimulus for 0.8 s, and repeating the stimulus again in the same way in the subsequent seconds. This is a new concept of burst, in which a very fast pulse sequence is sent within a 1 Hz period, which proved to be more effective in tested *in-silico* models and pre-clinical settings to excite Aβ fibers and produce vagal neuromodulation[85,87].

Electrodes or needles should be placed on the superior concha, or on both the superior and inferior concha, and connected to the equipment (Figures 4 and 5). In paVNS, the microelectrodes with needles are connected *via* wires to a stimulation device fixed in the neck (Figure 5), and the points should be selected by transillumination[85] of the outer ear (to visualize auricular vascularization) or by electrical point detection[35,69].

The stimulus must be performed every day for as long as the patient remains hospitalized, with intervals of at least 3 h between sessions.

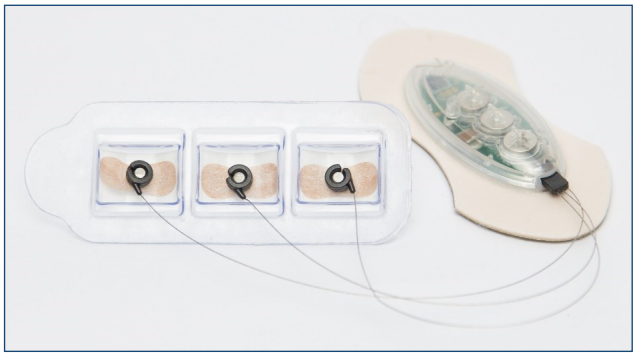

Figure 5. AuriStim for percutaneous auricular vagus nerve stimulation.

CONCLUSIONS

Vagus nerve stimulation modulates parasympathetic anti-inflammatory pathways and reestablishes sympathetic-vagal balance, which may help in the treatment of respiratory and cardiac diseases. As it is a simple and safe clinical procedure, it may have a promising role as a co-adjuvant treatment for inflammatory manifestations caused by COVID-19 and similar viruses, requiring larger clinical studies before a more solid recommendation can be made about its use.

One of the simplest ways to stimulate the vagus nerve and restore autonomic balance is through stimulation of its auricular branch (aVNS), which, in addition to producing effects like those achieved by cervical vagal stimulation, has the advantage of being non-invasive.

aVNS is a procedure with few side effects and contraindications, occurring in less than 1% of cases. Furthermore, different devices are available on the market with European CE certificates and American FDA approval for various pathologies.

There is still a vast field of research for this therapeutic method, involving different populations at risk (such as the elderly), other potentially serious inflammatory diseases, and different stimulation parameters.

AUTHORS' CONTRIBUTIONS

FMS: Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review and editing. **LBS:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization. **RCLR:** Conceptualization, Formal Analysis, Methodology, Writing – original draft. **MBS:** Data curation, Project administration, Validation. **RBSP:** Data curation, Project administration. **EK:** Methodology, Supervision, Writing – review and editing. **SLMC**: Supervision, Validation. **LWC:** Visualization, Writing – review and editing. **JCS:** Writing – review and editing.

Acquired knowledge:

In this review article, we discuss the mechanisms of action of transcutaneous atrial vagal stimulation (taVNS) and its therapeutic effects, providing experimental and clinical evidence that supports its use in inflammation, sympathetic-vagal balance, and respiratory and cardiovascular dysfunctions in COVID-19. Finally, we propose stimulation parameters based on recent studies for the treatment of the latter.

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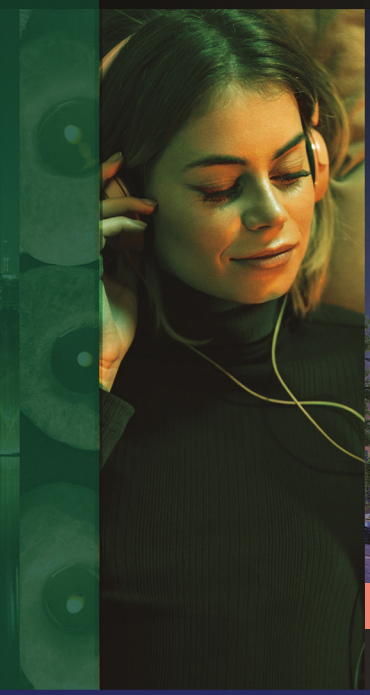

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