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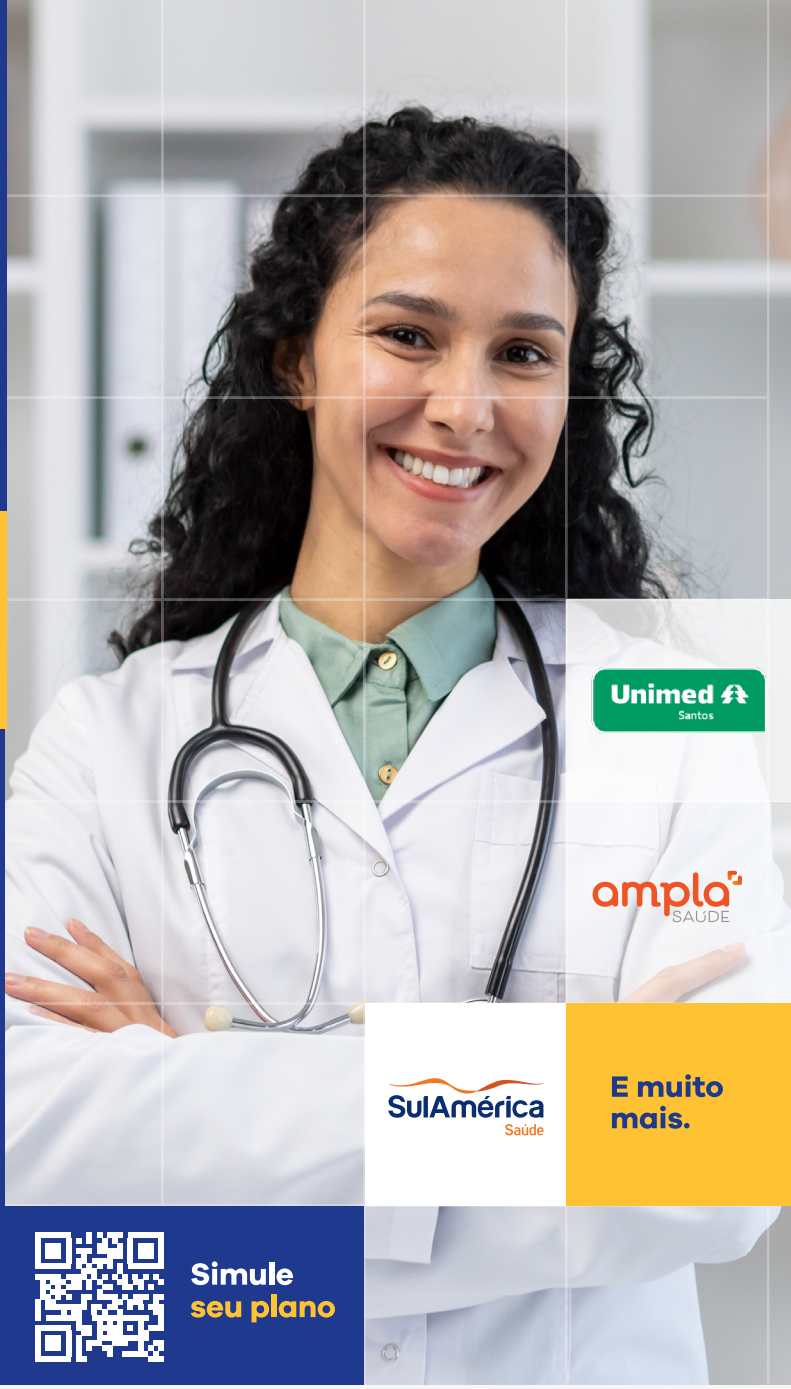

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Financial sustainability and the incorporation of technologies in the Brazilian Unified Health System: advances, challenges, and perspectives

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The incorporation of new health technologies represents one of the greatest advances in modern medicine, enabling more precise diagnosis, personalized treatment, and less invasive surgical procedures. However, this progress has brought significant challenges to the Brazilian Unified Health System (SUS), whose mission is to guarantee universal and comprehensive access while operating within budget constraints and social inequalities.

In 2022, Brazil allocated 9.6% of its gross domestic product (GDP) to health, a percentage considerably lower than that recorded in developed countries. In the same period, per capita health expenditure stood at approximately US$ 1,700, adjusted for purchasing power parity, which represents less than one-third of the Organisation for Economic Co-operation and Development (OECD) average, estimated at US$ 5,300. In contrast, nations such as the United States (US$ 12,740), Switzerland (US$ 8,910), Norway (US$ 8,640), and Germany (US$ 8,540) invested more than five times what Brazil did, highlighting the magnitude of the gap in national investments.[1,2]

This underfunding scenario is especially challenging for highly complex areas such as oncology. Recent estimates indicate that per capita spending on cancer in Brazil is projected to rise by about 200% by 2050. This increase is driven by three main factors: population aging, which accounts for a projected growth of 124%; greater patient survival, which prolongs treatment duration by up to 47%; and the rising costs of new technologies and innovative therapies, such as high-cost medications and advanced diagnostic methods.[3]

In recent years, the diagnosis and treatment of lung cancer have undergone significant transformations following advances in precision medicine. The management of the disease, once limited to general approaches, such as conventional chemotherapy and radiotherapy, has evolved into personalized strategies based on the molecular characteristics of the tumor and the clinical profile of each patient. Economic evaluation studies indicate that the incorporation of these technologies can increase per patient spending by up to four times compared with traditional chemotherapy regimens.[4]

In the surgical field, the incorporation of minimally invasive techniques, such as robot-assisted thoracic surgery has lead to greater precision, shorter recovery times, and a reduction in postoperative complications.[5,6] This scientific and technological advancement, which represents a milestone in improving clinical outcomes, presents the challenge of balancing innovation with sustainability on SUS. The discrepancy between the actual costs of procedures and the amounts reimbursed by the public system highlights the structural fragility of its financing.

Pulmonary lobectomy, considered the gold standard for the treating of early-stage lung cancer, is currently reimbursed by SUS at only R$ 3,282, according to data from the Procedure Table Management System (SIGTAP).[7] In contrast, a study comparing the costs of lobectomy performed by robotic-assisted thoracic surgery (RATS) and video-assisted thoracoscopic surgery (VATS) found very similar average costs between the two techniques, estimated at R$ 32,832.86 for RATS and R$ 32,500.00 for VATS, figures that exceed the amount currently reimbursed by SUS by almost tenfold.[8]

Similarly, a study using the Society of Thoracic Surgeons (STS) database evaluated the hospital costs of lobectomy in patients with early-stage lung cancer. The results indicated an average cost of approximately US$ 45,000 per procedure, without complications.[9]

This mismatch between the reimbursement offered by SUS and the real costs incurred by institutions compromises the sustainability of services, reinforcing the need for a periodic review of the reimbursement table and the adoption of more realistic costing methodologies that effectively reflect the complexity and inputs used in cancer treatments.

The debate regarding sustainability also extends to the incorporation of advanced surgical technologies such as robotic surgery. Introduced in Brazil in the mid-2000s and consolidated in private centers, robotic surgery has been applied in various areas, including gynecology, oncology, urology, and thoracic surgery.

Recently, SUS incorporated robotic surgery for the treatment of prostate cancer, following a recommendation by the National Commission for the Incorporation of Technologies into SUS (CONITEC), in a historic decision that opens the door to expanding its use to other specialties.[10] Despite potential clinical benefits such as greater precision and faster recovery, its diffusion still faces significant barriers, especially due to the high cost of acquisition, maintenance, and disposable supplies. Furthermore, systematic reviews indicate that to date, there is no robust evidence of cost-effectiveness when compared with established techniques such as video-assisted thoracic surgery.[11]

The process of assessing the incorporation of technologies within SUS is one of the pillars of ensuring that decisions are made based on evidence. Coordinated by CONITEC, this process involves Health Technology Assessment (HTA), which examines not only the efficacy and safety of innovations but also their economic, social, and ethical impacts.[12,13] An example of this rigor is the 2024 incorporation of new diagnostic tests for non-small cell lung cancer, such as positron emission tomography (PET) and RT-PCR for EGFR mutation, as well as the drug durvalumab for advanced stages.[14] These technologies had been available in the private health sector since 2014,[15] however, they were only recently incorporated into SUS after a detailed analysis of cost-effectiveness and budget impact.

On one hand, the incorporation of new technologies offers improvements in quality of care; on the other hand, the slow pace of the process and gaps in access generate a growing phenomenon: the judicialization of health. In 2024, the Ministry of Health recorded expenses of R$ 3.2 billion resulting from lawsuits related to medications, and over 50% of municipalities reported providing medications not incorporated into SUS through administrative channels.[16] Scarcity of resources and social pressure intensify this scenario, creating distortions in financing and compromising equity. Recent regulations stating that non-incorporated medications should not be granted through lawsuits, except under specific circumstances, represent an important step toward rationalizing resources and reinforcing the legal security of the system.[17]

Given this scenario, the central challenge is to balance innovation and sustainability to ensure that every Brazilian real invested yields proven clinical benefits and collective reach. Strategies such as the adoption of managed access models, risk-sharing agreements, periodic reviews of the SUS reimbursement table, enhancing efficiency, and strengthening the HTA are fundamental. The incorporation of value-based payment models has also emerged as a promising alternative, as it considers outcomes relevant to patients in relation to the total costs throughout the care cycle.

Financial sustainability, therefore, should not be seen as a barrier to innovation but as a foundation for ensuring that new technologies are cost-effective, accessible, and capable of transforming patients' lives in an equitable and lasting way. Only then can the SUS continue to be a global reference in universal coverage, balancing the imperatives of technological modernization with the responsibility of maintaining public health that is both financially viable and socially just.

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The difference in hematocrit and albumin levels and the risk of sepsis for patients with acute pancreatitis: a retrospective cohort study based on the MIMIC-IV database

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AUTHOR'S KEYWORDS:
Hematocrit-albumin.
Acute pancreatitis.
Sepsis.
Association

ABSTRACT

BACKGROUND: Acute pancreatitis (AP) is a major cause of gastrointestinal hospitalization, with an annual global incidence of 3.07%. Severe AP develops in up to 20% of cases, with sepsis occurring in 40–70% of such cases, leading to higher mortality. The early detection of sepsis is crucial. Hematocrit (HCT) and albumin (ALB) levels are individually linked to sepsis. Their combined measure, HCT-ALB, indicates blood and nutritional health. HCT-ALB can predict sepsis and infection outcomes; however, its effectiveness in treating AP-related sepsis has not been investigated.

OBJECTIVE: This study aimed to examine the association between HCT-ALB values and sepsis risk in patients with AP.

METHODS: This retrospective cohort study used Medical Information Market for Intensive Care IV database data. The primary outcome was the risk of sepsis in patients with AP. The HCT-ALB value refers to the difference between HCT and ALB levels, which we categorized into three groups according to quantiles: < 0.5, 0.5–7.6, and ≥ 7.6. Logistic regression models were used to assess the association between HCT-ALB values and sepsis. The predictive value of HCT-ALB was assessed using a receiver operating characteristic curve. Subgroup analyses were conducted for different subgroups.

RESULTS: Among 565 patients with AP, 163 developed sepsis. In the multivariable model, HCT-ALB ≥ 7.60 was associated with sepsis risk for patients with AP [odds ratio (OR) 1.82, 95% confidence interval (CI) 1.06–3.14]. The area under the curve (AUC) value of HCT-ALB in predicting sepsis risk among patients with AP was 0.599 (95% CI 0.544–0.654), which was higher than that of the bedside index for severity in acute pancreatitis score (AUC 0.558, 95% CI 0.509–0.607). Subgroup analysis showed that HCT-ALB was only related to sepsis risk in male patients with acute kidney injury and Sequential Organ Failure Assessment in < 2 subgroups.

CONCLUSION: HCT-ALB values ≥ 7.6 were associated with increased sepsis risk in patients with AP. HCT-ALB may contribute to identifying the risk of sepsis in patients with AP.

INTRODUCTION

Acute pancreatitis (AP) is considered the primary reason for hospital admissions related to gastrointestinal disorders in the United States and in several other countries.[1] A meta-analysis assessing trends in the global incidence of AP highlighted an annual rise in the overall incidence rate of AP of 3.07%, placing an increasing burden on healthcare systems.[2] Approximately 15–20% of patients with AP may experience exacerbation, resulting in the development of systemic inflammatory response syndrome (SIRS) and multiple organ failure. Ultimately, this progression can culminate in severe AP.[3] Sepsis is a life-threatening SIRS resulting from an uncontrolled immune reaction to infection, leading to septic shock and subsequent multiple organ failure.[4] Secondary pancreatic infection and sepsis, occurring in 40–70% of patients with AP, are associated with elevated mortality rates and a poor prognosis.[3] Early identification of sepsis risk among such patients is crucial in reducing mortality rates and alleviating the burden of disease.

Hematocrit (HCT) levels represent the proportion of red blood cells within the total volume of whole blood, serving as a critical biomarker for diagnosing anemia.[5] One retrospective cohort study reported that an elevated HCT level was a risk factor associated with the development of postoperative sepsis among older adult patients.[6] Albumin (ALB) is a pivotal biomarker associated with infection.[7] In older adult patients with hip fractures, ALB levels < 38 g/L are associated with a higher risk of postoperative infections.[8] Moreover, ALB levels are used to

indicate the severity of sepsis.[9] HCT-ALB values, which represent the difference between HCT and ALB levels, have recently been used to indicate a patient's nutritional status.[10–12] HCT-ALB values have been widely reported as potential biomarkers in several studies. One retrospective study involving data derived from two large databases reported a significant association between elevated HCT-ALB values and an increased risk of intensive care unit (ICU) and hospital mortality among older adult patients with sepsis.[11] In a retrospective case-control study published in 2020, Dai et al.[12] reported that elevated HCT-ALB values were observed in patients diagnosed with infectious diseases. Therefore, determining the HCT-ALB value (> 10.25) could potentially be a valuable tool for rapid diagnosis of infectious diseases. However, few studies have investigated the potential value of HCT-ALB in patients with AP.

This retrospective cohort study aimed to investigate the association between HCT-ALB values and the risk of sepsis among patients with AP using data derived from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database.

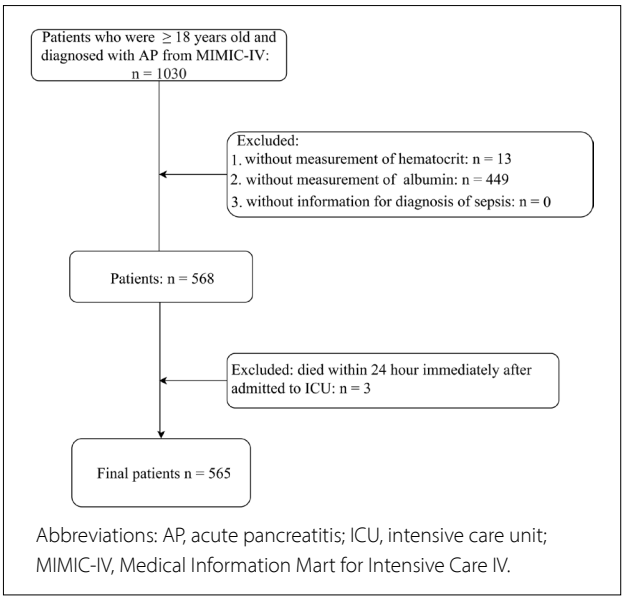


Figure 1. Patient flowchart

MATERIALS AND METHODS

Data sources

Data were obtained from the MIMIC-IV database, a large, single-center, free public database containing clinical information in relation to patients at Beth Israel Deaconess Medical Center in Boston between 2008 and 2019.[13] Patient demographics, admission records, vital signs, laboratory tests, medications, and survival data are recorded in the MIMIC-IV database. Access to this database was approved by the Institutional Review Committee of the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center.

Study population

The study inclusion criteria comprised patients aged ≥ 18 years old and diagnosed with AP. Patients with AP were identified using International Classification of Diseases (ICD) (9th revision, code 5770; 10th revision, code K85) codes.[14] The exclusion criteria comprised patients with missing information regarding HCT or ALB levels, or those with a diagnosis of sepsis. We also excluded patients who had died within 24 h of admission to the ICU. Finally, 565 patients diagnosed with AP were included in the subsequent analysis (**Figure 1**).

Data collection

The primary outcome was the risk of sepsis in patients with AP. A sepsis diagnosis was made based on Sepsis-3 criteria, which involves patients exhibiting signs of infection and a sudden increase in their sequential organ failure assessment (SOFA) score by at least 2 points.[15] HCT-ALB values, reflecting the difference between the HCT (%) and ALB (g/L) levels, were categorized into three groups according to quantiles, namely, < 0.5, 0.5–7.6, and ≥ 7.6.

Possible confounding variables were included in this analysis, as follows: age (years); sex; ethnicity; marital status; mean blood pressure (MBP, mmHg); respiratory rate; temperature (°C); creatinine (mg/dL), hemoglobin (g/dL), blood urea nitrogen (BUN, mg/dL), and platelet (K/uL) levels; red blood cell distribution width (RDW, %); chloride (mEq/L), bilirubin (mg/dL), sodium (mEq/L), bicarbonate (mEq/L), potassium (mEq/L), phosphate (mg/dL), alanine aminotransferase (ALT, IU/L), glucose (mg/dL), aspartate aminotransferase (AST, IU/L), and oxygen saturation (SpO_2, %) values; prothrombin time (PT, seconds); the international normalized ratio (INR, %); lipase (U/L) levels; the bedside index for severity in acute pancreatitis (BISAP), SOFA, and Glasgow Coma Scale (GCS) scores; the Charlson comorbidity index (CCI); the diagnosis of heart failure, hypertension, diabetes mellitus, renal failure, liver disease, acute kidney injury (AKI), and chronic obstructive pulmonary disease (COPD); and the use of antibiotic treatment, renal replacement therapy (RRT), mechanical ventilation, vasopressors, and enteral nutrition. For patients with multiple IUC admissions, only data in relation to their initial ICU admissions were analyzed.

Ethics approval and consent to participate

MIMIC-IV is a public database, and ethical approval was obtained concerning the use of data in relation to patients registered in the database. Users can download relevant data free of research fees and publish relevant articles.

Statistical analysis

Continuous variables following normal distribution are described using mean and standard deviation (SD, mean ± SD), and *t*-tests were conducted for group comparisons. Non-normal data are presented as median and interquartile spacing (M [Q_1, Q_3]), and group comparisons were analyzed using a Mann–Whitney U rank sum test. Categorical variables are reported as the number of cases and composition ratio (n [%]), and a chi-square test was used for group comparisons. The specified predictive mean matching method was used to interpolate all missing variables, and a sensitivity analysis of the data was performed pre- and post-interpolation (**Appendix 1**). A univariate logistic regression model was used to identify potential confounding variables related to sepsis (**Appendix 2**). Univariate and multivariate logistic regression models with HCT-ALB as the independent variable and sepsis as the outcome variable were used to assess the association between HCT-ALB values and sepsis risk in patients with AP. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were then calculated. Receiver-operating characteristic (ROC) curve analysis was used to assess the predictive value of HCT-ALB. Subgroup analyses were conducted for the following predefined populations: stratified by sex (male/female), by history of AKI (yes/no), and by Sequential Organ Failure Assessment (SOFA) score (< 2 or ≥ 2). The significance threshold was set at $P < 0.05$, and statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina) software.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

RESULTS

Patient characteristics

This study included 565 patients with AP (women, n = 246 [43.54%]; men, n = 319 [56.46%]). As shown in **Table 1,**the average patient age was 57.80 ± 17.61 years, while the median HCT-ALB value was 4 (range, −1–9.6). Based on the development of sepsis, patients with AP were categorized into two groups, namely, those with sepsis (sepsis, n = 163) and those without (non-sepsis, n = 402), and patient characteristics were compared between the two patient groups (**Table 1**). The sepsis group had decreased ALB and MBP values and higher HCT-ALB values and SOFA scores than in the non-sepsis group.

Association between HCT-ALB values and the risk of sepsis

As shown in **Appendix 2**, the identified confounding variables encompassed age, sex, ethnicity, marital status, MBP, creatinine, BUN, phosphate, SOFA, BISAP, antibiotic therapy, mechanical ventilation use, vasopressor use, RRT, and enteral nutrition in this analysis ($P < 0.05$). In the univariate logistic regression model (**Table 2**), HCT-ALB values ≥ 7.6 positively correlated with the risk of sepsis in patients with AP (OR 2.21, 95% CI 1.41–3.49; $P < 0.001$). In the multivariate logistic regression model, after adjusting for all potential confounding factors (**Table 2**), HCT-ALB values ≥ 7.6 positively correlated with the risk of sepsis in patients with AP (OR 1.82, 95% CI 1.06–3.14; $P = 0.030$) compared with a low HCT-ALB (< 0.5) quantile. We also compared the predictive values of HCT-ALB and BISAP using ROC curve analysis. As shown in **Figure 2**, the area under the curve (AUC) value of HCT-ALB in predicting the risk of sepsis in patients with AP was 0.599 (95% CI 0.544–0.654), surpassing the BISAP score (AUC 0.558, 95% CI 0.509–0.607).

Subgroup analyses

We performed subgroup analyses based on sex, a history of AKI (no/yes), and SOFA scores (< 2 or ≥ 2) to assess the stability of the association between HCT-ALB values and the risk of sepsis. In **Table 3**, our findings show that male patients with AP and HCT-ALB values ≥ 7.6 in the AKI and SOFA < 2 subgroups had a higher risk of sepsis than those with HCT-ALB values < 0.5, after adjusting for all confounding variables.

DISCUSSION

This is the first study to investigate the association between HCT-ALB values and the risk of sepsis in patients diagnosed with AP. We observed an association between HCT-ALB values ≥ 7.6 and an increased risk of sepsis in patients with AP. This association was particularly robust in relation to men and those in the AKI and SOFA < 2 subgroups. Our data supports the clinical utility of HCT-ALB as a biomarker to assess the risk of sepsis in patients with AP.

Recently, with the advancement of research, some biological markers have gained extensive utilization in the clinical prognosis of diseases, such as HCT and ALB.[16–18] ALB is synthesized in the liver. Serum ALB levels have frequently been reported to be associated with prognosis in hospitalized older adult patients,[19] as well as in patients with malnutrition,[20] heart failure,[21] and sepsis.[19] ALB exerts various physiological effects, encompassing the regulation of osmotic pressure, safeguarding the microvascular system and mitigating heightened vascular permeability.[22] It also exhibits antioxidant properties by scavenging free radicals, possesses anticoagulant effects, contributes to maintaining acid-base equilibrium, and demonstrates anti-inflammatory characteristics.[23] The prognostic value of a single serum ALB measurement, however, may be limited owing to its susceptibility to influence from chronic diseases, nutritional support, and inflammation. A combination of ALB and other indicators may yield more accurate

Table 1. Baseline characteristics between the non-sepsis and sepsis groups

Variables	Total (n = 565)	Groups		Statistics	P value
		Non-sepsis (n = 402)	Sepsis (n = 163)		
Age, years; mean ± SD	57.8 ± 17.61	58.56 ± 18.10	55.91 ± 16.26	t = 1.62	0.105
Sex, n (%)					
Women	246 (43.54)	173 (43.03)	73 (44.79)	χ^2 = 0.145	0.704
Men	319 (56.46)	229 (56.97)	90 (55.21)		
Ethnicity, n (%)					
African American	55 (9.73)	41 (10.2)	14 (8.59)		
European	348 (61.59)	253 (62.94)	95 (58.28)	χ^2 = 2.358	0.501
Other	67 (11.86)	44 (10.95)	23 (14.11)		
Ethnicity not stated	95 (16.81)	64 (15.92)	31 (19.02)		
Marital status, n (%)					
Married	223 (39.47)	161 (40.05)	62 (38.04)		
Never married	178 (31.5)	120 (29.85)	58 (35.58)		
Divorced	43 (7.61)	32 (7.96)	11 (6.75)	χ^2 = 3.381	0.496
Widowed	53 (9.38)	42 (10.45)	11 (6.75)		
Unknown	68 (12.04)	47 (11.69)	21 (12.88)		
HCT, %; mean ± SD	34.06 ± 6.91	33.96 ± 6.4	34.31 ± 8.04	t = –0.48	0.628
ALB, g/L; mean ± SD	29.78 ± 6.23	30.43 ± 6.16	28.17 ± 6.14	t = 3.97	< 0.001
HCT-ALB, M (Q_1, Q_3)	4.00 (–1, 9.6)	3.20 (–1.3, 8.5)	6.3 (0.4, 13.1)	Z = 3.69	< 0.001
HCT-ALB, n (%)					
< 0.50	184 (32.57)	143 (35.57)	41 (25.15)		
0.50–7.60	193 (34.16)	144 (35.82)	49 (30.06)	χ^2 = 14.115	< 0.001
≥ 7.60	188 (33.27)	115 (28.61)	73 (44.79)		
MBP, mmHg; mean ± SD	91.71 ± 19.17	93.25 ± 18.57	87.9 ± 20.11	t = 3.03	0.003
Respiratory rate, mean ± SD	21.66 ± 6.67	21.6 ± 6.65	21.8 ± 6.75	t = –0.33	0.739
Temperature, °C; mean ± SD	36.84 ± 1	36.79 ± 0.96	36.97 ± 1.09	t = –1.83	0.069
Creatinine, mg/dL; M (Q_1, Q_3)	1.1 (0.7, 2)	1 (0.7, 1.6)	1.50 (0.9, 2.8)	Z = 4.417	< 0.001
Hemoglobin, g/dL; mean ± SD	11.28 ± 2.33	11.27 ± 2.2	11.31 ± 2.64	t = –0.18	0.854
BUN, mg/dL; M (Q_1, Q_3)	20 (12, 37)	17.5 (11, 35)	26 (17, 44)	Z = 4.797	< 0.001
RDW, %; mean ± SD	15.21 ± 2.18	15.14 ± 1.91	15.38 ± 2.73	t = –0.99	0.323
Platelet, K/uL; M (Q_1, Q_3)	182 (125, 265)	183.5 (128, 267)	181 (124, 248)	Z = –0.888	0.375
Bilirubin, mg/dL; M (Q_1, Q_3)	1.1 (0.6, 3)	1 (0.6, 3)	1.1 (0.6, 2.9)	Z = 0.726	0.468
Bicarbonate, mEq/L; mean ± SD	20.65 ± 5.66	21.08 ± 5.52	19.58 ± 5.88	t = 2.88	0.004
Sodium, mEq/L; mean ± SD	138.38 ± 5.91	138.3 ± 5.44	138.55 ± 6.93	t = –0.41	0.682
Potassium, mEq/L; mean ± SD	4.16 ± 0.91	4.12 ± 0.92	4.25 ± 0.88	t = –1.52	0.13
Chloride, mEq/L; mean ± SD	104.65 ± 7.33	104.31 ± 7.12	105.49 ± 7.78	t = –1.74	0.083
Phosphate, mg/dL; M (Q_1, Q_3)	3.3 (2.3, 4.2)	3.2 (2.2, 4)	3.6 (2.5, 4.9)	Z = 3.231	0.001
Glucose, mg/dL ; M (Q_1, Q_3)	124 (100, 174)	121 (99, 167)	137 (104, 194)	Z = 2.425	0.015
ALT, IU/L; M (Q_1, Q_3)	54 (25, 168)	54.5 (25, 168)	54 (26, 167)	Z = 0.109	0.913
AST, IU/L; M (Q_1, Q_3)	78 (38,187)	72.5 (35,182)	87 (46, 216)	Z = 2.115	0.034
SpO_2, %; mean ± SD	95.93 ± 4.58	96.01 ± 4.44	95.72 ± 4.93	t = 0.68	0.498
INR, M (Q_1, Q_3)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.4 (1.2, 1.7)	Z = 2.295	0.022
PT, seconds; M (Q_1, Q_3)	14.4 (13, 17.3)	14.2 (13, 17)	14.9 (13.2, 17.9)	Z = 1.839	0.066
Lipase, n (%)					
< 208 U/L	158 (27.96)	108 (26.87)	50 (30.67)		
≥ 208 U/L	217 (38.41)	156 (38.81)	61 (37.42)	χ^2 = 0.863	0.65
Unknown	190 (33.63)	138 (34.33)	52 (31.9)		
SOFA, M (Q_1, Q_3)	2 (0, 5)	2 (0, 4)	4 (1, 7)	Z = 6.027	< 0.001
BISAP, M (Q_1, Q_3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	Z = 2.28	0.023
GCS, mean ± SD	14.53 ± 1.58	14.56 ± 1.43	14.45 ± 1.91	t = 0.69	0.491
CCI, M (Q_1, Q_3)	2 (1, 3)	2 (1, 3)	2 (1, 4)	Z = 0.188	0.851
Heart failure, yes; n (%)	83 (14.69)	58 (14.43)	25 (15.34)	χ^2 = 0.077	0.782
Hypertension, yes; n (%)	321 (56.81)	234 (58.21)	87 (53.37)	χ^2 = 1.105	0.293

Continue...

Table 1. Continuation

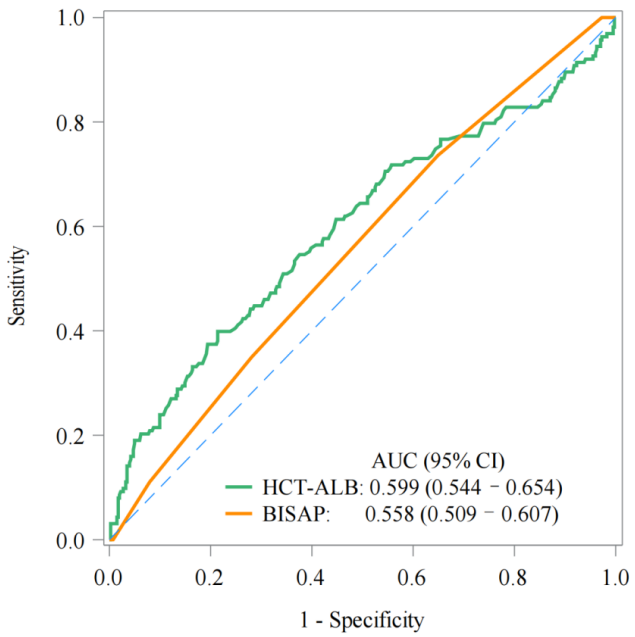
Variables	Total (n = 565)	Groups		Statistics	P value
		Non-sepsis (n = 402)	Sepsis (n = 163)		
Diabetes, yes; n (%)	170 (30.09)	127 (31.59)	43 (26.38)	$\chi^2 = 1.498$	0.221
Renal failure, yes; n (%)	61 (10.8)	37 (9.2)	24 (14.72)	$\chi^2 = 3.669$	0.055
Liver disease, yes; n (%)	124 (21.95)	86 (21.39)	38 (23.31)	$\chi^2 = 0.25$	0.617
COPD, yes; n (%)	24 (4.25)	17 (4.23)	7 (4.29)	$\chi^2 = 0.001$	0.972
AKI, yes; n (%)	278 (49.2)	164 (40.8)	114 (69.94)	$\chi^2 = 39.409$	< 0.001
Antibiotics, yes; n (%)	348 (61.59)	230 (57.21)	118 (72.39)	$\chi^2 = 11.295$	< 0.001
Mechanical ventilation use, yes; n (%)	443 (78.41)	293 (72.89)	150 (92.02)	$\chi^2 = 25.092$	< 0.001
Vasopressor use, yes; n (%)	154 (27.26)	69 (17.16)	85 (52.15)	$\chi^2 = 71.584$	< 0.001
RRT, yes; n (%)	49 (8.67)	24 (5.97)	25 (15.34)	$\chi^2 = 12.848$	< 0.001
Enteral nutrition, yes; n (%)	30 (5.31)	15 (3.73)	15 (9.2)	$\chi^2 = 6.905$	0.009

Abbreviations: AKI, acute kidney injury; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BISAP, bedside index for severity in acute pancreatitis; BUN, blood urea nitrogen; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; HCT, hematocrit; HCT-ALB, difference between HCT and ALB; INR, international normalized ratio; MBP, mean blood pressure; PT, prothrombin time; RDW, red cell distribution width; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; SpO2, oxygen saturation.

Table 2. Relationship between HCT-ALB and the risk of sepsis

Variables	Univariate logistic regression model		Multivariate logistic regression model	
	OR (95% CI)	P value	OR (95% CI)	P value
HCT-ALB				
< 0.5	Ref		Ref	
0.5–7.6	1.19 (0.74–1.91)	0.48	1.31 (0.76–2.26)	0.337
≥ 7.6	2.21 (1.41–3.49)	< 0.001	1.82 (1.06–3.14)	0.03

Univariate logistic regression model, not adjusted for confounding variables. Multivariate logistic regression model adjusted for all confounding variables, including age, sex, race/ethnicity, marital status, mean blood pressure, creatinine, blood urea nitrogen, phosphate, sequential organ failure assessment, bedside index for the severity of acute pancreatitis, antibiotics, mechanical ventilation use, vasopressor use, renal replacement therapy, and enteral nutrition. Abbreviations: CI, confidence interval; HCT-ALB, difference between hematocrit and albumin; OR, odds ratio.



Abbreviations: AUC, area under the ROC curve; BISAP, bedside index for the severity of acute pancreatitis; CI, confidence interval; HCT-ALB, hematocrit-albumin; ROC, receiver operating characteristic.

Figure 2. ROC curve analyses of HCT-ALB values and the BISAP score

prognostic predictions than the use of ALB alone. In 2022, Liu et al. reported that the lactate-to-albumin (LAR) ratio showed higher accuracy than ALB or lactate alone for all-cause mortality among patients with AP.[24] HCT-ALB values have recently been investigated as potential indicators. The HCT-ALB value is defined as the difference between the HCT and ALB levels. Previous studies have reported the prognostic significance of HCT-ALB in older adults with sepsis in relation to in-hospital mortality,[11] and have also reported elevated HCT-ALB values in patients with infectious diseases, thereby establishing it as a robust diagnostic indicator for such conditions.[12] Therefore, we hypothesized that the HCT-ALB value might also be a potential biomarker for sepsis risk in patients with AP.

After adjusting for age, sex, ethnicity, marital status, MBP, creatinine, BUN, phosphate, SOFA, BISAP, antibiotic therapy, mechanical ventilation use, vasopressor use, RRT, and enteral nutrition, we observed that, compared with a low HCT-ALB (< 0.5) quantile, a high HCT-ALB value (≥ 7.6) was associated with an increased risk of sepsis in patients with AP. The BISAP score, developed in 2008, can be easily calculated using data points available within the first 24 h of presentation to the emergency department, including BUN levels, an abnormal mental status,

Table 3. Subgroup analysis of the association between HCT-ALB and the risk of sepsis

Variables	Univariate logistic regression model				Multivariate logistic regression model			
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Subgroup I: Sex	**Male**		**Female**		**Male**		**Female**	
HCT-ALB								
< 0.5	Ref		Ref		Ref		Ref	
0.5–7.6	1.11 (0.55–2.21)	0.777	1.25 (0.65–2.42)	0.502	1.62 (0.67–3.9)	0.28	1.40 (0.62–3.18)	0.423
≥ 7.6	3.05 (1.64–5.66)	<0.001	1.43 (0.71–2.88)	0.313	3.43 (1.52–7.76)	0.003	1.13 (0.47–2.75)	0.78
Subgroup II: AKI	**No**		**Yes**		**No**		**Yes**	
HCT-ALB								
< 0.5	Ref		Ref		Ref		Ref	
0.5–7.6	1.85 (0.85–4.05)	0.121	0.78 (0.42–1.48)	0.454	1.71 (0.68–4.33)	0.257	1.12 (0.54–2.32)	0.77
≥ 7.6	2.40 (1.08–5.33)	0.032	1.62 (0.89–2.94)	0.112	1.69 (0.63–4.53)	0.295	2.21 (1.08–4.53)	0.031
Subgroup III: SOFA	**SOFA ≥2**		**SOFA <2**		**SOFA ≥2**		**SOFA <2**	
HCT-ALB								
< 0.5	Ref		Ref		Ref		Ref	
0.5–7.6	1.13 (0.63–2.04)	0.688	1.56 (0.65–3.78)	0.323	1.36 (0.68–2.72)	0.377	1.20 (0.4–3.6)	0.749
≥ 7.6	1.52 (0.87–2.64)	0.141	4.26 (1.81–10)	< 0.001	1.42 (0.74–2.74)	0.291	4.1(1.33–12.6)	0.014

Univariate logistic regression model, unadjusted confounding variables. Multivariate logistic regression model, Subgroup I: adjusted age, race/ethnicity, marital status, mean blood pressure, creatinine, blood urea nitrogen, phosphate, sequential organ failure assessment, bedside index for severity of acute pancreatitis, antibiotics, mechanical ventilation use, vasopressor use, renal replacement therapy, and enteral nutrition; Subgroup II: adjusted for age, sex, race/ethnicity, marital status, mean blood pressure, creatinine, blood urea nitrogen, phosphate, sequential organ failure assessment, bedside index for the severity of acute pancreatitis, antibiotics, mechanical ventilation use, vasopressor use, renal replacement therapy, and enteral nutrition; Subgroup III: adjusted for age, sex, race/ethnicity, marital status, mean blood pressure, creatinine, blood urea nitrogen, phosphate, bedside index for the severity of acute pancreatitis, antibiotics, mechanical ventilation use, vasopressor use, renal replacement therapy, and enteral nutrition. Abbreviations: HCT-ALB, difference between hematocrit and albumin; OR, odds ratio; CI, confidence interval; AKI, acute kidney injury; SOFA, sequential organ failure assessment.

evidence of SIRS, age ≥ 60 years, and the presence of pleural effusion.[25] It has been reported that the BISAP score can be used in the early prediction of severity and mortality in AP.[26,27] In this analysis, we compared the predictive value of HCT-ALB with the BISAP score in predicting the risk of sepsis in patients with AP. Our findings indicated that HCT-ALB might potentially serve as a prognostic indicator, enhancing clinicians' ability to predict sepsis risk among patients with AP and leading to improved management strategies. In the subgroup analysis, an association between HCT-ALB and the risk of sepsis was observed among men with AP, and those who had AKI or a SOFA score < 2. HCT-ALB may be more suitable for predicting sepsis risk among men with AP, those with a history of AKI, or those with a SOFA score of < 2. Further investigations are required to investigate the precise mechanism underlying this discovery in future research.

This study had some limitations. Concerning patients with multiple ICU admissions, only data concerning the first ICU admission were analyzed, which may have generated a selection bias. This retrospective cohort study used data derived from the MIMIC-IV database. Despite efforts to adjust for confounding variables, it is possible that there were unidentified potential confounders. Moreover, serum ALB or HCT levels may vary over time; however, we only focused on the initial HCT-ALB values without monitoring their dynamic fluctuations. Further validation of the prognostic value of HCT-ALB in patients with AP through prospective multicenter studies is warranted, along with exploration of its underlying mechanisms.

CONCLUSION

High HCT-ALB values ≥ 7.6 were associated with an increased risk of sepsis in patients with AP. Determining the HCT-ALB value may contribute to identifying the risk of sepsis in such patients, thereby improving risk assessment and guiding subsequent interventions.

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Appendix 1. Sensitivity analysis of data pre- and post-interpolation

Variables	Pre-interpolation	Post-interpolation	Statistics	P-value
MBP, mmHg, Mean ± SD	91.79 ± 19.17	91.71 ± 19.17	t = 0.07	0.943
Respiratory rate, Mean ± SD	21.58 ± 6.6	21.66 ± 6.67	t = −0.18	0.856
Temperature, °C, Mean ± SD	36.84 ± 1	36.84 ± 1	t = 0.01	0.991
BUN, mg/dL, M (Q_1, Q_3)	20 (12–37)	20 (12–37)	Z = 0.022	0.983
Creatinine, mg/dL, M (Q_1, Q_3)	1.1 (0.7–2)	1.1 (0.7–2)	Z = 0.003	0.997
RDW, %, Mean ± SD	15.21 ± 2.18	15.21 ± 2.18	t = −0.01	0.991
Bilirubin, mg/dL, M (Q_1, Q_3)	1.1 (0.6–3)	1.1 (0.6–3)	Z = 0.004	0.997
Bicarbonate, mEq/L, Mean ± SD	20.67 ± 5.65	20.65 ± 5.66	t = 0.05	0.959
Sodium, mEq/L, Mean ± SD	138.39 ± 5.9	138.38 ± 5.91	t = 0.03	0.974
Chloride, mEq/L, Mean ± SD	104.66 ± 7.33	104.65 ± 7.33	t = 0.02	0.982
Phosphate, mg/dL, M (Q_1, Q_3)	3.3 (2.3–4.3)	3.3 (2.3–4.2)	Z = 0.002	0.998
Glucose, mg/dL, M (Q_1, Q_3)	124.5 (100–174)	124 (100–174)	Z = 0.01	0.992
ALT, IU/L, M (Q_1, Q_3)	55 (25, 168)	54 (25–168)	Z = 0.11	0.913
AST, IU/L, M (Q_1, Q_3)	79.5 (38–187.5)	78 (38–187)	Z = 0.151	0.88
SpO_2, %, Mean ± SD	95.92 ± 4.58	95.93 ± 4.58	t = −0.03	0.979
INR, M (Q_1, Q_3)	1.3 (1.2–1.6)	1.3 (1.1–1.6)	Z = 1.348	0.177
PT, sec, M (Q_1, Q_3)	14.5 (13–17.5)	14.4 (13–17.3)	Z = 0.339	0.735
AKI, n (%)				
No	285 (50.62)	287 (50.8)	χ^2 = 0.003	0.953
Yes	278 (49.38)	278 (49.2)		
SOFA, M (Q_1, Q_3)	2 (0–5)	2 (0–5)	Z = −0.035	0.972
GCS, mean ± SD	14.53 ± 1.58	14.53 ± 1.58	t = −0.02	0.986

Abbreviations: MBP, mean blood pressure; BUN, blood urea nitrogen; RDW, red cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SpO_2, oxygen saturation; INR, international normalized ratio; PT, prothrombin time; AKI, acute kidney injury; SOFA, sequential organ failure assessment; GCS, Glasgow Coma Scale; SD, standard deviation.

Appendix 2. Screening of the confounding variables

Variables	OR (95% CI)	P value
Age	0.99 (0.98–1)	0.105
Sex		
Women	Ref	
Men	0.93 (0.65–1.34)	0.704
Marital status		
Married	Ref	
Never married	1.26 (0.82–1.93)	0.299
Divorced	0.89 (0.42–1.88)	0.765
Widowed	0.68 (0.33–1.41)	0.298
Unknown	1.16 (0.64–2.1)	0.623
Ethnicity		
African American	Ref	
European	1.1 (0.57–2.11)	0.775
Other	1.53 (0.7–3.37)	0.29
Not known	1.42 (0.67–2.98)	0.356
MBP	0.99 (0.98–0.99)	0.003
Respiratory rate	1 (0.98–1.03)	0.739
Temperature	1.21 (1–1.47)	0.056
Creatinine	1.15 (1.05–1.26)	0.004
Hemoglobin	1.01 (0.93–1.09)	0.842
BUN	1.01 (1.01–1.02)	0.002
RDW	1.05 (0.97–1.14)	0.254
Antibiotics		
No	Ref	
Yes	1.96 (1.32–2.91)	< 0.001
Platelet	1 (1–1)	0.454
Bilirubin	1.01 (0.98–1.05)	0.389
Bicarbonate	0.95 (0.92–0.99)	0.005
Sodium	1.01 (0.98–1.04)	0.65
Potassium	1.16 (0.96–1.41)	0.132
Chloride	1.02 (1.00–1.05)	0.084
Phosphate	1.16 (1.05–1.27)	0.002
Glucose	1 (1–1)	0.08
ALT	1 (1–1)	0.469
AST	1 (1–1)	0.191
SpO_2	0.99 (0.95–1.03)	0.5
INR	1.18 (0.99–1.41)	0.069
PT	1.01 (1–1.03)	0.107
Lipase		
< 208 U/L	Ref	
≥ 208 U/L	0.84 (0.54–1.32)	0.459
Unknown	0.81 (0.51–1.29)	0.383
SOFA	1.19 (1.12–1.26)	< 0.001
BISAP	1.23 (1.03–1.48)	0.025
GCS	0.96 (0.86–1.07)	0.438
CCI	1.01 (0.94–1.1)	0.728
Heart failure		
No	Ref	
Yes	1.07 (0.65–1.79)	0.782
Hypertension		
No	Ref	
Yes	0.82 (0.57–1.19)	0.294
Diabetes		
No	Ref	
Yes	0.78 (0.52–1.17)	0.222

Continue...

Appendix 2. Continuation

Variables	OR (95% CI)	P value
Renal failure		
No	Ref	
Yes	1.70 (0.98–2.95)	0.057
Liver disease		
No	Ref	
Yes	1.12 (0.72–1.72)	0.618
COPD		
No	Ref	
Yes	1.02 (0.41–2.5)	0.972
AKI		
No	Ref	
Yes	3.38 (2.29–4.98)	< 0.001
Mechanical ventilation use		
No	Ref	
Yes	4.29 (2.34–7.88)	< 0.001
Vasopressor use		
No	Ref	
Yes	5.26 (3.52–7.86)	< 0.001
RRT		
No	Ref	
Yes	2.85 (1.58–5.16)	< 0.001
Enteral nutrition		
No	Ref	
Yes	2.61 (1.25–5.48)	0.011

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BISAP, bedside index for severity in acute pancreatitis; BUN, blood urea nitrogen; CI, confidence interval; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; INR, international normalized ratio; MBP, mean blood pressure; OR, odds ratio; PT, prothrombin time; RDW, red cell distribution width; SOFA, sequential organ failure assessment; RRT, renal replacement therapy; SpO_2, oxygen saturation.

Patient activation levels in cardiovascular disease: a cross-sectional study in Brazilian community pharmacies

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ABSTRACT

BACKGROUND: Preventable cardiovascular diseases are among the leading causes of death in individuals aged < 70 years in Brazil.

OBJECTIVE: This study assessed the level of patient activation among individuals with cardiovascular disease in Brazilian community pharmacies.

DESIGN AND SETTING: This cross-sectional study included 348 Brazilian participants diagnosed with hypercholesterolemia and/or hypertension.

METHODS: The Patient Activation Measure (PAM-13) questionnaire was used. In addition, sociodemographic and clinical variables were collected, including coronary risk evaluation and quality of life assessment. Student's ***t***-test was used to compare baseline quantitative variables between groups, and the chi-square test was used to assess associations for categorical variables. Pearson's correlation was used to examine the relationships among the quality of life, clinical variables, sociodemographic data, and activation levels.

RESULT: Participants had an average age of 59.0 ± 16.7 years and a low to moderate risk. The mean patient activation level was 2.8 out of 4, with high self-care responsibility and treatment adherence but lower confidence in maintaining lifestyle changes. Factors linked to lower activity included low physical activity ($P < 0.001$), multiple chronic conditions ($P = 0.003$), smoking ($P = 0.016$), age > 65 years ($P = 0.033$), low quality of life ($P < 0.001$), and high CVR ($P < 0.001$).

CONCLUSION: Patient activation in cardiovascular care in the Brazilian population is positively affected by lifestyle factors, particularly physical activity. Intervention strategies that promote lifestyle changes can enhance patient activity and improve health outcomes in this population.

INTRODUCTION

The data from the World Health Organization (WHO)[1] stated that non-communicable chronic diseases (NCDs) were responsible for the deaths of 17.7 million individuals worldwide in 2023, and accounted for approximately 30.8% of premature deaths in Brazil in 2019.[2]

These diseases encompass a broad spectrum of chronic conditions typically linked to multiple causal factors. They are characterized by gradual onset, uncertain prognosis, and prolonged or indefinite duration, with a fluctuating clinical course involving durations of exacerbation and potential disabilities.[3] The World Health Organization (WHO) stated that NCDs, including cardiovascular diseases (CVDs), are typically chronic and arise from a combination of genetic, physiological, environmental, and behavioral factors. Modifiable risk factors such as tobacco use, physical inactivity, alcohol consumption, and unhealthy diet significantly increase the likelihood of mortality from these diseases.[4]

Healthcare systems face mounting challenges as the prevalence of chronic diseases continues to increase, both from the economic burden and limited capacity to manage these conditions effectively, particularly in the short term.[5] Evidence suggests that actively engaging patients in their healthcare can help maintain a balance between individual health outcomes and the sustainability of the healthcare system.[6]

Patient activation, as defined by Hibbard et al.,[7] refers to an understanding of their role in the care process and their knowledge, skills, and confidence in managing their health and healthcare. Active patients have the skills and behavioral repertoire to manage their illness, maintain their health functioning, prevent health deterioration, collaborate with their healthcare providers, and access appropriate, high-quality care.

The central role of patients in decision-making and in managing their care is increasingly being recognized.[8] This concept of activated patients is fundamental to the patient care experience. Increased patient activation is associated with improved health outcomes in several long-term chronic conditions, including reduced premature mortality and hospitalization.[7]

Understanding a patient's level of activation is essential for determining the best strategy to empower them in self-management of their disease, including reducing cardiovascular risk (CVR) through behavioral changes.[9] The majority of patients fall within Stage 3, where they have the necessary medical knowledge to take action; however, they sometimes lack the skills or confidence to adopt new health behaviors.[10,11] Public policies can be aligned with activation levels, directing resources toward vulnerable populations, such as those with low educational attainment, and supporting patients in developing the knowledge necessary for responsible health autonomy.[9]

One approach to bridge the gap in effective NCD management and reduce the burden on the healthcare system is to involve community pharmacists as key facilitators in promoting patient activation and exploring this condition.

OBJECTIVE

This study explored the activation levels in patients with CVD in Brazil.

METHODS

Study design

A cross-sectional study designed to assess patient activation levels using the PAM-13 questionnaire,[7] was conducted using an adapted and validated version for the Brazilian population.[12] The questionnaire and variables were administered and recorded by the research pharmacist.

Study population

Patients were recruited from urban community pharmacies (n = 13) throughout the country, except Amazonia, and were invited to participate voluntarily. Invitations to community pharmacists were distributed via an email campaign supported by the Pharmacy Association (Anfarmag), and pharmacists were directly recruited.

Participation was contingent on meeting the specific inclusion and exclusion criteria. Eligible participants were adults aged 18 years or older who were receiving treatment for hypertension and/or hypercholesterolemia and provided signed informed consent. Patients who did not provide informed consent or those who had a disability that prevented them from completing the PAM-13 questionnaire[7] were excluded.

The sample size was calculated using the following formula:

$$n = N^{*}Z^{2*}p\ (1-p)/(N-1)+e^{2}+Z^{2*}(1-p),$$

where *n* is the sample size, N is the total population, Z is the confidence level value (1-α) at 95%, P value is the expected proportion in the population, and e is the absolute precision. With a 5% margin of error, 80% power, and a known variability of 50%, the populations of patients with CVD in Brazil were considered according to Cardiovascular Statistics–Brazil 2020 (12,946,932).[13] The estimated sample size was 385 patients, accounting for a potential 20% dropoutrate (Figure 1).

Variables

Patient activation: Patient activation was measured using the PAM-13 questionnaire[7] (Insignia Health 1667562221). This 13-item tool assesses the belief that the patient's role is crucial, the confidence and knowledge necessary to take action, the implementation of actions to maintain and improve one's health, and the ability to stay committed to these actions even under stress.[12,14] Individual item scores range from 0

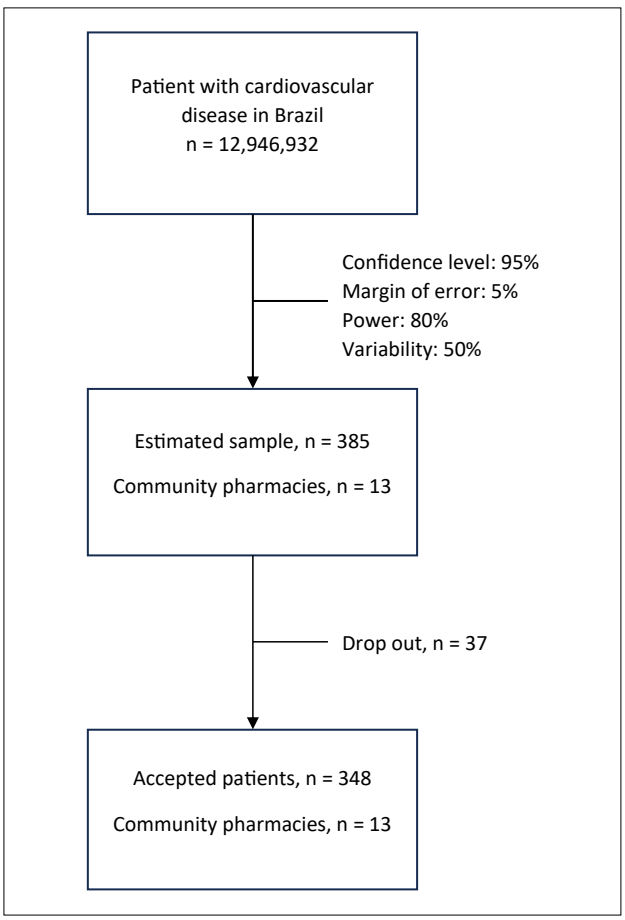

Figure 1. Study flowchart.

to 4 (0 = not applicable, 1 = strongly disagree, 2 = disagree, 3 = agree, and 4 = strongly agree) on a Likert Scale. The average PAM-13 score is converted into a total score ranging from 0 to 100, with higher scores indicating greater activity. Based on the Insignia Health guidelines,[15] PAM-13 scores were categorized into one of four activation levels. Level 1 corresponded to very low activation (0–47.0 points), indicating disengagement and feeling overwhelmed, Level 2 (47.1–55.1) represented becoming aware but still struggling, Level 3 (55.2–67.0) indicated taking action, and Level 4 (67.1–100) represented high activation, implying sustaining behaviors and continuing to improve.[7]

Quality of life: Quality of life refers to the evaluation of an individual's overall well-being and life satisfaction as influenced by or related to their health status. This was measured during the patient visit using a visual analog scale (VAS). The values ranged from 0 to 100, with 0 indicating the worst state of health and 100 indicating the best.

Sociodemographic variables: Age, sex, educational level, autonomy status, employment status, and health-related variables (comorbidities, smoking status, physical activity, and disease duration) were self-reported.

Clinical variables: Clinical variables were measured by the research pharmacist using blood pressure values measured by a sphygmomanometer in mmHg and total cholesterol values by an analysis performed by a doctor or in pharmacies with the equipment for measurement in mg/dL.

CVR factors: The CVR factors were measured using Systematic Coronary Risk Evaluation (SCORE). This table assesses CVR by calculating the probability of developing death of cardiovascular origin within 10 years according to sex, smoking status, age, systolic blood pressure, and total cholesterol. Increased CVR is considered to be higher than ≥ 5%.

Statistical analysis

Data were analyzed using SPSS version 28.0 (SPSS Inc., Chicago, Illinois, United States). Descriptive statistics, including frequency tables for qualitative variables and measures of central tendency (mean and standard deviation) for quantitative variables, were generated to characterize the study sample.

Student's *t*-test for independent samples was used to compare baseline quantitative variables between the different groups. For categorical variables, the chi-square test was used to assess the associations. Multivariate generalized ordinal logistic regression was used to compare the associations of sociodemographic factors and CVR with different PAM-13 levels. Pearson's correlation coefficients (r) were calculated to examine the bivariate relationships among quality of life, clinical variables, sociodemographic data, and activation levels.

Ethic approval

This study was conducted following the resolutions in force in Brazil on Research Ethics (Resolution CNS 466/12), although the indications and treatment of subjects participating in the study followed the same practical clinical routine, and no interference was present with them during the study. Similarly, the study was developed according to a protocol and based on procedures that guarantee compliance with ICH/BPC (International Harmonization Conference/Good Clinical Practice) standards. This project was approved by the Brazil Research Ethics Committee (CAAE: 52996521.9.0000.5553) on December 27, 2022.

RESULTS

The study included 348 patients with a mean age of 59.0 ± 16.7 years. An analysis of CVR revealed that the average blood pressure was 129.6 ± 19.1 mmHg for systolic pressure and 69.7 ± 17.2 mmHg for diastolic pressure. The mean total cholesterol level was 205.4 ± 38.0 mg/dL. The CVR assessed using the SCORE scale yielded a mean value of 2.8 ± 2.7, classified as having low to moderate CVR. The mean number of medications taken by patients was 4.5 ± 3.3, and the overall quality of life for the study population was assessed at 71.6 ± 19.7 out of 100 points (**Table 1**).

Most participants were women, comprising 61.1% (n = 212) of the sample. Regarding educational attainment, 31.9% (n = 111) of the patients had no formal education, whereas 17.8% (n = 62) had completed university-level education. In addition, 51.7% of participants (n = 180) were retired. Of the patients, 79.0 % (n = 275) were non-smokers, and 56.3% (n = 196) engaged in a certain form of physical activity, either occasionally or daily. A total of 63.2% (n = 220) had multiple comorbidities, with 57.2% (n = 199) having these conditions for more than 10 years. In terms of living arrangements, the vast majority of patients (79.0%, n = 275) were autonomous and lived with a companion, 12.6% (n = 44) lived alone independently, and 8.4% (n = 29) required caregivers (**Table 2**).

The patients had a good level of activation, with the majority between levels 3 (35.3%, n = 123) and 4 (30.7%, n = 107). Specifically, 17.5% of the patients were classified as Level 1, 16.4% as Level 2,

Table 1. Sociodemographic and cardiovascular data

Variable	Mean ± SD (min-max)
Age (years old)	59.0 ± 16.7
Systolic blood pressure (mmHg)	129.6 ± 19.1 (90-211)
Diastolic blood pressure (mmHg)	69.7 ± 17.2 (10-102)
Total cholesterol (mg/dL)	205.4 ± 38.0 (85-330)
SCORE* (low/moderate)	2.8 ± 2.7 (0-12)
Number of medications per patient	4.5 ± 3.3 (0-15)
Quality of life	71.6 ± 19.7

SCORE = Systematic Coronary Risk Evaluation; *SCORE is analyzed as a continuous variable based on its numerical score (mean and standard deviation) and is categorized as low or moderate according to established thresholds.

35.3% as Level 3, and 30.7% as Level 4 (**Table 2**). When categorized by PAM-13 level, a significant difference was observed in Level 2, with 77.2% of women (P = 0.039) with a low level of education; only 23.8% of patients were found in level 4 (P = 0.009). Moreover, 84.6% of patients who did not smoke and 74.4% of those who engaged in regular physical activity were at Level 4 (P = 0.022 and P < 0.001, respectively). In addition, presenting with multiple pathologies, 91.7% of the patients were at activation level 2 (P < 0.001), as were 83.3% of the patients who had been ill for more than 10 years (P = 0.049). Finally, 100.0% of patients with low/moderate CVR had an activation level of 4 (P < 0.001) (**Table 2**).

The results of the PAM-13 questionnaire[7] indicated a total score of 63.9 ± 19.6 out of 100, with a mean activation level of 2.8 ± 1.1 out of 4. The best-scored questions were question 1 ("After all, I am responsible for taking care of my health") 3.5 ± 0.7 out of 4 and question 7 ("I am sure that I can continue the medical treatment correctly at home") 3.5 ± 0.7, with the highest percentage of responses in complete agreement, 60.6% and 64.3%, respectively. In contrast, the lowest-scoring questions were question 13 ("I am sure that I can maintain my lifestyle changes, such as eating properly and exercising, even in times of stress") 2.7 ± 0.9 and question 9 ("I know the different treatment options for my health problems") 2.8 ± 1.0, with 8.6% and 10.4% of responses in total disagreement, respectively (**Table 3**).

Statistically significant correlations were observed between variables such as age, smoking, educational level, having more than one pathology, cardiovascular risk (SCORE), medication count, physical activity, and quality of life, with the vast majority of the questions of the PAM questionnaire (**Table 4**). A negative correlation among age, smoking habit, multiple conditions, CVR, and medication count, and a positive correlation with physical activity and quality of life with the item that considered oneself

Table 2. Descriptive statistics

Variable	n (%)	Level 1 (≤ 47.0) (n = 61)	Level 2 (47.1-55.1) (n = 57)	Level 3 (55.2-67.0) (n = 123)	Level 4 (≥ 67.1) (n = 107)	P value
Gender (female)	212 (61.1)	33 (45.9)	44 (77.2)	72 (59.0)	63 (58.9)	**0.039***
Educational level (no education)	111 (31.9)	30 (39.3)	19 (50.0)	35 (28.9)	2 (23.8)	**0.009***
Autonomy status (autonomous with companion)	275 (79.0)	55 (68.9)	23 (66.7)	99 (85.0)	98 (84.6)	0.628
Employment status (retired)	180 (51.7)	23 (26.3)	21 (34.6)	64 (38.4)	72 (44.3)	0.466
Smoking status (non-smoker)	275 (79.0)	47 (57.1)	29 (83.3)	102 (87.5)	97 (84.6)	**0.022***
Physical activity (yes)	196 (56.3)	17 (21.4)	12 (33.3)	82 (70.0)	85 (74.4)	**< 0.001***
Multiple conditions (yes)	220 (63.2)	63 (78.6)	32 (91.7)	78 (67.5)	47 (41.0)	**< 0.001***
Duration of disease (over 10 years)	199 (57.2)	53 (64.3)	29 (83.3)	50 (42.5)	67 (59.0)	**0.049***
SCORE** (low/moderate)	270 (77.6)	42 (44.4)	21 (66.7)	124 (88.9)	83 (100.0)	**< 0.001***

SCORE = Systematic Coronary Risk Evaluation.

*P < 0.05. Chi-square test.

**SCORE is analyzed as a continuous variable based on its numerical score (mean and standard deviation) and categorized as low or moderate according to established thresholds.

Table 3. Patient Activation Measure (PAM-13) questionnaire scores

Question	Mean ± SD	Totally Disagree (%)	Disagree (%)	Agree (%)	Totally Agree (%)
Q1. After all, I am responsible for taking care of my health	3.5 ± 0.7	2.4	6.3	30.7	60.6
Q2. Taking an active role in self-care is the most beneficial aspect of my health	3.4 ± 0.8	0.8	16.3	24.8	58.1
Q3. I am confident that I can take steps that will help prevent or reduce symptoms or problems related to my health	3.3 ± 0.8	1.6	13.3	36.7	48.4
Q4. I know what each of the medicines I have been prescribed are for	3.3 ± 1.0	8.6	9.4	25.0	57.0
Q5. I am confident that I am able to differentiate whether it is necessary to go to the doctor or whether I can solve the health problem myself	3.2 ± 0.9	4.0	16.0	35.2	44.8
Q6. I am sure I can tell the doctor about my concerns, even if he/she does not ask me	3.1 ± 0.9	6.3	20.3	28.9	44.5
Q7. I am sure that I can continue my medical treatment correctly at home	3.5 ± 0.7	2.3	7.8	25.6	64.3
Q8. I understand my health problems and their causes	3.2 ± 0.8	3.9	13.3	37.5	45.3
Q9. I am aware of the different treatment options for my health problems	2.8 ± 1.0	10.4	29.6	27.2	32.8
Q10. I have been able to maintain my lifestyle changes, such as eating right and exercising	3.0 ± 0.9	3.9	26.0	37.8	32.3
Q11. I know how to prevent health-related problems	3.1 ± 0.8	2.4	23.0	43.3	32.3
Q12. I am confident that I can find solutions when new health-related problems arise	3.1 ± 0.9	4.2	20.8	40.8	34.2
Q13. I am confident that I can maintain my lifestyle changes, such as eating right and exercising, even in times of stress	2.7 ± 0.9	8.6	35.2	33.6	22.7
Total score	63.9 ± 19.6				

responsible for taking care of one's health ($P < 0.05$ and $P < 0.001$) were observed. Similarly, a negative correlation among age, educational level, multiple conditions, CVR and medication count and a positive correlation with physical activity and quality of life with developing an active role in self-care, which was observed as the most beneficial aspect of one's health ($P < 0.05$ and $P < 0.001$) were observed. A negative correlation among age, educational level, multiple conditions, CVR, and medication count, and a positive correlation with physical activity and quality of life, with confidence in taking measures that would help prevent or reduce symptoms or health-related problems ($P < 0.05$ and $P < 0.001$) were observed. In addition, knowing the purpose of each prescribed medication correlated negatively with age, smoking habit, educational level, multiple conditions, CVR, and medication count, and positively correlated with physical activity and the quality of life ($P < 0.05$, $P < 0.001$). Age, educational level, multiple conditions, CVR, and medication count and positively correlated with physical activity and quality of life, with the ability to differentiate when it is necessary to visit a doctor versus solving a health problem independently ($P < 0.05$ and $P < 0.001$). Less smoking led to fewer medications prescribed and a higher quality of life ($P < 0.05$), and the more confident the patients were that they could inform their doctors what was bothering them, even if they were not asked. Furthermore, confidence in correctly following medical treatment at home was higher in younger patients ($P < 0.001$), those with a higher educational level ($P < 0.05$), fewer comorbidities ($P < 0.001$), lower CVR ($P < 0.001$), fewer medications prescribed ($P < 0.001$), and higher physical activity and quality of life ($P < 0.001$). Understanding their health problems and causes was significantly correlated with SCORE ($P < 0.05$), medication count, physical activity, and quality of life ($P < 0.001$). Knowledge of different treatment options for health problems was higher in younger patients ($P < 0.05$), non-smoking patients ($P < 0.001$), and those with lower CVR ($P < 0.05$), less prescribed medication ($P < 0.001$), more physical activity ($P < 0.001$), and higher quality of life ($P < 0.05$). Maintaining lifestyle changes, such as eating well

Table 4. Significant correlations between variables and the Patient Activation Measure-13 questionnaire, quality of life, and activation level

Question	Age (-)	Smoke (-)	Educational level (+)	Multiple Conditions (-)	SCORE (-)	Medication Count (-)	Physical Activity (+)	Quality of live (+)
Q1. After all, I am responsible for taking care of my health	0.253*	0.290**		0.302**	0.485**	0.308**	0.274*	0.315**
Q2. Taking an active role in self-care is the most beneficial aspect of my health	0.214*		0.175*	0.268*	0.605**	0.420**	0.367**	0.366**
Q3. I am confident that I can take steps that will help prevent or reduce symptoms or problems related to my health	0.322**		0.247*	0.338**	0.580**	0.505**	0.497**	0.506**
Q4. I know what each of the medicines I have been prescribed are for	0.307**	0.234*	0.290**	0.250*	0.524**	0.361**	0.260*	0.274*
Q5. I am confident that I am able to differentiate whether it is necessary to go to the doctor or whether I can solve the health problem myself	0.366**		0.240*	0.194*	0.321*	0.228*	0.305**	0.246*
Q6. I am sure I can tell the doctor about my concerns, even if he/she does not ask me		0.229*				0.184*		0.195*
Q7. I am sure that I can continue my medical treatment correctly at home	0.301**		0.261*	0.294**	0.412**	0.428**	0.332**	0.375**
Q8. I understand my health problems and their causes					0.387*	0.281**	0.303**	0.300**
Q9. I am aware of the different treatment options for my health problems	0.209*	0.312**			0.380*	0.337**	0.293**	0.237*
Q10. I have been able to maintain my lifestyle changes, such as eating right and exercising		0.195*	0.190*	0.207*	0.354*	0.206*	0.361**	0.381**
Q11. I know how to prevent health-related problems	0.308**			0.226*	0.408**	0.306**	0.233*	0.345**
Q12. I am confident that I can find solutions when new health-related problems arise	0.184*				0.269*			0.422**
Q13. I am confident that I can maintain my lifestyle changes, such as eating right and exercising, even in times of stress		0.235*	0.200*	0.233*	0.309*	0.254*	0.375**	0.336**
Quality of life	0.209*		0.205*	0.189*	0.250*	0.380**		
Activation level	0.148*	0.251*	0.222*	0.313*	0.576**	0.434**	0.434**	

*$P < 0.050$;

**$P < 0.001$.

Correlations are classified as follows: (–) negative Pearson's correlation ($r < 0$) and (+) positive Pearson's correlation ($r > 0$).

SCORE = Systematic Coronary Risk Evaluation.

and exercising, was negatively correlated with smoking, education level, concomitant diseases, CVR, and number of prescribed medications ($P < 0.05$), and positively correlated with physical activity and quality of life ($P < 0.001$). Understanding how to prevent health-related issues significantly correlated with age, multiple conditions, SCORE, medication count, physical activity, and quality of life ($P < 0.05$, $P < 0.001$), and the ability to find solutions when new health problems arose exhibited negative correlations with age and SCORE ($P < 0.05$) and positive correlations with the quality of life ($P < 0.001$) (**Table 4**).

We analyzed the correlations that could exist between the quality of life, level of activation, and level of CVR with different variables of the questionnaire and found that younger patients with university education, less concomitant pathology, fewer medications, and more physical activity had a better quality of life ($P < 0.05$, $P < 0.001$). In addition, younger patients who did not smoke, had fewer concomitant pathologies, lower CVR, fewer prescribed medications, and more physical activity had a higher level of activity ($P < 0.05$, $P < 0.001$) (**Table 4**).

The probability of having a low level of activation with low physical activity (OR = 3.87, 95%CI = 2.09–7.17, $P < 0.001$), having more than one pathology (OR = 1.48, 95%CI = 1.17–1.88, $P = 0.003$), smoking (OR = 1.64, 95%CI = 1.04–2.60, $P = 0.016$), being older than 65 years (OR = 1.25, 95%CI = 1.02–1.52, $P = 0.033$), having a low quality of life (OR = 0.96, 95%CI = 0.95–0.98, $P < 0.001$), and being at high CVR (OR = 3.47, 95%CI = 1.99–6.05, $P < 0.001$) was high (**Table 5**). In addition, performing occasional or daily physical activity was more likely to have a low/moderate CVR (OR = 2.69, 95%CI = 1.05–6.93, $P = 0.039$), controlled blood pressure (OR = 2.47, 95%CI = 1.15–5.31, $P = 0.025$), and fewer concomitant pathologies (OR = 1.42, 95%CI = 1.10–1.87, $P = 0.012$) (**Table 5**).

DISCUSSION

We found that factors such as low physical activity, smoking, advanced age, high CVR, and low QoL were significantly associated with reduced levels of patient activation. These findings underscore the need for targeted interventions to enhance the activation among patients with these risk factors, particularly through lifestyle modification and supportive care strategies.

Table 5. Logistic regression between patient activation level and physical activity and study variables

Low level of activation	OR	95%CI	P value
Low physical activity	3.87	2.09-7.17	< 0.001
Multiple condition	1.48	1.17-1.88	0.003
Smoke	1.64	1.04-2.60	0.016
Over 65 years	1.25	1.02-1.52	0.033
Low quality of life	0.96	0.95-0.98	< 0.001
High SCORE	3.47	1.99-6.05	< 0.001
Physical activity			
Low/moderate CVR	2.69	1.05-6.93	0.039
Controlled BP	2.47	1.15-5-31	0.025
Fewer concomitant pathologies	1.42	1.10-1.87	0.012

OR = odds ratio; CI = confidence interval; SCORE = Systematic Coronary Risk Evaluation; CVR = cardiovascular risk; BP = blood pressure.

Several validated methods are available to assess different facets of patient activation, including health locus of control,[16] self-efficacy in self-management behaviors,[17] and readiness to change health-related behaviors.[18] For example, the health locus of control has been used to explore the extent to which individuals believe they have control over their health outcomes, whereas self-efficacy measures assess the confidence of patients in executing specific health-related behaviors. The PAM-13 questionnaire[7] was selected as a tool to assess activation in terms of an individual's knowledge, skills, beliefs, and confidence in managing their health.[10,19] A preference for taking an active role in healthcare can significantly enhance a patient's ability to engage in shared decision-making with healthcare professionals.[20] This dynamic is particularly relevant for patients with chronic diseases, where control preferences, health promotion educational intervention, active participation in decision-making, and increased activation have been demonstrated to improve outcomes.[21-23]

Consistent with the findings of Magnezi et al.,[24] our study revealed a positive correlation between patient activity and quality of life. Specifically, among patients with visual impairment, PAM-13 revealed significant correlations with activation and the quality of life. Similarly, the average PAM-13 score was 53.4 ± 13.8 in patients with chronic renal disease, with the majority (73%) exhibiting low activation. Notably, patient activation decreased significantly with age and increased with higher educational levels.[25]

In studies on cardiovascular patients, such as that by Goevaerts et al.,[26] the baseline mean PAM-13 score was 59.2 ± 9.5, with 65% of patients at Level 3. We observed slightly higher PAM-13 scores in patients with CVD, with only 35.3% reaching Level 3, indicating a distinct distribution. Similar scores were reported by Hernar et al.,[27] who studied individuals at risk of early health deterioration, revealing an average PAM-13 score of 69.8 ± 14.8. Higher activation scores were generally associated with healthier behaviors across broader populations, including increased physical activity, a finding that aligns with our results, that demonstrated performing occasional or daily physical activity, it was more likely to have a low/moderate CVR, controlled blood pressure and fewer concomitant pathologies, and more level of activation.

Zang et al.[28] reported that in older adults at an increased risk of CVDs in rural areas, education, multimorbidity, and a family history of CVD positively and age negatively influenced activation. In line with these results, patients with low activation levels had multimorbidity, were older than 65 years, and had a high CVR.

General practitioners perceive patient activation as a crucial factor in CVD prevention and report that overcoming the

barriers to lifestyle counselling identified by family physicians is a prerequisite for effective patient-centered consultation on CVR factors. In addition, interprofessional collaboration with pharmacists could alleviate the burden on GPs and thus reduce these barriers.[29] Overall, lower levels of activation are often associated with advanced age, poor health-related quality of life, greater decisional conflict, and reduced medication adherence.[30] Patient activation is crucial for improving the quality of life among individuals with chronic diseases, as it encompasses patients' motivation, knowledge, and ability to manage both acute crises and chronic symptoms. Increasing evidence suggests that patients with higher activation are better equipped to engage in self-care,[31] which ultimately leads to improved health outcomes.[32]

This study had several strengths. This study was conducted across all regions of Brazil except Amazonia, allowing for a broad generalization of our results. In addition, validated instruments were used to measure the patient activity, quality of life, and CVR.

Limitations

We could not assess the temporal effects or determine causality due to the cross-sectional design of the study. Longitudinal studies are required to better understand the long-term influences on patient activation. The reliance on self-reported questionnaires may introduce potential misclassifications owing to socially desirable responses.

Variables such as waist circumference and body mass index were not measured due to opposition from several patients. Data such as complete lipid profile and glycosylated hemoglobin were not included because only one pharmacy had a measuring device, and insufficient data were obtained to ensure consistency in the statistical analysis.

Future directions

Patients with CVD feel more responsible for their healthcare and are more confident in being able to correctly follow medical treatment at home. However, they are less confident in being able to maintain lifestyle changes and are less aware of the different treatment options available for their health problems. Pharmacists play a decisive role in improving patients' understanding of their conditions, being able to actively involve them in their treatment, and transforming therapeutic success into personal achievement.

These findings suggest specific areas of strength and vulnerability in patient engagement, which may inform future research on tailored support strategies for individuals with CVD.

CONCLUSIONS

The level of patient activation in managing cardiovascular health is influenced by multiple factors, including physical activity, age, presence of comorbidities, and overall quality of life. Patients who engaged in regular physical activity demonstrated higher activation levels, better blood pressure control, and a lower CVR, highlighting the significance of promoting physical activity as a strategy for enhancing patient self-management and improving health outcomes. These findings underscore the need for targeted interventions to enhance activation among patients with these risk factors, particularly through lifestyle modification and supportive care strategies. Interventions emphasizing physical activity, self-efficacy, and individualized support are recommended to enhance patient empowerment and engagement in healthcare.

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Functional constipation in pediatric patients: an observational study in southern Brazil

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ABSTRACT

BACKGROUND: Functional constipation is characterized by a set of symptoms including hardened stools, abdominal discomfort, a tendency to retain stools, and eventual fecal incontinence. This condition negatively affects the quality of life of the affected individuals and has potential psychosocial repercussions.

OBJECTIVES: To assess the epidemiological, clinical, and therapeutic aspects of functional constipation in patients treated at a pediatric gastroenterology outpatient clinic.

DESIGN AND SETTING: Descriptive observational study with a quantitative approach using secondary data collected from the medical records of a pediatric gastroenterology outpatient clinic in Criciúma between 2018 and 2023.

METHODS: This study was approved by the Human Research Ethics Committee of the Universidade do Extremo Sul Catarinense (Unesc) under number 6.788.465. Sociodemographic, clinical, and therapeutic variables were evaluated in 67 patients aged 0–18 years who were diagnosed with Functional Constipation (ICD K590) during the study period. Data were analyzed using descriptive statistics in the Statistical Package for the Social Sciences (SPSS), version 25.0.

RESULTS: There was a predominantly female profile (36; 53.7%), with an average age at diagnosis of 7.75 years (± 3.96). The main symptoms included abdominal pain (52, 77.6%) and hardened stools (42, 62.7%), with an average interval of 4 days between bowel movements. Treatment consisted of macrogol prescriptions (60, 89.6%), with most patients showing complete symptom improvement (49, 73.1%).

CONCLUSION: Analysis of medical records highlighted the need for continuous monitoring and targeted interventions, considering the variability of symptoms and individual characteristics of patients.

INTRODUCTION

Functional gastrointestinal disorders are a group of medical conditions characterized by the persistence or recurrence of gastrointestinal symptoms, even in the absence of identifiable structural or biochemical alterations.[1] A prominent subtype is functional constipation (FC), which warrants specific attention.[2]

FC presents as persistent difficulty with bowel movements, which may involve excessive straining, hardened stools, and occasionally, fecal incontinence.[3] This condition, diagnosed by the Rome IV criteria,[3] has a significant impact on patients' quality of life, leading to pronounced abdominal discomfort and psychosocial repercussions.[1]

The global epidemiology of pediatric constipation has an estimated prevalence of 9.5%, with notable variations across regions, ranging from 0.5% to 32.2%.[4] In the Brazilian context, the latest data on prevalence indicated rates between 17.5% and 36.5%, suggesting a higher number of affected individuals compared to the global average.[5]

Biopsychosocial risk factors such as stress, childhood obesity, sedentary lifestyle, poor diet, and dysfunctional family environments may exacerbate symptoms.[6] Therefore, treatment aims at targeted interventions for these aspects, necessitating changes in dietary patterns, lifestyle, and medication use.[6,7] Macrogol, an osmotic laxative, is the primary substance used in the management of functional constipation across all age groups because of its efficacy and safety in long-term treatment.[7]

FC in children and adolescents is often underestimated and can substantially affect their quality of life, affecting daily activities and socio-emotional aspects. Characterizing pediatric patients with FC provides a foundation for identifying specific patterns and enabling more efficient and targeted treatments. This significantly improves clinical practice and the well-being of

these patients, leading to positive long-term outcomes. This study aimed to describe the epidemiological, clinical, and therapeutic aspects of patients with FC treated at the pediatric gastroenterology department of the Secretaria Municipal de Saúde de Criciúma (PMC) between 2018 and 2023.

METHODS

Study design

This was a descriptive observational study with secondary data collection.

Ethical aspects

This study was approved by the Research Ethics Committee of the Universidade do Extremo Sul Catarinense (Unesc) under number 6.788.465. The requirement for informed consent was waived because this was a retrospective study based on medical records with no identification of the participants.

Population

The target population included all individuals aged 0–18 years diagnosed with functional constipation (ICD K590), who were treated at a specialized pediatric gastroenterology service in the southern region of Santa Catarina between January 2018 and December 2023. Patients with an inconclusive diagnosis of functional constipation according to the Rome IV criteria were excluded.

Sample

The medical records of all patients fitting the target population during the period of January 2018 to December 2023 were included in the study, considering it a census data collection.[8] A total of 71 medical records were obtained during the evaluated period.

Data collection

Data from patients aged 0–18 years who were diagnosed with functional constipation (ICD K590) and treated at the pediatric gastroenterology outpatient clinic between 2018 and 2023 were analyzed. Medical records were retrieved from the Celk Saúde system in the Municipality of Criciúma. The variables analyzed included patient age, sex, age at symptom onset, signs and symptoms associated with functional constipation, interval between bowel movements, fecal incontinence episodes, nutritional quality, presence of comorbidities, daily medication use, prior macrogol treatment and dose, prescribed treatment, and clinical response.

The data collection instrument was a questionnaire developed by the researchers structured into four distinct sections to cover the research variables and provide a detailed understanding of the clinical and therapeutic panorama of children treated in the pediatric gastroenterology service. Section A contains the essential information for patient identification and characterization, including medical record number, age, and sex. Section B (Past Medical History) focused on evaluating the patients' medical history and gathering information on comorbidities and medication use. Section C explores the clinical details related to functional constipation and investigates factors such as abdominal pain and fecal incontinence. Section D addresses information on therapeutic interventions for gastrointestinal conditions as well as the observed clinical responses.

Statistical analysis

Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS), version 25.0. Descriptive analyses of the studied variables were performed, reporting the frequency and percentage of qualitative variables (sex, daily medications, comorbidities, nutritional quality, signs and symptoms, presence of fecal incontinence, prior treatment, type of treatment, dietary changes, and clinical response) and the mean and standard deviation of quantitative variables (current age, age at symptom onset, interval between bowel movements, and prior macrogol dose) if they followed a normal distribution, and median and interquartile range if they did not. The normality of the quantitative variables was assessed using the Kolmogorov-Smirnov test. All the results are expressed as graphs and/or tables.

RESULTS

During the analysis period, 71 medical records of patients aged 0–18 years with functional constipation (ICD K590) were selected. After excluding four cases with inconclusive diagnoses, the final sample comprised 67 patients, corresponding to 9.4% of the total (710) individuals who attended the specialized outpatient clinic. The mean age at the time of consultation was 7.75 (± 3.96) years. The minimum and maximum ages ranged from 1–16 years, with a predominance of females (36; 53.7%) (**Table 1**).

The average age of onset of functional constipation symptoms was 4.49 (± 3.93) years, with a predominance in younger age groups, as most episodes occurred in children up to 5 years old (41; 66.1%). The interval between the onset of the first symptoms

Table 1. Demographic characteristics of patients with functional constipation

Variables	Mean ± SD, n (%)
	n = 67
Age (years)	7.75 ± 3.96
Minimum	1
Maximum	16
Sexo	
Female	36 (53.7)
Male	31 (46.3)

and specialized consultation was at most two years in the majority of cases (32; 47.8%).

Among the signs and symptoms, the most prevalent were abdominal pain (52; 77.6%), which was particularly common in patients up to 10 years of age (43; 82.7%); hardened stools (42; 62.7%); and hematochezia (28; 41.8%), which were more common in the 6–15 years age group (21; 75%). Other manifestations such as excessive straining (20, 29.9%), abdominal distension (16, 23.9%), and fecal impaction (16, 23.9%) appeared in approximately one-third of the patients (**Table 2**).

The interval between bowel movements varied, ranging from a minimum of 1 (4; 6%) to a maximum of 30 days (1; 1.5%). However, the most common interval was 4 days (n = 15; 22.4%). Constipated patients with longer periods between bowel movements (4 or more days) had a higher occurrence of fecal incontinence episodes (15; 83.3%). In total, 23 (34.3%) reported this symptom. Despite dietary habits, 61.2% (n = 41) of patients followed a varied diet, while 35.8% (n = 24) ateselectively e. The occurrence rates of up to four symptoms were similar in both cases at 87% (36) and 83.3% (20).

Comorbidities were present in 34.9% (23) of the patients and were more prevalent in boys (14; 60.9%). A minority of patients were on daily medication (18, 26.9%). **Table 3** shows the clinical characteristics of the patients. The main coexisting conditions among those with functional constipation included Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and Intellectual Disability, each affecting six patients (26.1%). Of the 18 individuals using medications, risperidone was the most commonly used (10; 55.6%), primarily in the 6 to 15 years age group.

Among the individuals studied, a minority (24; 35.8%) had previously used macrogol, mainly at lower doses (11; 45.8%), and in only one patient (0.04%), at a higher dose than that prescribed by the specialist. The average previous dose, excluding records without explicit registration (12, 50%), was 13.99 g ± 8.25. Regarding prescribed pharmacological treatment, only seven children (10.4%) did not receive a prescription for macrogol, making it the main recommended medication (60; 89.6%). Other medications included lactulose and enemas (both in 17 patients; 25.4%), sorbitol + sodium lauryl sulfate (8 patients; 11.9%), and mineral oil (7 patients; 10.4%). **Table 4** shows the details of the observed therapies.

Nonpharmacological treatments have also been adopted in addition to drug interventions. Dietary modifications were recommended for just over half of the patients (38; 56.7%), with increased fiber intake and water consumption being the main suggestions, as indicated for 15 (39.5%) and 31 (81.6%) patients, respectively. Lifestyle changes, such as increased physical activity and the establishment of regular evacuation routines, were proposed for 35 (52.2%) individuals. Isolated non-drug therapy was prescribed for only three (4.47%) constipated patients, highlighting

Table 2. Clinical characteristics of patients with functional constipation

Variables	Mean ± SD, n (%)
	n = 67
Age of symptom onset	**4.49 ± 3.93**
Signs and symptoms	
Abdominal pain	52 (77.6)
Hardened stools	42 (62.7)
Hematochezia	28 (41.8)
Excessive straining	20 (29.9)
Abdominal distension	16 (23.9)
Impaction and/or rectal Mass	16 (23.9)
Fear of defecation	14 (20.9)
Nausea and/or vomiting	10 (14.9)
Tenesmus	10 (14.9)
Abdominal colic	4 (6)
Interval between bowel movements (days)	
1–3 days	16 (23.9)
4–10 days	33 (49.3)
14–30 days	5 (7.5)
Ignored	13 (19.4)
Fecal incontinence	
Yes	23 (34.3)
No	44 (64.7)
Dietary quality	
Varied diet	41 (61.2)
Selective diet	24 (35.8)
Ignored	2 (3)

Table 3. Clinical history of patients with functional constipation

Variables	Mean ± SD, n (%)
	n = 67
Comorbidities	
Yes	23 (34.9)
Attention deficit hyperactivity disorder	6 (26.1)
Autism spectrum disorder	6 (26.1)
Intellectual disability	6 (26.1)
Cerebral palsy	2 (8.7)
Oppositional defiant disorder	2 (8.7)
Down syndrome	1 (4.3)
Others	6 (26.1)
No	44 (65.7)
Medication use	
Yes	18 (26.9)
Risperidone	10 (55.6)
Imipramine	7 (38.9)
Methylphenidate	4 (22.2)
Amitriptyline	2 (11.1)
Sodium valproate	2 (11.1)
Fluoxetine	1 (5.6)
Others	9 (50)
No	49 (73.1)

Table 4. Therapeutic resources used in patients with functional constipation

Variables	Mean ± SD, n (%)
	n = 67
Previous treatment with macrogol	
Yes	24 (35.8)
Higher dose	1 (0.04)
Lower dose	11 (45.8)
Ignored	12 (50)
No	43 (64.2)
Previous dose of macrogol	13.99 ± 8.25
Pharmacological treatment	
Prescribed medications	
Macrogol	60 (89.6)
Lactulose	17 (25.4)
Enema	17 (25.4)
Sorbitol + sodium lauryl sulfate	8 (11.9)
Mineral oil	7 (10.4)
Macrogol 3350 + sodium bicarbonate + sodium chloride + potassium chloride	1 (1.5)
Others	3 (4.5)
Number of medications prescribed per patient	
Up to 1 medication	29 (59.2)
2–3 medications	16 (32.7)
4 or more medications	4 (8.2)
Non-pharmacological treatment	
Dietary modifications	38 (56.7)
Increased fiber intake	15 (39.5)
Remove cow's milk	8 (21.1)
Remove wheat	1 (2.6)
Increased fluid intake	31 (81.6)
Lifestyle change	35 (52.2)
Clinical response	
Complete improvement	49 (73.1)
Partial improvement	8 (11.9)
No change	1 (1.5)
Worsening	2 (3)
Relapse	1 (1.5)
Did not return for follow-up	6 (9)

the need for combined interventions to restore the intestinal health of those evaluated.

Regarding the clinical response, in the majority of the sample, complete symptom improvement was achieved with the use of up to one medication (29; 59.2%), which was the outcome observed in most patients (49; 73.1%). However, eight individuals (11.9%) showed partial improvement, and two (3%) reported worsening of symptoms. Additionally, six patients (9%) did not return for follow-up, limiting the reevaluation and prognosis of this group.

DISCUSSION

In the pediatric gastroenterology outpatient clinic, functional constipation was predominantly observed in girls, with an average age of 7.75 years at the time of consultation and initial episodes occurring mostly before the age of 5 years. The main reported symptoms were abdominal pain and hardened stools, with an average interval of 4 days between bowel movements. Additionally, 34.3% of the patients experienced episodes of fecal incontinence.

The overall prevalence of functional constipation in the population, including both adults and children, shows wide variation, with estimates ranging from 0.7% to 79% and a median of 16%.[9] In children, the rates range from 9.5% to 11.8%,[10,11] with reports from specialized pediatric outpatient clinics in Brazil ranging from 7.6% to 29%.[12,13] Internationally, the variation ranges from 3% to 46.7%, reflecting methodological and socioeconomic differences among studies.[14,15] In this study, the prevalence of consultations for functional constipation of 9.4%, was within the expected range for both the national and global pediatric population. This result supports previously published data, suggesting that, even in a regional sample, the observed rates remain consistent with those found in other locations.

The mean age at the time of the consultation was 7.75 years (± 3.96), ranging from 1 to 16 years. Although the age group with the highest prevalence of functional constipation has not been clearly defined,[14] the data obtained are similar to those reported in other studies, which reported average ages of 5.4 and 6.4 years.[16,9] These results suggest that functional constipation can occur at various pediatric ages, without a specific age trend. Regarding sex, there was a female predominance (36; 53.7%), which aligns with findings showing similar prevalence rates between boys and girls (8.6% versus 8.9%, respectively).[4] A Colombian study also found no significant gender predominance,[17] indicating that the differences observed in our sample may be specific to the analyzed population.

The data presented reveal the onset of symptoms of FC at ages younger than 5 years, with an age of 4.49 years (± 3.93). The predominance of initial episodes in children up to 5 years old, representing 66.1% of the cases, is consistent with existing literature, which predicts an average onset age around 2.3 years, with higher prevalence in preschool-aged children.[5,18–20] This suggests that factors such as dietary changes, transitions in sphincter control, and the start of schooling may play a significant role in triggering symptoms in this age group.[6,21–23] It was also observed that 47.8% of individuals waited up to 2 years to receive specialized care, reflecting a pattern consistent with studies that reported that 77.8% of patients experience delays of over a year for their first consultation.[13,24] This delay in treatment can exacerbate symptoms and lead to excessive use of rectal laxatives and other inappropriate interventions, resulting in significant morbidity for the pediatric population.[25]

Hard stools are the most prevalent symptom of pediatric functional constipation, affecting nearly all patients.[5,19,26] In the present sample, this symptom was observed in 62.7% of the cases, a

notable rate but lower than that reported in other Brazilian studies, which indicated prevalence of up to 86.5%.[13] This difference may suggest that some patients already experience partial symptom relief, possibly due to prior laxative use, or that the studied population has distinct clinical characteristics that influence this manifestation. On the other hand, abdominal pain was reported by 77.6% of the patients, a rate significantly higher than the 40% found in comparative studies.[27] This symptom can significantly contribute to children's resistance to evacuation, fueling a cycle of pain and retention that exacerbates constipation condition.[28–30]

Most individuals experienced fewer than two bowel movements per week. Additionally, children with FC and longer intervals between evacuations (4 or more days) showed a higher incidence of fecal incontinence (15; 83.3%), reflecting the significant overlap between these conditions, which is often observed in more severe cases.[28,31,32] Patients who experience this co-occurrence have a lower quality of life than those with isolated constipation,[24,33] and if not properly treated, fecal incontinence can lead to social isolation and long-term psychological issues.[24] Studies suggest that about one-quarter of patients experience this co-occurrence,continue to have symptoms in adulthood,[34] and present a lower quality of life than those with worse clinical outcomes over time.[31] This underscores the importance of early diagnosis and appropriate treatment. FI can lead to social isolation and long-term psychological issues.[7]

Regarding diet, although some studies have shown associated inadequate eating habits, such as low fiber intake and functional constipation,[1,3,35] others have found no significant correlation between diet and the disease.[32,36] These findings are consistent with those of this study, where most patients followed a varied diet (41; 61.2%), suggesting that dietary factors may play a less determining role in some pediatric populations. However, it is crucial to consider dietary interventions as part of a multidisciplinary approach for managing functional constipation.[7,37]

It was observed that 34.9% of the patients had comorbidities mainly characterized by neurodevelopmental disorders. The prevalence of ADHD in this sample (26.1%) was higher than the average reported in the literature (13.87 %),[38] suggesting particularities of the study population. However, this comorbidity is not necessarily associated with a higher risk of gastrointestinal disorders compared to the general population, and medication for ADHD does not seem to significantly affect the rates of consultations for defecatory disorders.[38,39] In contrast, children with ASD have a high prevalence of constipation, occurring in up to 85% of cases,[26] and also a higher risk of needing medication, as exemplified by the use of risperidone in 26.9% of patients in this study. Constipation is a common side effect of risperidone in children with ASD,[40,41] suggesting a possible relationship between the use of antipsychotics and the worsening of gastrointestinal symptoms.

In the literature, most patients received prior treatment in primary care before being referred to a specialist, with the main interventions being the use of laxatives (such as macrogol), dietary modifications, and lifestyle changes.[18,42] Malowitz et al.[18] and Bongers et al.[34] found that although the peak onset of functional constipation occurs early, the search for specialized care usually occurs later, after prolonged episodes and inadequate management in primary care, with the presentation of more severe symptoms, indicating that previous treatments were insufficient.[18,34] In the present study, we found a minority of individuals (24; 35.8%) who had used macrogol previously, with an estimated average dose of 13.99 g ± 8.25. Although this average does not take into account the children's weight, and thus it is not possible to confirm whether it is within the recommended dose range of 0.93 ± 0.28 g/kg/day, with a maximum of 30 g/day,[43] it is plausible that the previous treatment followed guidelines, even though the available data do not allow for a conclusive analysis.

Macrogol is the primary pharmacological treatment for pediatric functional constipation, as recommended by the guidelines of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, due to its safety and efficacy in increasing the water content in stools, thus relieving symptoms.[44,45] When it is unavailable or poorly tolerated, lactulose is the preferred alternative, although it causes more side effects.[45–49] Other laxatives, such as mineral oil, may be used as a second-line option if osmotic laxatives fail or are insufficient.[50] Despite these alternatives, macrogol remains the most prescribed agent, as reflected in the study sample, which showed a low rate of non-prescription (7; 10.4%). Studies suggest that enemas, while useful for immediate relief, are not recommended for continuous therapy, which justifies their reduced use in the clinic (17; 25.4%).[9,44,51,52] Mineral oil, although effective, is restricted due to risks such as aspiration and lipoid pneumonia as well as the potential for intestinal dependencewith prolonged use,[53–56] explaining its low prescription rate in the sample (7; 10.4%).

Although they do not have a prophylactic role,[32,36] there is a recognized need for concurrent non-pharmacological measures for the effective management of functional constipation.[44] In the present study, this therapeutic approach was recommended for just over half of the patients (38; 56.7%). This aligns with the literature, which points out that low water and fiber intake is associated with harder stools, worsening the condition, and is a critical component in managing chronic functional constipation.[57] Lifestyle changes, such as increased physical activity and the establishment of a regular evacuation routine, were proposed for 35 (52.2%) individuals. However, no randomized studies have evaluated the effect of increased physical activity on childhood constipation, limiting evidence regarding its effectiveness.[44]

Most children who received prescriptions used up to one medication to achieve complete symptom improvement, a stage

reached by most patients (49; 73.1%). The number of medications required for the successful management of functional constipation can vary significantly based on individual responses to treatment and severity of the condition. For 60–90% of children, a single medication, typically macrogol, may be sufficient; however, some may not achieve satisfactory results and require additional therapies,[58] as evidenced by eight patients in the present study who showed only partial improvement. Furthermore, 6 patients (9%) did not return for follow-up, and various factors contributed to this lack of follow-up, including socioeconomic barriers, lack of awareness among parents about the importance of follow-up, and logistical challenges such as transportation or scheduling issues.[59] Without appropriate follow-up, healthcare providers may miss the opportunity to modify treatment plans or intensify care for those who do not respond adequately,[44,46,60,61] resulting in chronic constipation and unsatisfactory long-term outcomes.[58]

Although the analyzed medical records were comprehensive, some limitations should be acknowledged. The observational nature of this research, combined with its reliance on secondary data, may restrict the availability of information and prevent the inference of associations between variables. Additionally, the sample in this study, although relevant to the context of southern Santa Catarina, had limited national representativeness, which may have affected the generalizability of the results. Finally, factors such as lack of information on clinical progression and absence of follow-up data may affect the evaluation of the effectiveness of the proposed interventions.

This study provides an updated sociodemographic, clinical, and therapeutic profile of pediatric functional constipation in Brazil, addressing the scarcity of recent data in the national literature. With only one recent study available in 2021 and others dating back to the 2000s and the 2010s, the observations highlight distinct characteristics that may influence the understanding and management of the condition. Furthermore, by including a representative sample of the population attending a pediatric outpatient clinic, the results offer valuable insights into the development of more effective treatment and follow-up strategies tailored to the specific needs of this population.

CONCLUSIONS

The analysis of 67 patients with functional constipation, representing 9.4% of the 710 pediatric gastroenterology outpatient visits at the PMC, revealed a predominantly female profile (36; 53.7%), with symptom onset before the age of 5 years and a mean age at consultation of 7.75 (± 3.96) years. The most commonly reported symptoms included abdominal pain (n = 52, 77.6%), hardened stools (n = 42, 62.7%), and fecal incontinence (n = 23, 34.3 %). Pharmacological treatment was characterized by frequent macrogol prescriptions (60, 89.6%), with most patients (49, 73.1%) achieving complete symptom relief. Non-pharmacological interventions such as dietary modifications were also implemented in more than half of the cases (38; 56.7%), reinforcing the importance of a multidisciplinary therapeutic approach.

For future research, a longitudinal approach is recommended to allow patient follow-up over time and to evaluate factors influencing treatment response, in addition to multicenter studies aimed at a more comprehensive understanding of functional constipation and its nuances.

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The effect of methadone and ketamine on quality of recovery in patients undergoing laparoscopic cholecystectomy: a prospective cohort study

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ABSTRACT

BACKGROUND AND OBJECTIVES: Acute pain following laparoscopic cholecystectomy is most intense in the first 24 h. The use of shorter-acting opioids for pain management may contribute to increased postoperative morbidity. The combination of methadone and ketamine has been associated with lower postoperative pain scores and less opioid use. We aimed to determine whether the combination of ketamine and methadone improves the quality of recovery.

METHODS: This prospective cohort study included patients undergoing laparoscopic cholecystectomy. Patients who received either methadone alone or a combination of methadone and ketamine (0.3 mg/kg) were followed up for 24 h after surgery. The primary outcome was the quality of recovery, measured using the quality of recovery-40 (QoR-40) questionnaire. Secondary outcomes included postoperative pain intensity, opioid consumption, and the incidence of nausea and vomiting.

RESULTS: The QoR-40 scores were higher in patients who received methadone and ketamine than in those who received methadone alone [197 (194.7–198) versus 195 (189–197), P = 0.01]. Postoperative pain scores, the incidence of postoperative nausea and vomiting, and postoperative opioid use were similar between the groups. The combination of methadone and ketamine was not associated with lower incidence of moderate-to-severe pain in propensity score analysis.

CONCLUSION: Although the combination of methadone and ketamine showed a slight increase in QoR-40 scores at 24 h postoperatively, the observed difference between the groups was not clinically significant. Moreover, the absence of a reduction in postoperative pain intensity and similar perioperative opioid consumption between the groups further support the hypothesis that small, isolated doses of ketamine may not be effective in improving recovery quality compared with methadone alone.

INTRODUCTION

Acute pain following laparoscopic cholecystectomy is complex in nature and typically most intense on the day of surgery and the subsequent day.[1] The conventional use of shorter-acting opioids administered in bolus doses for perioperative analgesia may lead to intervals of insufficient pain control due to fluctuating antinociceptive levels.[2] Conversely, literature indicates that excessive perioperative opioid administration, contrary to its intended purpose, is correlated with increased postoperative morbidity, including pain.[3,4] Although not fully elucidated, evidence has highlighted the role of N-methyl-D-aspartate (NMDA) receptors in the pathways involved in pain activation.[4]

NMDA receptor antagonists, such as ketamine and methadone, have been investigated as part of multimodal strategies for managing acute postoperative pain. These agents demonstrate potential for preemptive analgesia by impeding central sensitization to nociceptive stimuli.[4] Ketamine acts mainly as a competitive antagonist of NMDA receptors, while methadone functions as a long-acting μ-opioid receptor agonist with additional activity at κ- and σ-opioid receptors and also inhibits the reuptake of monoamines and catecholamines.[5] Brinck et al.[6] concluded that perioperative ketamine is associated with a reduction on postoperative pain scores and analgesic requirements. Methadone has similarly been proposed as an alternative for perioperative pain management,[7] including in patients undergoing ambulatory procedures[8] and surgeries with next-day discharge.[9]

Although the association between methadone and ketamine has been studied in patients with spinal disorders,[10] the potential benefits of such a combination in other populations are lacking. Data regarding the effect of this combination on the quality of recovery remain scarce. This prospective cohort study aimed to assess whether adding ketamine to a methadone-based regimen improves postoperative recovery quality in patients undergoing laparoscopic cholecystectomy. The primary outcome was the quality of recovery (QoR-40) score measured 24 h after surgery. Secondary outcomes included postoperative pain at rest and during movement, opioid consumption, and the incidence of postoperative nausea and vomiting (PONV).

MATERIALS AND METHODS

From January 2022 to July 2022, all patients scheduled for elective laparoscopic cholecystectomy were screened and enrolled after obtaining approval from the Research Ethics Committee (Protocol No. 4.959.204; CAAE: 51393621.4.0000.0087), and written informed consent was obtained. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11]

Inclusion and exclusion criteria

Patients were selected based on the daily schedule of elective laparoscopic cholecystectomy. Inclusion criteria included patients aged 18 to 65 years, classified as American Society of Anesthesiologists Physical Status Classification (ASA-PS) I or II, and a body mass index (BMI) of ≤ 30 kg/m^{-2}. Exclusion criteria were as follows: (i) cardiovascular diseases associated with coronary ischemia, (ii) cardiac conduction disorders (defined as QTc > 450 ms), (iii) poorly controlled psychiatric disorders, (iv) significant liver disease (cirrhosis or hepatic failure), (v) preoperative chronic renal insufficiency or failure, (vi) a history of alcohol or drug abuse, (vii) allergy to methadone or ketamine, (viii) acute cholecystitis, (ix) intraoperative cholangiography, (x) chronic opioid use, (xi) concurrent surgical procedures, (xii) unplanned intraoperative endoscopic retrograde cholangiopancreatography, (xiii) bleeding with hemodynamic instability, (xiv) conversion to open surgery, (xv) unplanned transfer to the intensive care unit, (xvi) surgical reintervention, and (xvii) refusal to participate.

Perioperative care

All patients were continuously monitored using electrocardiography, pulse oximetry, non-invasive blood pressure measurement, capnography, a skin temperature probe, train-of-four stimulation, and bispectral index monitoring. Premedication was not routinely administered. Anesthesia was induced with propofol (1-2 mg/kg), remifentanil (1 mcg/kg), and rocuronium (1.2 mg/kg). After induction, all patients received intravenous methadone (0.15 mg/kg) and intravenous dexamethasone (10 mg). Intravenous ketamine (0.3 mg/kg) was administered at the discretion of the attending anesthesiologist. Anesthesia was maintained with remifentanil (0.1-0.5 mcg/kg/min) and target-controlled infusion propofol (1-4 mcg/ml) to achieve bispectral index values between 40 and 60 and mean arterial pressures within 20% of baseline measures. At the end of surgery, all patients received intravenous ketoprofen (100 mg), intravenous metamizole (2 g), and intravenous ondansetron (8 mg). Notably, metamizole, a non-narcotic pyrazolone derivative, is the most widely used analgesic in some countries and remains a commonly prescribed drug in Brazil for pain relief.[12] Intravenous fluids were administered continuously at a rate of 5 ml/kg/h. Hypotension was treated with ephedrine (5 mg), metaraminol (0.5 mg), or fluid boluses. Normothermia was maintained using a convective air-circulation heating system (Bair Hugger; 3M-Switzerland, Rüschlikon, Switzerland). Neuromuscular blockade was reversed with sugammadex, following recommended guidelines. Patients were extubated in the operating room and transferred to the post-anesthesia care unit (PACU).

In the PACU, patients experiencing moderate to severe pain (defined as a numeric rating scale [NRS] score > 3) received intravenous morphine: 0.03 mg/kg for moderate pain and 0.05 mg/kg for severe pain. The goal was to reduce pain to an NRS score of 3 or lower (0, no pain; 10, worst pain imaginable). Patients presenting with PONV were treated with 30 mg of intravenous dimenhydrinate. In the ward, all patients followed the institutional protocol and received intravenous metamizole (2 g every 6 h), intravenous ketoprofen (100 mg every 12 h), intravenous ondansetron (4 mg as needed for nausea), and intravenous tramadol (100 mg every 6 h if NRS > 3). Patients who required tramadol were reassessed 30 min after administration. For patients with moderate-to-severe pain after administration of metamizole, ketoprofen, and tramadol, a medical evaluation was requested, and intravenous morphine (2 mg) was administered every 15 min until mild pain was achieved.

Data collection and outcomes

Patients were followed for 24 h, beginning with the preoperative assessment and continuing through the postoperative period. In the preoperative area, a research team member calculated the Apfel score for all patients. Data collected from the anesthesia records included the time to extubation, duration of surgery, and cumulative intraoperative doses of remifentanil and propofol. Extubation time was defined as the interval between the end of anesthetic drug infusion and the patient's eye opening in response to verbal commands. In the PACU, patients were assessed for pain every 15 min. Pain severity was categorized using the NRS: scores of 1–3 indicated mild pain, 4–6 moderate

pain, and 7–10 severe pain. Nurses recorded the total amount of intravenous morphine administered, instances of PONV, and postoperative complications such as cardiac arrhythmias and respiratory depression. Residual sedation was assessed at 15 and 30 min after PACU admission using the modified Wilson sedation scale.[13]

In the inpatient ward, pain assessments were conducted at rest and during movement within the first hour and again 6 h after admission. Nurses recorded episodes of PONV during the first 24 postoperative hours. Following the institutional protocol, patients were instructed to ambulate with assistance 3 h after ward admission and could request additional pain assessments if needed. All relevant data were recorded, and opioid doses administered in the ward were converted to morphine equivalents.

At 24 h post-admission and before hospital discharge, a research team member, blinded to the patient's group allocation, administered a questionnaire to assess the quality of postoperative recovery. The Quality of Recovery questionnaire is a patient-reported tool that evaluates physiological values, functional recovery, and patient-reported outcomes.[14]

Statistical analysis

The sample size was determined from the available data, i.e., all patients who underwent elective laparoscopic cholecystectomy at our institution from January 2022 to July 2022. No *a priori* power calculations were performed. However, a *post hoc* power analysis was performed using the actual sample size and parameter estimates derived from the dataset. For an effect size of 0.5 (total QoR-40 score in the methadone–ketamine (MK) group compared with the methadone-only (ME) group [197 (194.7–198) versus 195 (189–197), respectively] and a significance level of 5%, a t-test yielded a critical t-value of 0.66 and statistical power (1-β) of 0.82.

Categorical variables are presented as absolute values and percentages. The normality of continuous variables was assessed using the Shapiro–Wilk test, with results reported as mean (SD) and median (IQR). Given the non-normal distribution and clear negative skewness of the original QoR-40 score data, the Wilcoxon rank-sum test was used for nonparametric comparisons at each time point. Internal reliability of the QoR-40 was assessed using Cronbach's alpha. All outcomes were analyzed using univariate logistic regression.

To identify independent predictors of moderate-to-severe postoperative pain, a multivariate logistic regression model was used. Variables with P-values < 0.20 in the univariate analysis were considered candidates, and stepwise selection retained those with P-values < 0.10. Effect sizes were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). To adjust for potential confounding due to the non-randomized use of ketamine, inverse probability treatment weighting (IPTW) was applied. This method accounted for imbalances in confounding factors between the ME and MK groups. Propensity scores (PSs) were generated using a wide array of independent variables: age, sex, BMI, diabetes mellitus, hypertension, ASA-PS classification, history of nausea and vomiting, Apfel score, extubation time, duration of surgery, cumulative doses of remifentanil and propofol, Wilson sedation score, NRS > 3 in the PACU, and incidence of PONV in the PACU. Patients in the MK group were weighted by the inverse of the PS, while those in the ME group were weighted by the inverse of (1-PS), thus forming the IPTW-adjusted cohort. Covariate balance before and after IPTW adjustment was assessed using standardized mean differences, with a standardized mean difference < 10% considered optimal and < 20% acceptable.[15] IPTW-adjusted logistic regression models were used to estimate the odds of moderate-to-severe pain, improving the validity of causal inferences in this non-randomized setting.

All P-values were calculated using two-tailed analyses, and a cut-off of < 0.05 was adopted to reject the null hypothesis. R software (version 3.4.4; R Foundation for Statistical Computing, Austria) was used for all analyses.

RESULTS

A total of 213 patients were screened from January 2022 to July 2022. After excluding 133 patients and accounting for three patients lost to follow-up, the final sample consisted of 77 patients (**Figure 1**). Among these, 37 patients received methadone at 0.15 mg/kg, and 41 patients received a combination of methadone 0.15 mg/kg and ketamine 0.3 mg/kg. The mean age of the included patients was 39 ± 9.6 years, and the average BMI was 27.4 ± 2.2 kg/m². Regarding comorbidities, 3% of the patients had type II diabetes, and 14% had hypertension. No statistically significant differences were observed between the ME and MK groups in terms of age, BMI, sex, ASA-PS classification, comorbidities, APFEL score, and smoking habits (**Table 1**).

Details regarding anesthetic management and postoperative residual sedation in the PACU are shown in **Table 1**. Extubation time was not prolonged in the MK group compared with the ME group. Surgical duration did not differ between the study arms. No difference was found in cumulative intraoperative doses of remifentanil [mcg, 520 (409.6–698.5) versus 687.2 (408.5–954.6), P = 0.21] and propofol [mg, 678.2 (283.5) versus 746.6 (262.9), P = 0.28] between the ME and MK groups. Analysis of postoperative sedation using the Wilson sedation scale revealed no difference between the groups.

Postoperative sedation levels in the PACU were evaluated using the modified Wilson sedation scale. In the ME group, 54% of patients (n = 20) received a score of 1, indicating that they were alert and oriented, while 46% (n = 17) scored 2, indicating

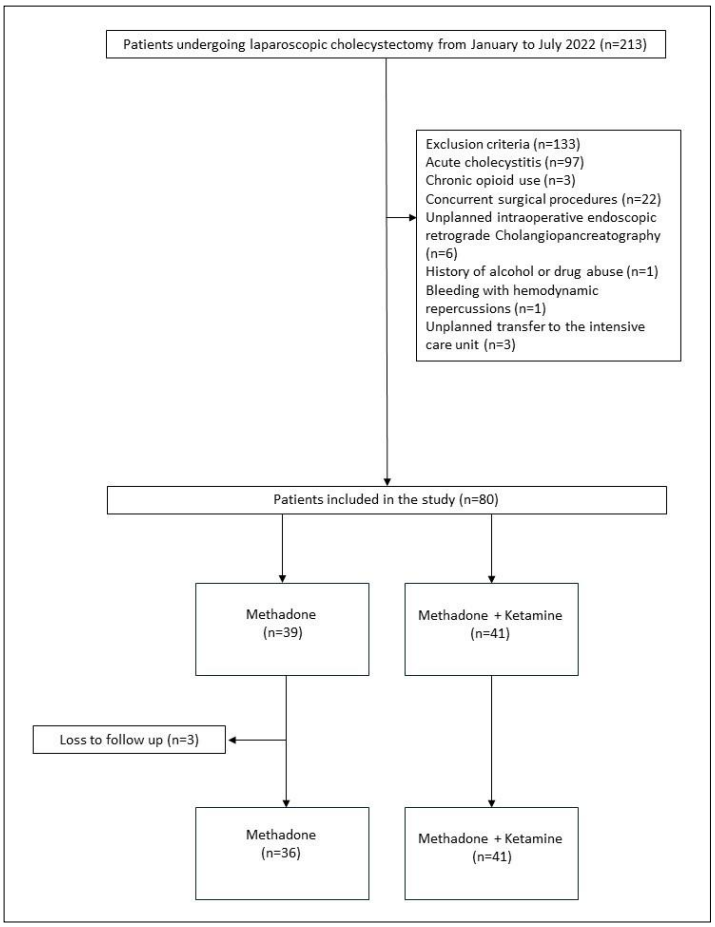

Figure 1. Study flow diagram.

wakefulness with drowsiness. In the MK group, 36% (n = 15) scored 1 and 64% (n = 26) scored 2. No patients in either group exhibited deeper sedation levels (scores ≥ 3), and no episodes of respiratory depression or delayed emergence were observed. Overall, Wilson sedation scale scores did not differ between the groups (P > 0.05).

Primary outcome

The postoperative scores of the five dimensions of the QoR-40 are summarized in **Table 2**. At 24 h after surgery, the total QoR-40 score was higher in the MK group than in the ME group [197 (194.7–198) versus 195 (189–197), P = 0.01]. No significant differences were observed between groups in the dimensions of physical independence and psychological support. By contrast, the ME group had significantly lower scores in physical comfort, emotional state, and pain than the MK group (P < 0.05). The overall Cronbach's alpha for the total QoR-40 score for both groups was 0.93.

Secondary outcomes

Pain levels, postoperative complications, nausea and vomiting, and the accumulated dose of morphine in the PACU and ward are shown in **Table 3**. The percentage of patients reporting an NRS > 3 at rest and during movement did not differ between groups at PACU admission and at 1, 6, and 12 h after admission to the ward. No episodes of respiratory depression or cardiac arrhythmia occurred in the PACU. In addition, no significant

Table 1. Baseline characteristics, anesthetic management, and postoperative residual sedation in the PACU

	Overall		Groups				P value
			Methadone (ME)		Methadone and ketamine (MK)		
Age, mean (SD), yr	38.9	(9.6)	38.6	(10.6)	39.2	(8.5)	0.75
BMI, mean (SD), kg/m²	27.1	(6.8)	27.4	(5.7)	27.1	(6.1)	0.45
ASA-PS classification							
I, n (%)	36	(46)	24	(58)	12	(33)	0.05
II, n (%)	41	(53)	17	(41)	24	(67)	
Diabetes, n (%)	2	(3)	1	(2)	1	(3)	1
Arterial hypertension, n (%)	11	(14.)	4	(10)	7	(19)	0.38
History of nausea and vomiting, n (%)	1	(1)	0	(0)	1	(3)	0.95
Smoking, n (%)	8	(10)	6	(15)	2	(6)	0.35
APFEL score							
1, n (%)	10.4	(8)	4	(10)	4	(11)	
2, n (%)	48	(37)	19	(46)	18	(50)	0.9
3, n (%)	41.6	(32)	18	(44)	14	(39)	
Extubation time, mean ± SD, min	8.8	(4.1)	8.1	(4.1)	9.6	(4.1)	0.11
Duration of surgery, mean ± SD, min	55	(45–65)	55	(43–65)	60	(51.5–63.5)	0.31
Cumulative dose of remifentanil, median (IQR), µcg*	545	(409.6–849.6)	520	(409.6–698.4)	687.2	(408.5–954.6)	0.21
Cumulative dose of propofol, mean (SD), mg*	710.2	(274.4)	678.2	(283.5)	746.6	(262.9)	0.28
Wilson sedation score							
1, n (%)	35	(45)	22	(54)	13	(36)	0.19
2, n (%)	42	(54)	19	(46)	23	(64)	

Abbreviations: BMI: body mass index; ASA-PS classification: The American Society of Anesthesiologists Physical Status; yr: years. * Total cumulative dose of anesthetics administered during the intraoperative period.

differences were found in the incidence of PONV between the two groups. The total dose of morphine administered in the PACU (in milligrams) did not significantly differ between the groups [5.4 (2.6) vs. 6.8 (3.2), P = 0.48]. Similarly, in the ward, no significant differences were observed in the dose of morphine equivalents administered [ME 4.0 (5.6) versus MK 4.8 (5.7), P = 0.28] or in the incidence of PONV. Within the first 24 h postoperatively, the incidence of moderate-to-severe pain in the ward showed no difference between the ME and MK groups. The total morphine dose administered during this period also did not differ between groups (P = 0.28).

Univariate analysis revealed no factors independently associated with moderate-to-severe postoperative pain in the PACU. In the multivariate analysis, adjusted using PS methods, the combined administration of methadone and ketamine was not significantly associated with the occurrence of moderate-to-severe pain compared with methadone alone (OR = 0.79; 95% CI; 0.29–2.12). However, longer surgical duration was slightly associated with a higher incidence of postoperative pain (OR = 1.02; 95% CI; 1.004–1.05) (**Table 4**).

Table 2. Primary outcome: Subcomponents of the Quality of Recovery-40 score 24 h after surgery in patients receiving either intraoperative methadone (ME) or methadone–ketamine combination (MK)

Subcomponents of the Quality of Recovery-40 score	Groups				P value
	ME		MK		
Physical comfort (60)	58	(57–59)	59	(57–60)	0.02
Emotion state (45)	45	(42–45)	45	(44–45)	0.04
Physical independence (25)	24	(22–24)	24	(22.75–24)	0.33
Psychological support (35)	35	(34–35)	35	(35–35)	0.13
Pain (35)	34	(33–34)	34	(34–35)	0.01
Total score (200)	195	(189–197)	197	(194.7–198)	0.01

The maximum score for each dimension is reported in parentheses; values are medians (25th and 75th percentiles).

Table 4. Factors associated with the incidence of pain (NRS > 3) at the post anesthesia care unit—summary of propensity-weighted analysis

	Propensity-weighted analysis		
	Estimate (OR)	95% CI	P value
Groups			
Methadone	1		0.64
Methadone and ketamine	0.79	0.29 – 2.12	
Duration of surgery, min	1.02	1.004 – 1.05	0.03
Cumulative dose of propofol, mg	1	0.99 – 1.001	0.45
Smoking	7.5	1.1 – 149.4	0.07

These estimates correspond to the prevalence ratio (OR). CI = confidence interval; propensity score was estimated using a logistic regression model.

Table 3. Secondary outcomes: Pain at rest, pain with movement, cardiac arrhythmias, respiratory depression, nausea and vomiting, and total dose of morphine

	Overall		Groups				P value
			Methadone		Methadone and ketamine		
Level of pain at rest (NRS > 3)							
On PACU admission, n (%)	43	(56)	24	(58)	19	(53)	0.78
1 h after admission to the ward, n (%)	15	(19)	7	(17)	8	(22)	0.78
6 h after admission to the ward, n (%)	5	(6)	3	(7)	2	(6)	1
12 h after admission to the ward, n (%)	4	(5)	2	(5)	2	(6)	1
Level of pain with movement (NRS > 3)							
1 h after admission to the ward, n (%)	3	(4)	2	(5)	1	(3)	1
6 h after admission to the ward, n (%)	5	(6)	3	(7)	2	(6)	1
12 h after admission to the ward, n (%)	4	(5)	2	(5)	2	(6)	1
PACU							
Cardiac arrhythmias, n (%)	0	(0)	0	()	0	(0)	1
Respiratory depression, n (%)	0	(0)	0	()	0	(0)	1
Nausea and vomiting, n (%)	5	(6)	3	(7)	2	(6)	0.98
Total dose of morphine, mean (SD)	5.9	(2.2)	5.4	(2.6)	6.8	(3.2)	0.48
Ward							
Total dose of morphine equivalents, mean (SD), mg	4.3	(5.2)	4.0	(5.6)	4.8	(5.7)	0.28
Nausea and vomiting, n (%)	11	(14)	6	(14)	5	(14)	0.95

Abbreviation: NRS: numeric rating scale.

DISCUSSION

This prospective cohort study aimed to evaluate whether adding ketamine to a methadone-based regimen would influence QoR-40 scores in young patients undergoing laparoscopic cholecystectomy. The results demonstrated a slight improvement in QoR-40 scores 24 h post-surgery in patients who received both methadone and ketamine compared with those who received methadone alone. However, incidences of moderate to severe pain and PONV showed no differences between groups, as was opioid consumption. These findings suggest that administering low-dose ketamine at anesthesia induction did not substantially impact pain management or postoperative complications in this cohort. No episodes of cardiac arrhythmia or respiratory depression were reported.

Postoperative recovery is a key outcome for anesthesiologists, as it directly influences patient satisfaction.[16] The QoR-40, a validated 40-item questionnaire, is regarded as one of the most effective tools for assessing the complex and multidimensional aspects of recovery following general anesthesia and surgery.[16] Nonetheless, interpreting QoR-40 scores requires caution. Both groups in this study presented high QoR-40 scores, indicating good recovery[17] and an acceptable symptom burden.[18] Although statistically significant differences were observed in individual domains such as pain, comfort, and emotional well-being, the overall difference in QoR-40 scores between groups did not reach the 6.3-point threshold, which is the proposed cutoff for clinical significance.[18] While QoR-40 scores are applicable to assess postoperative patient recovery following any type of procedure, lower scores might be expected in patients undergoing more complex and painful surgeries. In such cases, an intervention such as the one we proposed could potentially offer greater benefit. Conversely, young and otherwise healthy patients undergoing laparoscopic cholecystectomy report higher QoR-40 scores, which may reduce the observable effect size of additional interventions. Within this context, the addition of ketamine to a methadone-based regimen did not result in a clinically meaningful improvement in postoperative recovery.

Multiple factors may contribute to the lack of differences observed not only in QoR-40 scores, but also in postoperative pain scores and opioid consumption between the groups. A key consideration is the timing of administration, whether ketamine was given before or after skin incision, which may play a critical role.[19,20] Ketamine is a "use-dependent" drug: it blocks NMDA channels only after they have been activated by intense or repeated noxious stimuli.[21] In other words, the more severe the pain, the more efficient ketamine tends to be. Therefore, the additive analgesic effect of ketamine would be expected to be more pronounced in surgeries associated with higher pain potential. A retrospective cohort study[22] involving 115,775 patients from 105 different institutions examined postoperative pain in 179 procedures. Despite the complex nature of laparoscopic cholecystectomy, the median NRS was 5, ranking it 94th in plain intensity. Conversely, three of the six surgeries with the highest pain scores were major spinal surgeries. These variations in pain stimuli among different surgical types may explain why low-dose ketamine has demonstrated efficacy as an adjuvant in highly painful orthopedic procedures[23] but not in laparoscopic cholecystectomy, as observed in our findings.

Another key component that may affect ketamine's effectiveness is the administration regimen.[24] Continuous intravenous infusion throughout surgery and into the recovery phase is generally more effective for preventing post-surgical pain; however, this approach seems impractical for short-duration surgeries.[25] In an animal model, subanesthetic doses of ketamine greatly alleviated provoked pain by preventing hyperalgesia and the development of opioid tolerance.[26] Nonetheless, in patients undergoing laparoscopic cholecystectomy, different ketamine doses administered before skin incision failed to produce differences in either QoR-40 scores or postoperative pain scores compared with placebo.[19] Similarly, the PODCAST trial,[27] where patients were given placebo, 0.5 mg/kg or 1 mg/kg of ketamine, did not show a reduction in postoperative opioid consumption or pain scores. The lack of benefit from a single dose may be attributed to ketamine's rapid decline in plasma concentration.[24] For instance, following a bolus dose, plasma concentrations fall below 150 ng/ml within 10 min for a 0.5 mg/kg dose and within < 25 min for a 1 mg/kg dose.[21] Hence, the dose and method of administration (i.e., bolus instead of a continuous infusion) in our study might have been insufficient to reach steady plasma concentrations necessary to reduce moderate to intense postoperative pain in patients receiving ketamine.

All the patients received intravenous methadone, ketoprofen, and metamizole. Multimodal analgesia has been associated with reduced opioid consumption and improved postoperative pain scores, but not with improved quality of recovery.[28] Other adjuvants, such as intravenous acetaminophen, which has been demonstrated to be more effective than ketamine in reducing postoperative pain,[29] are not available in Brazil and therefore was not administered. Concurrently, no increase in adverse effects commonly associated with ketamine, such as nausea and vomiting, was observed. Although higher doses of ketamine might offer more robust pre-emptive analgesia, such doses could also increase the occurrence of emergence hallucinations, nightmares, and other side effects that may limit its use, particularly in short-duration surgeries.[23]

Although methadone use in the operating room has increased, the literature presents conflicting findings regarding its perioperative administration and its association with ketamine. Compared with shorter-acting opioids, one study found no association between methadone and lower pain scores or improved QoR-40 scores.[30] By contrast, Kharasch et al.[9] showed that a single dose of methadone

reduced opioid requirements in next-day discharge patients. Administration of methadone in that context may have decreased the effect size between the groups. The potential benefits of methadone and ketamine remain unclear. An experimental rat model of neuropathy suggested a supra-additive effect between ketamine and methadone,[31] a phenomenon observed in patients undergoing spine surgery,[32] where the combination led to a greater-than-expected reduction in opioid use and postoperative pain scores.[33]

Despite the potential analgesic benefits of the MK combination in short-duration surgeries such as cholecystectomy and the use of low doses of ketamine after induction, our study did not find synergistic analgesic effects. A recent cohort study in cardiac surgery reported that even with higher doses of both methadone and ketamine (approximately twice those used in our study), the observed benefit was limited to delaying the time to first rescue opioid administration, without a lasting effect beyond the first postoperative day.[34] These findings suggest that the analgesic synergy between ketamine and methadone may be highly context-dependent and influenced by surgical invasiveness, nociceptive load, duration of noxious stimuli, and the timing and method of ketamine delivery.

This study has some limitations. First, the absence of randomization and the allocation of patients at the discretion of the attending anesthesiologist introduce a significant risk of selection bias. However, **Table 1** shows that the groups were similar at baseline. Second, although laparoscopic cholecystectomy presents a risk for long-term pain management, with chronic pain occurring in up to 10–40% of cases,[35,36] and perioperative methadone has been associated with lower pain scores at 3 months after surgery,[37] our follow-up was specifically designed for the early postoperative period and did not evaluate long-term effects. Third, the use of single-dose ketamine at the beginning of surgery may have been insufficient to reduce the incidence of moderate-to-severe pain upon PACU admission. Finally, neither methadone nor the MK combination provided sufficient analgesia in the PACU for most patients, suggesting a need for further studies comparing different doses of intravenous methadone alone[9] or in combination with ketamine. At 1 and 6 h after ward admission, 81% and 93% of patients, respectively, reported NRS scores < 3.

We conclude that small doses of ketamine, when administered as part of a multimodal analgesic regimen, do not improve the quality of recovery, as assessed using the QoR-40 questionnaire, following methadone-based anesthesia for laparoscopic cholecystectomy. Although the MK combination showed a slight increase in the quality of recovery scores 24 h postoperatively, the observed difference between the groups was not clinically significant. Further research is warranted to evaluate the impact of different pain management approaches, considering both short- and long-term effects of MK combination on postoperative recovery.

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Static cold package for transporting organs for transplants: a validation method and pilot test

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ABSTRACT

BACKGROUND: Logistic and temperature challenges contribute to organ loss during transplantation. Ensuring the safety of static cold packaging for organ transport is essential to improve patient access to transplants. This study aimed to verify a method for validating the packaging used to transport organs for transplantation.

DESIGN AND SETTING: Validation study and pilot test using experimental surgery on porcine organs.

METHODS: Data collection considered the variables related to organ integrity before and after transportation, including temperature (measured thrice with three instruments per organ), macroscopic evaluation (based on photographic and observational assessments), histology (structural analysis of the collected samples), and packaging contamination (triple-swab sampling for microorganism growth). Data analysis was performed using descriptive statistics, visual assessment, histological processing, and microbiological evaluation.

RESULTS: By the end of transportation, all the organs reached the ideal temperature range for transplantation. The similarity in swine weight and size enabled macroscopic comparisons. Histological analysis revealed no significant injuries or morphological changes. Regarding packaging, environmental microorganisms predominate, with sustainable post-transport differences.

CONCLUSION: The method developed to validate the package used for transporting organs for transplantation was successfully verified. Furthermore, this method addresses the existing gap in the process of documenting a robust validation method for packaging intended for organ transportation.

INTRODUCTION

Organ donation and transplantation in Brazil are among the world's most advanced, with approximately 25,000 transplants performed by 2023. However, nearly 60,000 people remained on waiting lists.[1] The leading cause of organ loss was family refusal to donate (42%), followed by clinical contraindications (17%) and logistical issues (15%).[1] These challenges highlight the need for strategies to improve donation rates and optimize organ transportation.[2–3]

Brazil's vast territory and extreme temperature variations complicate its transportation logistics. Organs must be kept between 2°C and 8°C,[4–7] while some regions exceed 45°C.[8] A 2023 report noted a 3°C temperature increase, which further affects safe transport.[9] Given these constraints, evaluating the safety and efficacy of organ transport packaging is crucial.

A literature search revealed that no comprehensive method for validating static cold packages to ensure organ integrity. To address this gap, we developed a robust, reliable, and replicable validation method for organ transport packaging.

This study aimed to verify a method for validating the packaging used for transporting organs for transplantation.

METHODS

This was a validation study and pilot test for experimental surgery using porcine organs. This experimental study assessed the variables before and after the transportation of porcine organs (Landrace swine). Four categories were analyzed to evaluate organ integrity and packaging: temperature, macroscopic appearance, histology, and microbiological growth. This research report refers to the development of two pilot tests of the method conducted in November (P1) and December (P2) of 2022 and describes all modifications in the method until the final protocol based on the results.

Packaging regulations

In accordance with Brazilian legislation, each organ must be packaged in three sterile plastic bags. The first bag contains the organ and preservation solution, the second bag encloses the first bag and the cold physiological solution, and the third bag contains both the previous bags. All these packages are placed in a domestic plastic cooler with ice for transportation (static cold).[4]

Animals

Human research is not feasible due to ethical constraints, the need for thorough organ analysis, and the requirement for a controlled environment, which is impractical in clinical transplantation. Despite its limitations, hypothermic static cold storage with ice remains the preferred global method for organ transport, yielding positive outcomes despite the gaps in data on organ integrity.

To address these challenges, we used porcine organs from Landrace swine, given their anatomical similarity to human organs and their role in xenotransplantation trials.[10] This pilot test involved two female Landrace pigs (≈25 kg) from a farm affiliated with the Universidade Federal de São Paulo (Unifesp). The animals received proper care before transportation and were housed in a ventilated wooden transport box under veterinary supervision upon arrival.

Anesthesia, monitoring, and surgical procedure

Animals received pre-anesthetic medication with ketamine (15 mg/kg) and midazolam maleate (0.2 mg/kg) intramuscularly, followed by intravenous propofol (7 mg/kg) after 3 minutes. They were then intubated with a 7.0 orotracheal tube with a cuff and maintained under inhaled anesthesia (1.5–2% isoflurane) for 4 hours. Analgesia was provided with fentanyl citrate (2.5 mg/kg) at surgery initiation and every 2 hours, with propofol, as needed. Electrodes and oximeters were used for continuous monitoring.

After thoracoabdominal incision and aortic clamping, the animals were declared dead and cold ischemia was initiated. The heart, liver, pancreas, and kidneys were retrieved under the supervision of physicians and veterinarians to ensure minimal suffering. The animals remained on the surgical table throughout the procedure, and at the end of the procedure, all organs were reintroduced into the cavity. The animals were then stored in a freezer until collection by São Paulo city's specialized service. The experiment was conducted at the Laboratory of Operative Technique and Experimental Surgery, Unifesp, under the supervision of two physicians, a veterinarian, and a veterinary assistant.

Data collection

Data were collected at various time points throughout the experiment. After organ retrieval, the first collection of macroscopic aspects was performed. Each organ was then placed on a back table where other researchers, nurses, and undergraduate students proceeded with perfusion and continued with data collection and packaging. Once packaging was complete, the organs were transported by car through a simulated circuit. After their return, all data collection steps were repeated (**Figure 1**).

Temperature

Data related to the "temperature" variable was collected at different stages: H0: as soon as the organ was retrieved from the animal cavity; H1: after perfusion on the back table, before packaging; H2: after transportation.

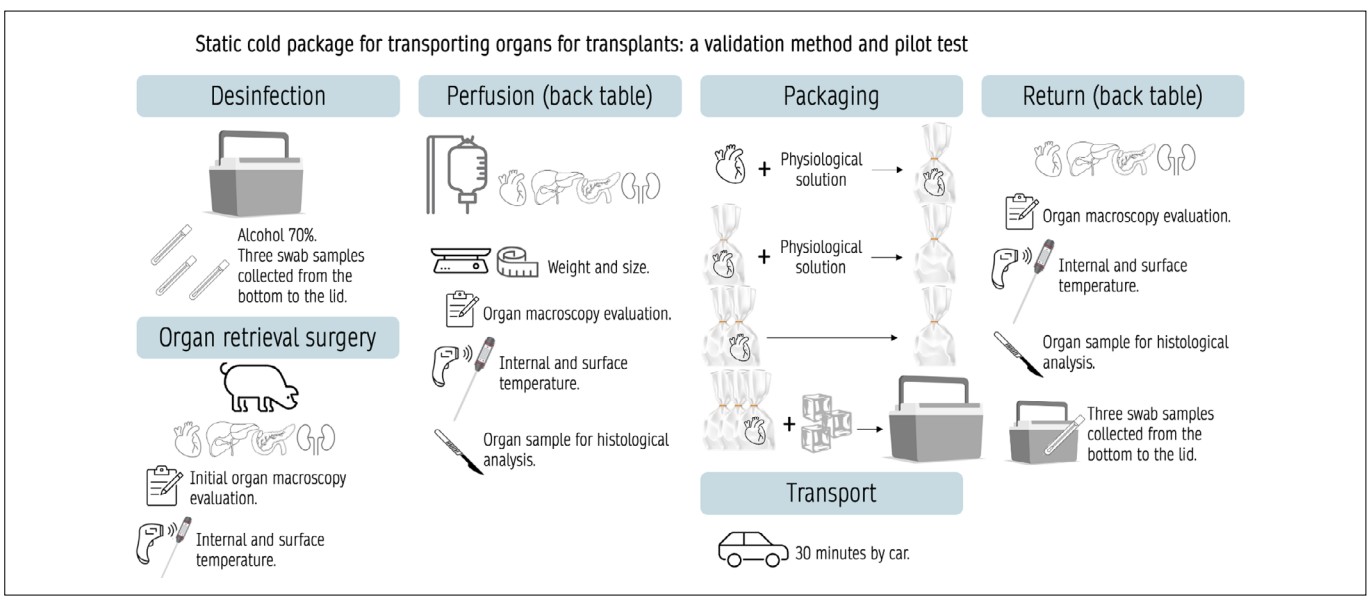


Figure 1. Data collection method.

Temperature measurements of the pancreas were not performed at time point H1 because, after the initial data collection, the pancreas did not undergo perfusion and was immediately placed in the packaging.

In the first surgery (P1), only one thermometer was used to measure the internal temperature. However, in the second surgery (P2), we employed an additional thermometer to obtain the average internal temperature for each organ and an infrared thermometer to measure the surface temperature. This paper presents the values from the internal thermometers for the first surgery and the averages from the second surgery derived from the internal thermometers, in addition to the superficial readings.

Organ macroscopy

Organ macroscopic data were recorded using study-specific forms based on macroscopic evaluation studies.[11–14] Each organ had a unique form, which was completed at retrieval, after perfusion, and post-transport by physicians and nurses. Evaluations included visual inspection with responses in "yes/no" format or on a 1–10 scale.

Weight was measured using a scale and size was measured with a ruler. From the second experiment onward, each organ was photographed immediately after perfusion and post-transport to document the changes.

Histology

The tissue samples were collected after perfusion and post-transport unpacking. Each sample was fixed in 4% paraformaldehyde (phosphate buffer) for 24 hours, then processed through dehydration in graded alcohol, diaphanization with xylene, and paraffin impregnation at 60°C.

The samples were then embedded for histological cross-sectional analysis. Using a Minot-type microtome, 4 µm sections were cut with 50 µm spacing and mounted on slides for hematoxylin and eosin (H&E) staining (histomorphometric analysis).

Packaging

Before surgery, the transport packaging was disinfected by applying 70% alcohol to the interior, followed by wiping the internal walls and lid with disposable paper in unilateral motion. This process was repeated twice and applied to the external walls.

Three swab samples were collected from the bottom to the lid, following microbiological sampling standards (sample, test, and control). After transportation, the researchers removed the ice and repeated the swab collection. Initially, samples were collected from each internal wall. However, after the first analysis, the protocol was standardized to three swabs from the entire packaging.

DATA ANALYSIS

Temperature

Temperature data were subjected to quantitative analysis using descriptive statistics, specifically calculating the average temperature.

Macroscopy

Pre-transport assessments included tissue/parenchymal quality, overall organ quality, perfusate appearance after 5 min, and perfusion quality (parenchymal discoloration). Post-transport evaluations considered tissue/parenchyma quality, overall organ quality, and perfusion quality.

Overall organ quality was rated on a scale of 1–10, with 10 being the highest. On average, the stability indicated no change, an increase suggested improvement, and a decrease indicated deterioration. Abnormalities including lesions were documented before and after transport for comparison. Parenchymal coloration was assessed for homogeneity (ideal) or heterogeneity (potential perfusion issues) in both phases.

Histology

Histological samples were analyzed using H&E staining, enabling the differentiation of basophilic (stained by hematoxylin) and acidophilic or eosinophilic (stained by eosin) structures. This technique allows the observation of images via light microscopy using an optical microscope. In H&E staining, cell nuclei appear as blue-purple shades owing to their basophilic nature, as the cell nucleus contains deoxyribonucleic acid (DNA), which attracts hematoxylin, a basic dye. Conversely, the cell cytoplasm, with its more basic character, was stained pinkish-red by eosin staining. Some regions of the cytoplasm appear bluish because of the presence of ribonucleic acid (RNA), which is stained with hematoxylin. Organ structures were carefully observed and analyzed to identify morphological alterations.

Microbiologic samples

The laboratory provided a report on microbial growth within the packaging after processing the samples using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Data analysis relied primarily on the measurement of colony-forming units (CFU).

Ethics statement

This study was conducted in strict accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals of the National Health Authority. The study protocol was approved by the Committee on the Ethics of Animal Experiments of the Universidade Federal de São Paulo (Unifesp; Protocol No. 4197081221). All efforts were made to minimize animal suffering.

RESULTS

Temperature

Because the surgery replicated human organ procurement in swine, temperature data were collected at critical moments when fluctuations could occur. The duration for which each organ remained in the packaging from the initial (H1) to the final (H2) temperature measurements is detailed in **Table 1**.

Figure 2 illustrates all the temperature measurements from the two experiments. The temperature patterns obtained from the internal thermometers of each organ during the first surgery (P1) are shown in **Figure 2a**. The patterns obtained from the average of the internal thermometers used in the second surgery (P2) compared with the surface temperature measurements are presented in **Figure 2b** for each organ. **Figure 3** shows the thermometers used and the temperature measurement process.

Table 1. Duration of each organ storage in minutes within the packaging (P1 + P2)

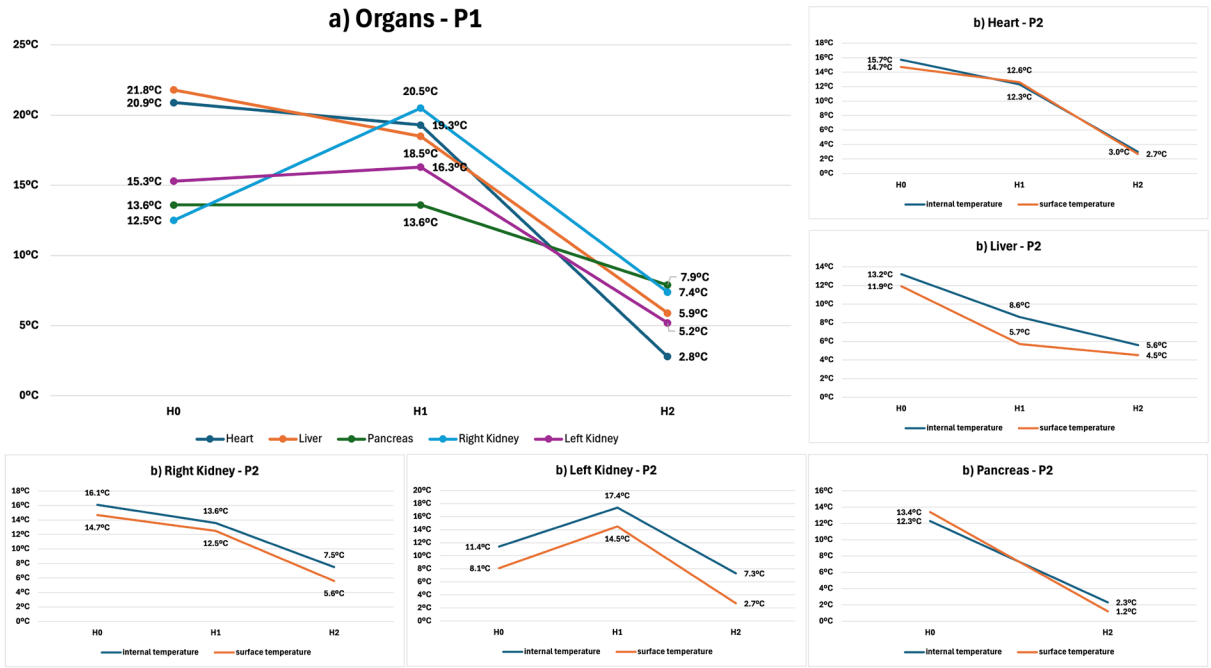
Organs	P1 (min)	P2 (min)	Average (min)
Heart	163	110	131,5
Liver	89	114	101,5
Pancreas	86	115	100,5
Right kidney	75	99	87
Left kidney	71	96	83,5
Total			**100,8**

Organ macroscopy

The average weight in the two experiments for each organ was 158,5 g for the hearts, 607 g livers, 64 g pancreas, and 69,2 g for the kidneys. **Table 2** presents the qualitative macroscopic evaluation

a) Measurement methods. b) Thermometer used to assess the internal temperature: after the insertion, researchers keep the thermometer in the parenchyma until the temperature mark stabilizes. c) Infrared thermometer: researchers keep the thermometer at a distance of 2 cm for 2–3 s according to the manufacturer's guidance provided in the product manual.

Figure 3. Temperature measurement process and thermometers.



a) Temperature patterns obtained from the internal thermometers of each organ during the first surgery (P1). b) Patterns obtained from the average of the internal thermometers used in the second surgery (P2) compared with the surface temperature measurements.

Figure 2. Temperature patterns of each organ in the surgeries (P1 and P2).

data for each organ (heart, liver, pancreas, right kidney, and left kidney) in both pilot experiments (P1 + P2), as assessed using the forms developed.

Comparative photographs of the organs after perfusion before and after transportation in P2 are shown in **Figure 4**.

Histology

The morphological structures of the organs were examined. Each organ was analyzed separately (**Figure 5**).

In the heart (**Figure 5a**), the myocardial morphology of both ventricles was similar across the study groups. The myocardium consists of small elongated cardiac fibers with one or two central nuclei that display transverse striations surrounded by small capillaries. The endocardium was lined by simple squamous epithelium with a small amount of connective tissue beneath it, whereas the epicardium showed loose connective tissue with some adipose cells.

The hepatic parenchyma exhibits integrity in its histological structure and is composed of a high concentration of hepatocytes arranged in cords that converge towards the central lobular vein, forming approximately hexagonal geometric figures. Between the cords of hepatocytes, hepatic sinusoids were observed, lined by endothelial cells with nuclei of various shapes,

Table 2. Macroscopic evaluation data in each pilot test (P1 + P2)

Heart	**Pre transport**		**Post transport**		**Evaluation**	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**
Abnormality of the organ	None	None	None	None	No change	No change
Tissue quality	10	10	10	10	No change	No change
Overall quality	10	10	10	10	No change	No change
Perfusate appearance on the bench after 5 minutes	8	7	–	–	Improved	Improved
Perfusion quality (degree of parenchymal discoloration)	8	6	10	10		
Homogeneous coloration of the parenchyma after perfusion	Yes	No	Yes	Yes	No change	Improved
Liver	**Pre transport**		**Post transport**		**Evaluation**	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**
Abnormality of the organ	None	None	None	None	No change	No change
Parenchyma quality	7	10	5	9	Worsened	Worsened
Overall quality	7	10	6	9	Worsened	Worsened
Perfusate appearance on the bench after 5 minutes	6	8	–	–	Worsened	Improved
Perfusion quality (degree of parenchymal discoloration)	7	9	6	10		
Homogeneous coloration of the parenchyma after perfusion	No	Yes	No	Yes	Improved	Improved
Pancreas	**Pre transport**		**Post transport**		**Evaluation**	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**
Color	Pink-gray	Yellow	Pink	Milky white	Improved	Improved
Tissue injury	None	None	None	None	No change	No change
Calcification	None	None	None	None	No change	No change
Stiffness	None	None	None	None	No change	No change
Hematoma	No	No	No	No	No change	No change
Edema	No	No	No	No	No change	No change
Right kidney	**Pre transport**		**Post transport**		**Evaluation**	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**
Abnormality of the organ	None	None	None	None	No change	No change
Parenchyma quality	10	10	8	10	Worsened	No change
Overall quality	10	10	9	10	Worsened	No change
Perfusate appearance on the bench after 5 minutes	9	10	–	–	Worsened	Improved
Perfusion quality (degree of parenchymal discoloration)	10	9	9	10		
Homogeneous coloration of the parenchyma after perfusion	Yes	Yes	No	Yes	Worsened	No change
Left kidney	**Pre transport**		**Post transport**		**Evaluation**	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**
Abnormality of the organ	None	None	None	None	No change	No change
Parenchyma quality	10	10	8	10	Worsened	No change
Overall quality	10	10	9	10	Worsened	No change
Perfusate appearance on the bench after 5 minutes	8	9	–	–	Worsened	No change
Perfusion quality (degree of parenchymal discoloration)	9	8	9	10	No change	Improved
Homogeneous coloration of the parenchyma after perfusion	No	Yes	No	Yes	No change	No change

Source: Dabare et al.;[13] Dare et al.;[12] Kulu et al.;[14] Tierie et al.[11]

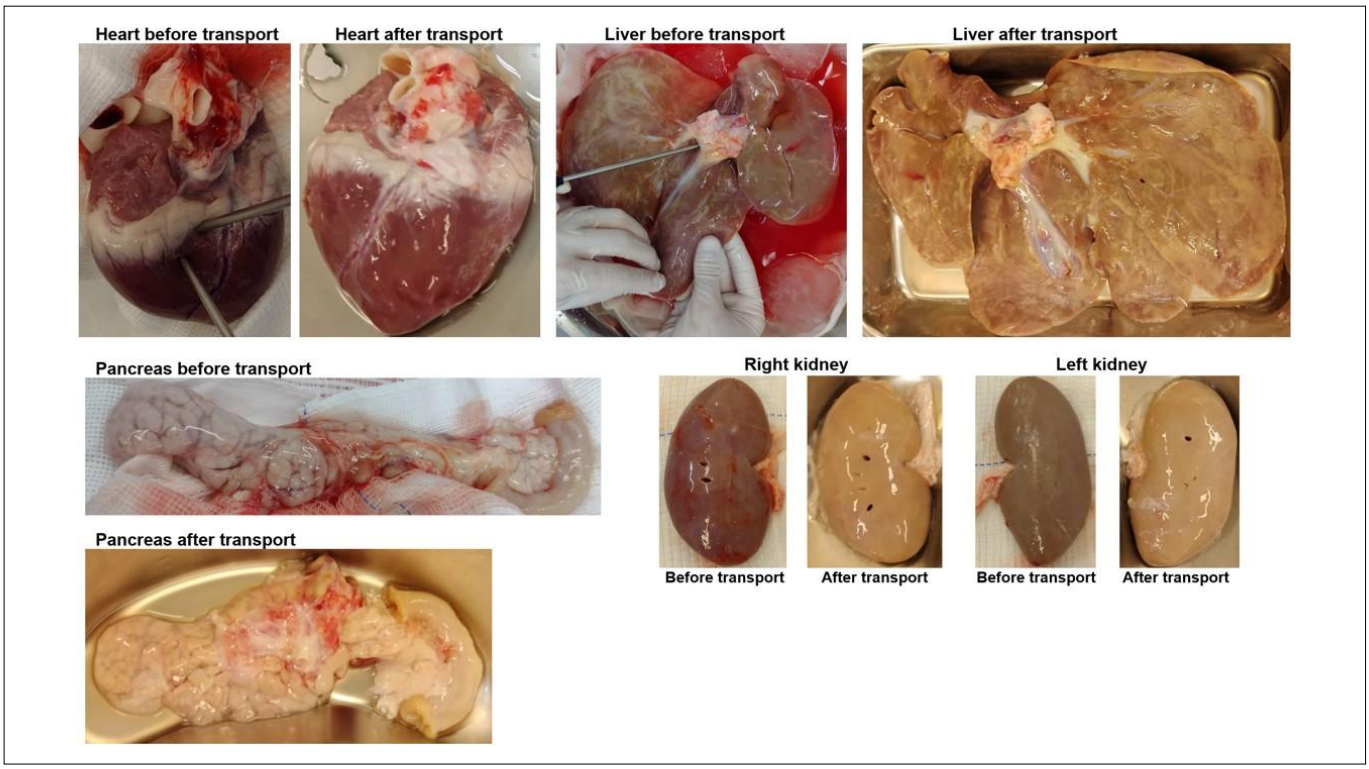


Figure 4. Photographs of organs after perfusion, before and after transportation, in P2.

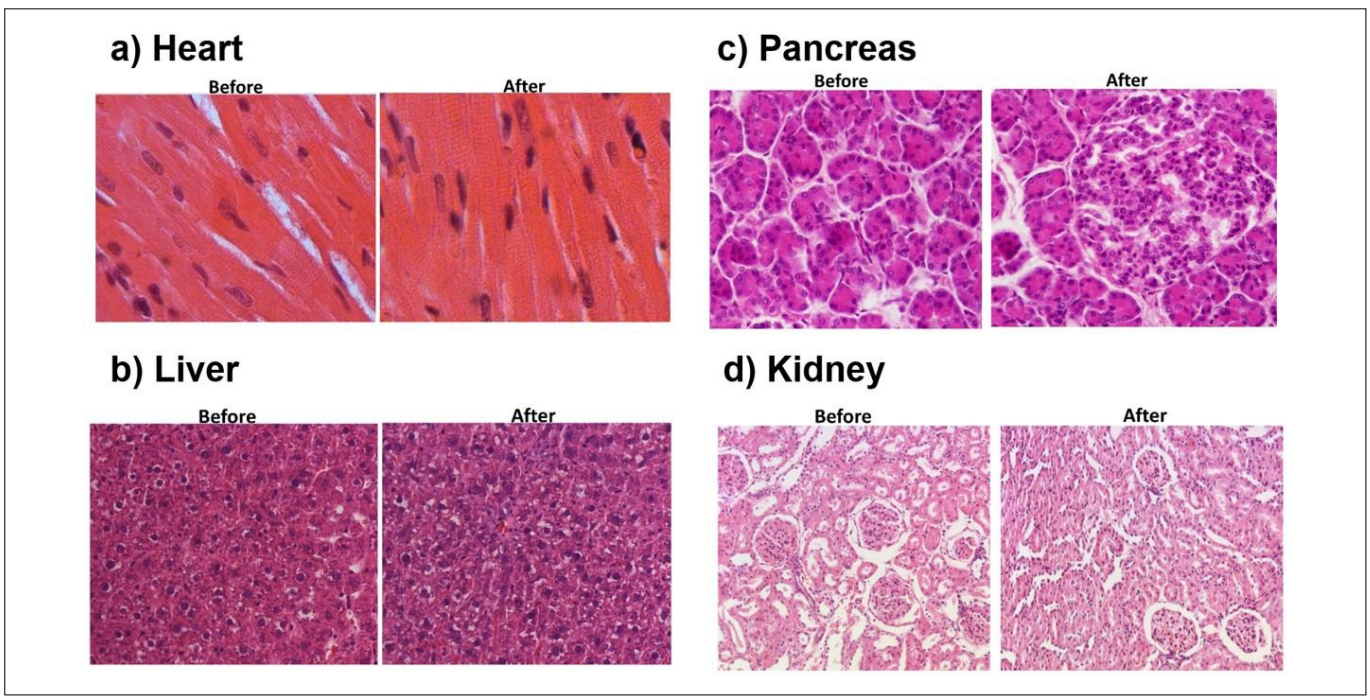


Figure 5. Photomicrograph showing sections of pig hearts, livers, pancreas, and kidneys before and after transportation. 20× HE.

ranging from elongated to spherical, and usually heterochromatic. Hepatocytes are voluminous polyhedral cells with one or two centrally positioned spherical nuclei rich in chromatin and well-defined nucleoli.

The cytoplasm was not homogeneous and displayed areas with basophilic and eosinophilic characteristics. Red blood cells were identified within the sinusoidal capillaries. Within the portal space, at least one branch of the portal vein, hepatic artery, or bile duct

can be identified. Connective tissue cells and rare collagen fibers surrounded these structures (**Figure 5b**).

The pancreas (**Figure 5c**) is a mixed gland with both exocrine and endocrine components. The exocrine portion is formed by numerous acini, among which we identified endocrine portions called the pancreatic or Langerhans islets. The acini are globular structures composed of prismatic cells containing spherical nuclei located in the middle of the cells or slightly shifted towards the basal region. The pancreatic islets are formed from cords containing cells with spherical nuclei.

The kidneys (**Figure 5d**) showed preserved renal parenchyma, especially in the cortical region, with intact glomeruli, and proximal and distal convoluted tubules. The renal corpuscles, including the intact Bowman's capsule with a visible urinary space and glomeruli composed of endothelial-lined capillaries, podocytes, and mesangial cells, showed no visible histological alterations. Most of the renal cortex comprises glomeruli and tubules.

Microbiological growth

As described in the Methods section, data collection was standardized after the second surgery. In this paper, the results obtained following the data collection pattern at P2 are presented. **Table 3** shows the microorganisms found in the packages, comparing pre- and post-transport results.

DISCUSSION

Temperature

Regarding the temperature range, it's important to note that while the typical range cited in literature falls between 2°C and 8°C, there are varying ranges reported. Factors such as the preservation solution and the time between organ retrieval and packaging may contribute to this variation. However, studies examining organ integrity, transplant outcomes, and organ transportation have shown a range of temperatures from 0°C to 10°C.[5–7,15–20] In this study, we have chosen to use the most common temperature range as our reference point for analyzing the impact of temperature on organ integrity.

During the first surgery, the organs tended to warm after perfusion. To improve the outcomes, we introduced additional variables in the second experiment (P2) to better control the data collection. These included maintaining a stable room temperature (18°C), using three liters of physiological solution within the animals' cavities, tightly regulating temperature with a freezer, and employing smaller pieces of crushed ice to lower cavity temperatures.

These experiments did not use preservation solutions but instead used physiological solutions. We emphasize the need for future research to incorporate appropriate preservation solutions to enhance the resemblance to human surgical conditions and improve overall organ quality.

Macroscopy

In the context of organ macroscopy, the similarity in the weight and size of the pigs in both experiments (P1 and P2) facilitated a comparative analysis. The qualitative interpretation of each organ using the data collection instrument revealed substantial differences, particularly in the case of the liver, before and after transportation. This discrepancy underscores the susceptibility of the liver to transportation-induced stress.[21] Other organs, despite being transported, demonstrate good color and perfusion characteristics. Although the evaluation was qualitative and subject to the researcher's judgment, it may serve as a valuable tool to be validated for application in human scenarios.

The amalgamation of data from instruments and photographs aids in understanding the rationale behind these classifications. Moreover, it provided visual evidence to facilitate data comparison. Photographs serve as a resource for future comparative studies by establishing defined patterns.[22]

Histology

The assessment of organ integrity, a combination of macroscopic analysis in two distinct ways, and histological analysis helped identify areas of damage during transportation. These analyses shed light on the changes that the organs undergo during transportation. Histological analysis indicated that the examined groups

Table 3. Standardized protocol for sample collection and results obtained in the second pilot experiment (P2), considering samples collected pre-transport (pre) and post-transport (post)

Transported organ	Sample 1		Sample 2		Sample 3	
	Pre	Post	Pre	Post	Pre	Post
Liver	None	None	None	None	None	None
Pancreas	None	None	None	None	None	None
Heart	*Micrococcus luteus* (90CFU) *Staphylococcus warneri* (20CFU) *Penicillium* spp.	None	*Micrococcus luteus* (40CFU) *Staphylococcus warneri* (10CFU)	None	*Micrococcus luteus* (20CFU) *Staphylococcus warneri* (5CFU)	None
Kidney	None	None	None	None	None	None

CFU: Colony Forming Unit

did not exhibit significant injury or morphological alterations. However, it has become evident that structural analysis alone may not reveal all the damage, prompting consideration of the inclusion of immunohistochemical analysis in future experiments.[23]

Microbiology

Specific discussions of microorganisms have provided interesting insights. *Micrococcus luteus* is commonly found in natural environments, such as soil and water resources, and is considered a normal inhabitant of human skin and oropharynx mucosa.[24–25] *Staphylococcus warneri* is part of the normal skin flora, particularly in the nares, head, legs, and arms.[26] *Corynebacterium imitans* is present within the human oral cavity and airways,[27] while *Penicillium* spp. is one of the most widespread fungi in various environments.[28]

The presence of environmental microorganisms in the pre-transport phase, despite following cleaning and disinfection protocols, suggests that microorganisms may proliferate even with proper protocol adherence. This highlights the need for maintaining high standards of disinfection. Although packaging is not sterile, some growth is expected; however, the use of ice effectively inhibits microorganism proliferation.

Comparison with prior work

Previous studies on organ transportation have predominantly focused on examining individual variables associated with organ integrity. Recent research efforts have been directed towards developing new products and packages aimed at enhancing the safety of organ transportation for transplantation. Conversely, previous studies have concentrated on the feasibility of transporting organs on ice.[29–34] To the best of our knowledge, this is the first study to specifically investigate organ transport for transplantation, encompassing the analysis of four variables (temperature, organ macroscopy, histology, and microbiological growth within the package) to ascertain the safety of such transportation method.

Limitations

The first limitation pertains to the duration for which each organ remains in the package. Although the analysis yielded satisfactory results, it required an average time of 100.8 minutes. Another limitation is the use of a limited number of animals. This limitation was implemented to minimize suffering; hence, we restricted the pilot test to two animals. Finally, this report presents a pilot test aimed at validating the method and underscores the necessity for replicability by incorporating diverse scenarios to substantiate the concept.

CONCLUSION

After interpreting the data and conducting experiments, this pilot test successfully verified the developed method for validating the packaging used to transport organs for transplantation.

Considering the variables under investigation, it is evident that temperature measurement methods are effective tools for monitoring the temperature patterns in the studied organs. The combination of macroscopic and histological analyses and photography offers comprehensive insights into the condition of the examined organs. The inclusion of standardized histological analyses provides valuable information about organ integrity, and standardized microbiological analyses effectively demonstrate microbiological growth.

The method developed in this study can serve as a valuable tool for validating packaging used in the safe transportation of organs for transplantation. This research is significant because it addresses the existing gap in documenting a robust validation method for packaging intended for organ transportation. By integrating complementary data and scrutinizing variables that directly affect organ integrity and package safety, this method effectively ensures product reliability.

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Is the atherogenic index of plasma a predictor for mortality in ischemic stroke patients?: a retrospective cross-sectional study

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Ischemic stroke.
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Mortality.

ABSTRACT

BACKGROUND: The atherogenic index of plasma (AIP), derived from the logarithmic transformation of the triglyceride to high-density lipoprotein cholesterol ratio, is frequently used to predict cardiovascular events.

OBJECTIVE: This study aimed to investigate the association between AIP and 1-month mortality in patients with acute ischemic stroke (AIS).

DESIGN AND SETTING: Retrospective study was conducted in Türkiye.

METHODS: In total, 530 AIS patients were enrolled in this study. Clinical, demographic, and laboratory characteristics were recorded within 24 hours of admission. One-month mortality outcomes were analyzed in relation to the AIP of the patients.

RESULTS: Of the 530 patients, 140 patients did not survive during the follow-up period. The mean AIP was 0.50 ± 0.33 in survivors and 0.11 ± 0.27 in the mortality group (P = 0.001). In the receiver operating characteristic analysis, the AIP value of 0.291 had a sensitivity of 74.4%, specificity of 76.4%, positive predictive value of 75.92%, and negative predictive value of 74.9% for mortality. The AIP value above 0.291 had an AUC (area under curve) of 0.829 (95% CI [confidence interval] 0.78–0.88, P = 0.0001). In Cox regression analysis, AIP values below 0.291 (HR 3.962; 95% CI 2.643–5.937) were identified as an independent predictor of mortality. Higher mortality rates were observed in patients with cryptogenic stroke and AIP below 0.291 after stratification by stroke TOAST (P = 0.003).

CONCLUSIONS: Lower AIP is an independent predictor of short-term mortality in AIS patients, surpassing the sensitivity of traditional lipid parameters. This study provides a valuable prognostic tool for clinicians, offering a non-invasive and cost-effective test for a condition associated with substantial mortality and morbidity.

INTRODUCTION

Stroke remains a significant health concern owing to its considerable impact on morbidity and mortality.[1] The early impairment of motor functions, progressive clinical deterioration, and potential for permanent disabilities pose substantial challenges for both patients and their families. Despite advancements in examination and treatment strategies, the prognosis in stroke cases has not shown satisfactory improvement.[2] Acute ischemic stroke (AIS), comprising 70% of all strokes, is particularly concerning.[3] Existing classifications for predicting poor prognosis lack clear evidence of superiority, necessitating the exploration of new parameters for assessing prognosis in ischemic stroke patients.[4,5] Numerous studies have attributed atherosclerosis as a primary cause of ischemic stroke. The evaluation of lipid parameters to predict the atherosclerotic process has become a widely used approach. The atherogenic index of plasma (AIP), calculated as the logarithmic transformation of the triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio (log [TG/HDL-C]), is a key parameter for the assessment of dyslipidemia and atherosclerosis. Previous studies have shown that low TG levels are associated with adverse post-stroke conditions. This is generally explained by collateral circulatory dysfunction and low TG levels not responding adequately to increased metabolic stress. Many studies have focused on the positive association between AIP and conditions such as diabetes mellitus, coronary artery disease, and vascular diseases; however, studies on its association with AIS are limited.

OBJECTIVE

This study aimed to establish the AIP as a predictor of 1-month mortality in patients with ischemic stroke.

METHODS

Study population

Patients with AIS over the age of 18 years were included in this study. A retrospective analysis was conducted by reviewing the files of patients with AIS between 2012 and 2022. Patients admitted to the hospital with AIS were considered for inclusion, whereas those with strokes occurring after 24 hours were excluded. The exclusion criteria included individuals with hematological diseases, those using immunosuppressive drugs, individuals with a history of malignancy, those with an active infection in the last month, patients with a history of stroke in the last 6 months, those with involvement outside the cortex, and individuals with active diseases directly influencing mortality. The study criteria are shown in **Figure 1**.

Study protocol

A total of 530 patients were included in the study, including 390 surviving and 140 non-surviving patients. The patients were systematically classified based on their demographic, clinical, and laboratory characteristics. Furthermore, the AIP, Modified Rankin classification, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification were assessed. Stroke was confirmed using computed tomography and magnetic resonance imaging. Mortality status was verified within 1 month of admission by cross-referencing with the national health screening database (E-Nabız) system. The average acute period of stroke is 15 days. During the chronic period, liquefaction necrosis develops in the brain, which repairs itself and stabilizes. Considering that more than one independent factor will have an impact on mortality in the period after 1 month, 1 month was chosen as the follow-up period. The causes of death of deceased patients were validated through communication with their respective physicians.

Patient information, including age, diabetes mellitus, hypertension, history of coronary artery disease, and use of anti-aggregant and anti-coagulant medications, was obtained using an inquiry questionnaire. Comprehensive assessments, incorporating hemogram and biochemical tests, were performed, with specific attention paid to lipid levels. The AIP was calculated based on lipid levels using the formula log (TG/HDL-C).

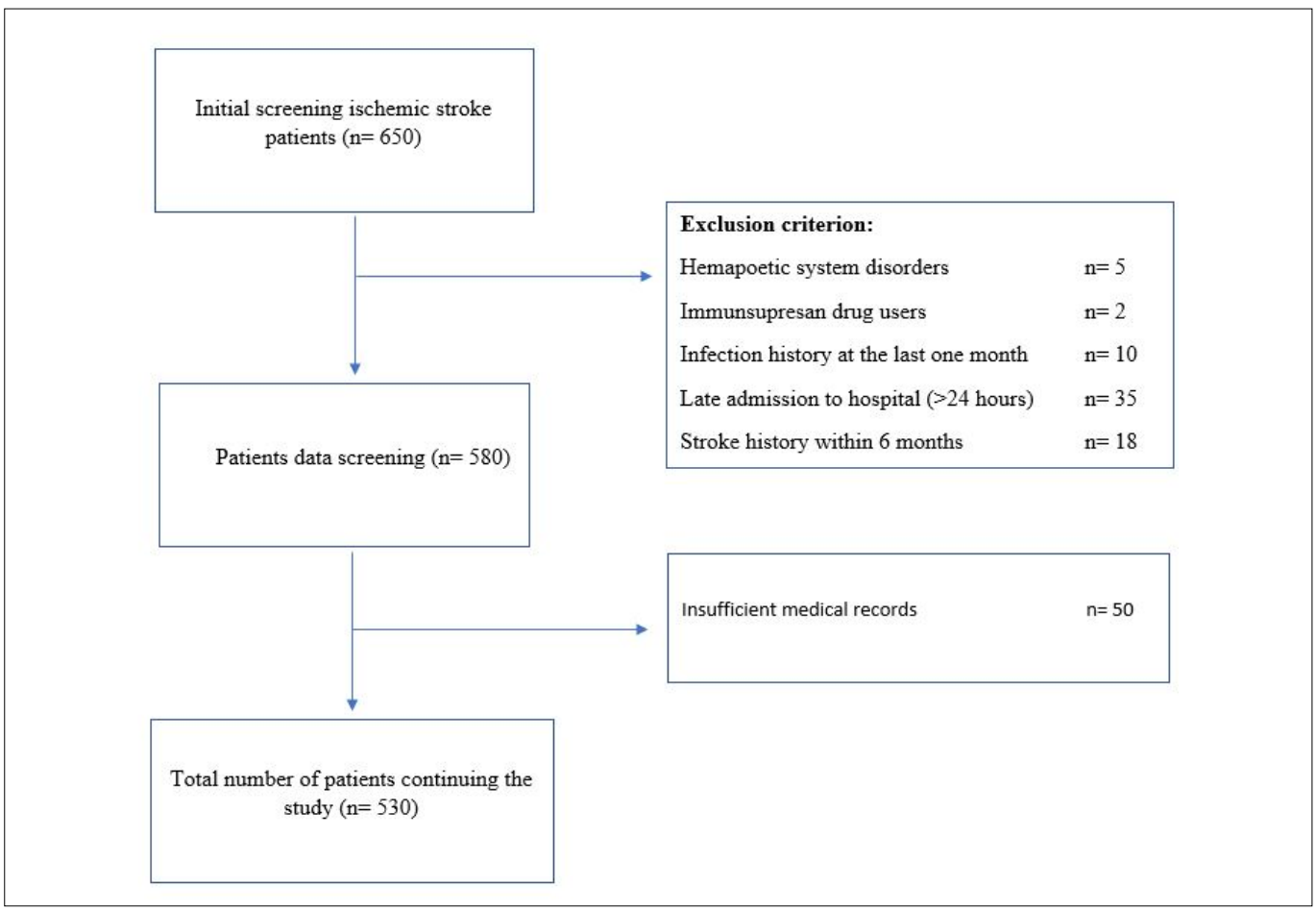

Figure 1. Study flow chart.

Statistical analysis

Data analysis was conducted using SPSS software (version 20.0; SPSS Inc., Chicago) and presented as mean ± standard deviation or median (interquartile range). The normality of distribution was assessed using the Kolmogorov–Smirnov test. Independent Student's t-tests were employed to compare differences between two groups, while the Mann–Whitney U test was used for non-normally distributed variables. Categorical variable differences were assessed using the chi-square test.

Kaplan–Meier survival analysis was performed to explore the association between the median AIP value and mortality. Cox regression analysis was performed to identify predictors of 30-day mortality. The independent variables included in the regression model were age, glucose levels, alanine aminotransferase level, diabetes mellitus, hypertension, coronary arterial disease, WBC count, antiplatelet treatment, and AIP. Receiver operating characteristic (ROC) analysis was performed to determine the specificity and sensitivity of the study. Kaplan–Meier survival estimates for AIP in AIS and survival for AIP were compared according to the median AIP value using the log-rank test. Power analysis was performed using the GPower 3.1.9.7 packet program, which determined the power of a sample size of 530 patients to detect differences in AIP to be 80.5%.

Ethical considerations

This study was approved by the Ethics Committee for Research Involving Human Subjects of the Faculty of Medicine at Necmettin Erbakan University (protocol no. 2024/4781, issued on February 2, 2024). This study adhered to the ethical principles of the Declaration of Helsinki (1964).

RESULTS

In patients with ischemic stroke, the mean age of the surviving group (390 patients) was 66.7 ± 13.3 years, whereas the mean age of the mortality group (140 patients) was significantly higher at 78.5 ± 12.6 years (P value < 0.001). No statistically significant differences were observed between the groups in terms of hypertension, diabetes mellitus, history of coronary artery disease, insulin use, or antiplatelet therapy use. However, variables such as age, glucose level, total cholesterol level, HDL-C level, and WBC count were significantly higher in the mortality group (**Table 1**).

There were no significant differences in TG and HDL-C levels between the two groups (116 ± 79.4, 111.7 ± 69.1 mg/dL for TG, 37 ± 13, 39.1 ± 13.1 mg/dl for HDL-C, P > 0.05); however, AIP was significantly lower in the mortality group (0.11 ± 0.27) than in the surviving group (0.50 ± 0.33) (P value = 0.001, Z value = −11.5) (**Table 1**).

ROC curve analysis revealed that an AIP value of 0.291 had a 74.4% sensitivity and 76.4% specificity for predicting 1-month mortality. The positive predictive value of AIP for predicting 1-month mortality was 75.92%, with a negative predictive value of 74.9%. The AUC was 0.829 (95% CI 0.78–0.88, P = 0.0001) (**Figure 2**).

Table 1. Demographic and laboratory findings of surviving and deceased patients

	Surviving (n = 390)	Deceased (n = 140)	P value	Z value
Age, y (mean ± SD)	66.7 ± 13.3	78.5 ± 12.6	0.001	
Hypertension (%)	61.3	65.7	NS	
Diabetes mellitus (%)	31	36.4	NS	
CAD (%)	14.1	8.6	NS	
Antiplatelet	5.9	3.6	NS	
Warfarin	4.6	10.7	0.014	5.9*
Oral antidiabetic	12.1	5.7	0.036	5*
Insulin	6.2	11.4	NS	
Glucose (mg/dL), Median (IQR)	113 (75.3)	129 (63.3)	0.008	−4
Creatinine (mg/dL), (mean ± SD)	0.9 ± 0.93	1.02 ± 1.1	NS	
AST	22 ± 18.2	23 ± 11.5	NS	
ALT	19 ± 21.8	15 ± 12.7	NS	
Total cholesterol (mg/dL), (mean ± SD)	173.5 ± 65	162 ± 47.4	0.004	−2.64
Triglyceride (mg/dL), Median (IQR)	116 (79.4)	111.7 (69.1)	NS	
LDL (mg/dL), (mean ± SD)	106 ± 37.1	96 ± 38.6	0.001	−3.51
HDL (mg/dL), (mean ± SD)	37 ± 13	39.1 ± 13.1	0.043	−2.53
Hemoglobin	13.1 ± 1.8	12.9 ± 2.4	NS	
WBC	8.6 ± 4	10.2 ± 4.9	0.002	−3.34
PLT	235 ±1 01.1	235 ± 126.8	NS	
AIP	0.50 ± 0.33	0.11 ± 0.27	0.001	−11.5

CAD, coronary artery disease; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not significant; WBC, white blood cell; PLT, platelet; AIP, atherogenic index of plasma. * Chi-square.

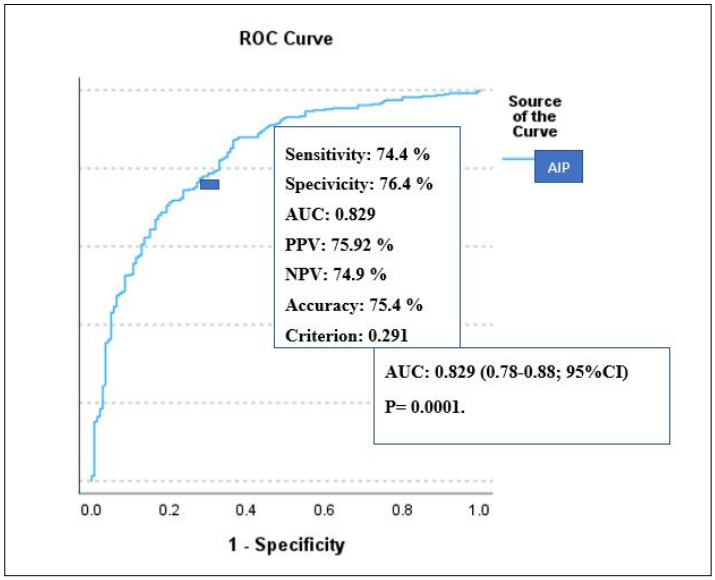

Figure 2. Receiver operating characteristic curve of atherogenic index of plasma prediction of mortality in acute ischemic stroke.

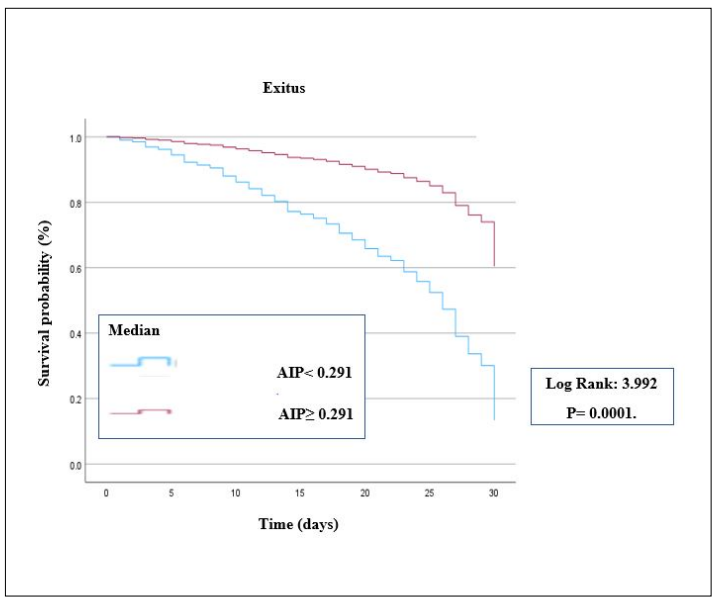

Figure 3. Kaplan–Meier survival estimates for atherogenic index of plasma in acute ischemic stroke and a comparison of survival for AIP according to the median AIP value with long rank test.

Kaplan–Meier analysis demonstrated a significant difference between the two groups based on the AIP value of 0.291 (**Figure 3**). Age and AIP were identified as independent risk factors for mortality in the Cox regression analysis, with hazard ratios (HR) (95% CI) of 1.048 (1.032–1.064) for age, 3.992 (2.648–6.020) (first step) for AIP, and 3.962 (2.643–5.937) (last step) for AIP (P value < 0.001) (**Table 2**). TGs and HDL-C were not independent predictors in the Cox regression analysis (HR: 1.000 (0.999-1.002), p = 0.581; HR: 1.001 (0.990-1.012), p = 0.889, respectively).

DISCUSSION

This study aimed to explore the role of the AIP in the pathogenesis of stroke and its impact on 1-month mortality in patients with AIS.

Atherosclerosis and dyslipidemia are commonly implicated causes of ischemic stroke. Although lipid parameters appear to offer insights into atherosclerosis, the results can be inconclusive. Lipid parameters were not identified as independent predictors in this study. Therefore, these new parameters are needed. Literature reports have highlighted the AIP as a parameter with a higher predictive value than other lipid parameters. Numerous small low-density lipoprotein cholesterol (LDL-C) particles traversing the vascular endothelium interact with glycoproteins in the vascular wall, leading to lipid accumulation.[6]

Moreover, oxidized LDL-C particles create an environment that facilitates the transformation of monocytes into macrophages with hormonal effects. This process results in foam cell formation and aggregation, triggering the release of large amounts of lipid particles from atherosclerotic plaque and ultimately contributing to stroke. Elevated TG and reduced HDL-C levels are significant risk factors for vascular diseases, regardless of LDL-C levels. Even if LDL-C levels are effectively managed with statin therapy, the vascular risk may persist. Some studies have suggested that the logarithmic ratio of TG to HDL-C has a more predictive effect than considering each parameter individually.[7,8]

The HDL-C level, which is reported in numerous studies to have protective effects against coronary artery diseases, exerts a significant impact on cardiovascular diseases. However, recent studies have reported conflicting data. Cheng et al.[8] demonstrated in a study that very high HDL-C levels (> 60 mg/dl) and very low HDL-C levels (< 25 mg/dl) were associated with mortality in patients undergoing percutaneous coronary intervention. Furthermore, evidence suggests that elevated TG levels are a vascular risk factor. The negative impact of these two parameters on lipid metabolism and atherosclerosis is indisputable when considered in isolation. However, the present study indicates that their individual effects on mortality prediction are notably poor. Therefore, the AIP may be deemed as a more sensitive indicator of mortality, given its logarithmic ratio of TG/HDL-C.

Wu et al.[9] established in a study involving 696 patients that the AIP independently predicted the risk of cardiovascular disease. Another study conducted by Garg et al.,[10] which focused on 267 patients with symptomatic carotid artery stenosis, identified AIP as an independent predictor of carotid vascular risk compared to other lipid parameters. Similarly, a study in China revealed a close correlation between AIP and the severity of cardiovascular disease in patients undergoing coronary angiography.[11] Won et al.[12] demonstrated that the AIP exhibits higher sensitivity than traditional risk assessment in detecting an increase in plaque burden in the coronary arteries. Although the study emphasized the pathological nature of a high AIP value in atherosclerosis, it primarily addressed the evaluation of atherosclerosis and the associated

Table 2. Cox regression results for the predictors of mortality

Variables	HR (95% CI)	P value
First step		
Age	1.052 (1.035–1.069)	< 0.001
Glucose	1.002 (0.999–1.005)	0.114
ALT	1.001 (1–1.003)	0.077
WBC	1.027 (0.995–1.059)	0.096
*AIP**	3.992 (2.648–6.02)	< 0.001
Hypertension	1.346 (0.934–1.941)	0.111
Diabetes mellitus	0.817 (0.553–1.206)	0.309
CAD	1.338 (0.737–2.432)	0.339
Antiplatelet	2.136 (0.859–5.317)	0.103
Last step		
Age	1.048 (1.032–1.064)	< 0.001
*AIP**	3.962 (2.643–5.937)	< 0.001

ALT, alanine aminotransferase; WBC, white blood cell; CAD, coronary artery disease; AIP, atherogenic index of plasma. * AIP was included in the regression model as a dichotomous variable as above the median (> 3.962) and below or equal to the median (≤ 3.962).

stroke frequency rather than mortality. Given this distinction, our study should be regarded as a pilot study exploring the potential differences in mortality pathogenesis compared to atherosclerosis.

In the context of coronary artery disease, the AIP is frequently employed as a parameter that indicates the presence of atherosclerosis. Its applicability is more restricted in cerebrovascular and peripheral vascular diseases. However, in recent years, there has been a growing interest in this parameter. Yu et al.[13] identified AIP as the most crucial determinant of intracranial atherosclerosis. Furthermore, Wang et al.[14] demonstrated a significant positive linear association between the AIP and ischemic stroke. According to the RICAS study, AIP was positively and linearly correlated with asymptomatic intracranial atherosclerotic stenosis in middle-aged and older patients.[15] One contributing factor to this association is the disappearance of the anti-atherosclerotic effect of estrogen in the postmenopausal period, coupled with an increase in dyslipidemia with aging. Numerous studies in the literature stated above are vascular risk studies and suggest that a higher AIP may cause cardiological and cerebrovascular diseases. However, such studies have not focused on the outcome and mortality, which is different from our mortality study.

Deng et al.[16] underscored the significance of a lower TG/HDL-C ratio in terms of 3-month mortality in their study, which is consistent with the results of our study. Liu et al.[17] demonstrated through multivariate logistic regression analysis that AIP independently predicted poor prognosis in patients with AIS, aligning with the outcomes observed in our study. Liu et al.[18] revealed in their study that a higher AIP was associated with poor prognosis in patients with AIS during the first 3 months, and its predictive value surpassed that of other lipid parameters. A cohort study conducted by Weir et al.[19] reported that a lower AIP in stroke patients was linked to unfavorable outcomes. The study conducted by Liu et al.[18] focused on patients with AIS and identified higher AIP as an independent predictor of atherosclerosis occurring in large vessels in stroke mortality. The study stated above was a mortality study; however, it suggested that higher AIP levels were related to mortality, in contrast to our study, which suggested that lower AIP levels were related to mortality. The study cut-off value of AIP in that study ([0.112, HR: 1.84 {95% CI, 1.23–2.53, P = 0.007}]) is different from the cut-off our study ([0.291, HR: 3.962 {95% CI, 2.643–5.937, P < 0.001}]), with a lower sensitivity (59%), and specificity (70%) than our results (sensitivity of 74.4% and specificity of 76.4% in the ROC analysis). Chang et al.[8] suggested in a cohort study involving approximately 50 thousand patients that a higher TG-to-HDL-C ratio was associated with positive outcomes. These findings are consistent with those of our study.

Çoban et al.[20,21] highlighted higher TG and TG/HDL-C ratios in young ischemic stroke patients than in older individuals with AIS. The finding was similar to that of our study; the mortality group had mostly older patients compared to the survivors in our results. However, in this study, the AIP was an independent predictor of mortality from age.

In our study, stroke of undetermined etiology exhibited higher AIP values according to TOAST classification (**Table 3**). The reason undermined etiology differs from others may be the combination of more than one risk factor; however, the number of samples was relatively small when compared to other groups. Another noteworthy aspect of our study was its focus on mortality rather than prevalence. While numerous studies have explored the correlation between elevated AIP and vascular risk, data regarding the association between AIP and mortality are scarce. This literature supports the notion that lower AIP values, particularly in acute stroke patients undergoing metabolic stress, play a role in meeting the heightened energy demands of TGs, which serve as stored glucose (i.e., low AIP value). The outcomes of these studies are consistent with those of the present study.

Sujatha et al. and Xu et al.[22,23] found a positive relationship between high AIP and stroke risk. However, the results of our study differ from these results. In our study, we investigated the relationship between AIP and stroke mortality. Several studies have shown that increased TG levels disrupt the vascular bed and increase the risk of stroke. However, there is insufficient evidence suggesting that high TG levels directly affect mortality. Decreased TG levels may reflect malnutrition and increased energy deficits. As a result, the destruction process begins in the body and mediators effective on the endothelium are secreted, which further disrupts the vascular bed. The TG and HDL-C levels in the deceased and living groups were very close and were not statistically significant their differences were not statistically significant. However, as a result of the plasma atherogenicity index calculated with the help of these parameters, mortality can be predicted in ischemic stroke patients. This index is a more sensitive risk predictor than the classical lipid profile.

The present study has some limitations. The first is the single-center design of the study, which may affect the generalizability of the findings to broader populations. Furthermore, the age distribution of the patients in our study leans towards advanced age groups. It is crucial to recognize that different results may have been observed in a younger patient cohort. Therefore, caution should be exercised when extrapolating the study outcomes to more diverse populations or varying age groups. Future research involving multiple centers and encompassing a broader age range could provide a more comprehensive understanding of the association between AIP and outcomes in AIS patients.

CONCLUSION

Dyslipidemia is a significant risk factor of ischemic stroke, and atherosclerosis exerts adverse effects on the entire vascular system. Hyperlipidemia and low TG levels are important risk factors for mortality. Numerous studies have investigated various lipid and non-lipid parameters to highlight the unfavorable prognosis of patients with ischemic stroke. However, traditional lipid parameters and other variables do not demonstrate the same level of sensitivity and specificity as AIP in indicating poor prognosis and mortality associated with ischemic stroke. The present study with higher prognostic accuracy and the fact that AIP is a noninvasive and cost-effective test is poised to serve as a valuable resource for clinicians. The findings of this study have the potential to effectively guide clinicians in the future, particularly in the context of stroke, a condition characterized by high mortality and morbidity.

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Table 3. A comparison of median AIP ratio values among stroke subtypes and the relationship between AIP ratio and survival status for each stroke subtypes

	AIP			
Stroke subtype	**Total**	**Surviving**	**Dead**	**P value**
Major arterial	142 (27.2%)	62 (11.9%)	80 (15.3%)	NS
Cardioembolic	83 (15.9%)	36 (6.9%)	47 (9%)	NS
Minor arterial	115 (22%)	35 (6.7%)	80 (15.3%)	NS
Idiopathic	145 (27.8%)	48 (9.2%)	97 (18.6%)	NS
Cryptogenic	37 (7.1%)	23 (4.4%)	14 (2.7%)	0.003

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The systemic immune-inflammatory index in high-risk patients with hypertension: a cross sectional-study

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ABSTRACT

INTRODUCTION: Essential hypertension is an important health condition responsible for conditions such as heart attack, stroke, and kidney disease. Traditional risk factors and their control are important for reducing mortality. Inflammation caused by organ damage plays a role in the undesirable outcomes of hypertension. Biomarkers, such as the systemic immune-inflammatory index (SII), are predictors, but their relationship with risk factors is poorly understood.

OBJECTIVE: To evaluate the correlation between the SII and risk factors in patients with hypertension.

METHODS: This cross-sectional study was conducted in 2020 in Bahia with hypertensive patients from an outpatient clinic. We collected demographic and clinical data such as age, body mass index, and the following biomarkers: low-density lipoprotein level, glomerular filtration rate, interleukin 6 level, C-reactive protein level, neutrophil/lymphocyte ratio (NLR), hemogram, creatinine level, urea level, ferritin level, and vitamin D level.

RESULTS: A total of 61 patients, most of them black women, participated in the study. The prevalence of type 2 diabetes was 19%, and there was no prevalence of stroke or heart attacks. According to the Framingham risk index, a large part of the sample presented high and very high risks. The bivariate analysis between SII and NLR was positive. Multivariate analysis showed that age, renal function, and NLR were positively correlated with the SII. The patients' Framingham risk did not correlate with the SII.

CONCLUSION: Inflammation is important for vascular damage in arterial hypertension caused by increased oxidative stress. We evaluated SII and NLR as indices of correlation with risk factors. The SII is a low-cost tool that can be used to screen for chronic conditions, such as hypertension. In summary, higher SII was positively associated with older age and worse renal function in patients with high-risk hypertension.

INTRODUCTION

Hypertension is a chronic non-communicable disease characterized by permanently elevated blood pressure. It is a complex syndrome influenced by genetic, epigenetic, environmental, and social variables, and is linked to cardiovascular disease (CVD).[1,2] In the Americas, the condition affects over 25% of women and 40% of men.[1] In Brazil, a national pool inquiry reported a prevalence of 23% of hypertension in young adults in 2013, reaching 47% in adults older than 74 years. Despite a reduction in the age-adjusted mortality model in the last three decades due to public prevention programs, the most vulnerable and economically disadvantaged population had a lesser impact on these policies in the northern and northeastern regions of the country.[2] Data from the Brazilian Cardiovascular Statistics Registry show that CVD has been the most important cause of death in Brazil in the last 30 years, with coronary disease as the leading cause of CVD.[3]

Higher blood pressure is linked to the development of atherosclerosis, a contributing factor to CVD.[3] Adequate control of risk factors such as obesity, dyslipidemia, smoking, glycemic control, and sedentarism can prevent around 75% of CVD.[2] The underlying physiological mechanism between CVD and hypertension is characterized by persistent inflammation and microcirculatory abnormalities.[3,4] Biomarkers associated with chronic inflammation play a direct role in the development of atherosclerosis. These biomarkers include C-reactive protein (CRP), interleukins, and primary hematological indices such as the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), and the systemic immune-inflammatory index (SII) which measures the balance between the inflammatory, immunological, and thrombotic statuses.[4–6] The SII is calculated using the formula: (platelets × neutrophils) ÷ total lymphocyte levels.[7] The higher the index, the worse the inflammation status. The SII outperforms indices such as the NLR in

predicting some types of cancer.[8] Additionally, the SII can predict unfavorable cardiac outcomes and the standard uncontrolled risk factors with a reduced cost following coronary intervention.[4,5]

The study aimed to evaluate the impact of the traditional CVD risk factors among adults with hypertension and its correlation with the SII in a hypertension public facility unit care.

METHODS

Study design

This study employed a cross-sectional design utilizing quantitative and population-based methods. This study was conducted in the Barreiras district of northeastern Brazil. This district is responsible for a local gross domestic product (GDP) of approximately US$ 1,400,000, compared to the overall Brazilian GDP of approximately US$ 2,126 trillion.[9]

Study location and period

All participants in the hypertension follow-up program were invited to participate in the study, which spanned from April 2019 to January 2020, before the beginning of the COVID-19 pandemic in Barreiras, Bahia. The health unit in Barreiras is a countryside reference in Bahia that diagnoses, treats, and monitors patients with hypertension.

Study population and eligibility criteria

Participants who were both over the age of 18 and diagnosed with hypertension were included in the study after providing written consent. Individuals who had received cancer therapy within the past five years, individuals with hepatitis and HIV, individuals with rheumatologic illnesses, pregnant women, and individuals who regularly used steroids were excluded from the study.

Data collection

The data were collected between April 2019 and January 2020. The demographic data of each patient and risk factors for CVD were collected. The risk factors studied included dyslipidemia, diabetes, smoking, obesity, and CVD onset. A standard blood pressure measurement was used to define the arterial hypertension stage according to the Brazilian arterial hypertension guidelines, aligned with the American Heart Association recommendation.[2]

The estimated glomerular filtration rate (eGFR) was evaluated with the serum creatinine result and the CKD-EPI equation.[10] Chronic kidney disease (CKD) diagnosis followed the Kidney Disease Global Initiative Outcomes (KDIGO) guideline with a persistent eGFR below 60 ml/min/1,73 m² for more than twelve weeks.[11] The Framingham stratification CVD risk score and the inflammatory condition assessed the cardiovascular risk with the hs-CRP, interleukin-6 (IL-6), the NLR, and the SII.[6,12]

Data analysis and statistical analysis

The data analysis began in February 2020. Data distribution was checked using the Kolmogorov-Smirnov test. The variables of height, waist circumference, LDL, IL6, hs-CRP, and creatinine presented a non-homogeneous distribution, described as the median, 25th percentile, and 75th percentile. Non-parametric tests were used to analyze variables with different distributions. Bivariate relationships between quantitative variables were analyzed using Spearman's correlation test. A significance level of 0,05 (5%) was used in this study.

We performed multivariate analysis using multiple linear regression to evaluate the influence of age, body mass index, LDL, eGFR, IL6, hs-CRP, and NLR on the SII. Bootstrapping procedures (1000 resamples; 95% CI BCa) were carried out to obtain better reliability of the results, correct deviations from the normality of the sample distribution, and to present a 95% confidence interval (95% CI) for the Multiple Linear Regression.[13] The selection of the Enter method made it possible to run the regression test in conjunction with the bootstrapping procedure.

An exploratory analysis was performed to correlate the Framingham risk score, stratified into low-, intermediate-, high-, and very high-risk groups, with the SII. Framingham risk strata were considered ordinal variables. We divided the four risk strata into two groups: low + intermediate risk and high + very high risk, and used Mann–Whitney analysis to evaluate the correlation with the SII.

Ethical and legal aspects of the research

This study followed the STROBE systematization for cross-sectional studies (REF) and received local ethics approval (no. 3.286.842). Data were entered using Microsoft Excel software and the statistical package was SPSS v. 21.0 (IBM, Armonk, New York).

RESULTS

The demographic and laboratory parameters of the patients are shown in **Table 1**. The 61 participants had a median age of 58 years, with a predominance of women (56%) of black ethnicity and without chronic kidney disease. No patient had a history of stroke, acute myocardial infarction, or secondary hypertension. The prevalence of type 2 diabetes was 19,6%, and 46% had dyslipidemia. The mean fasting glucose level of the sample was 111,6 mg/dl, indicating reasonable glycemic control. Only 13% reported smoking tobacco cigarettes. The hypertensive sample showed that 71% patients received angiotensin enzyme converting inhibitors (ACEi) or angiotensin receptor blockers (ARB) as renin-angiotensin-aldosterone system inhibition (RAASi).

The results of the inflammatory tests, such as hs-CRP, SII, NLR, and IL6, showed that the cohort of patients presented a median hs-CRP result of 0,21 and a median SII result of 371,20. The Framingham CVD risk score was calculated among the sample

individuals, revealing nine patients with low risk, 13 with intermediate risk, 37 with high risk, and two with very high risk. There was no significant difference between the risk stratification evaluation and the patient's sex.

Table 2 shows Spearman's correlation test between the dependent variable, SII, and the rest of the parameters. There was no correlation between SII and the other laboratory variables, only with the NLR.

The multivariate linear regression results demonstrated that the independent variables had a substantial impact on the SII (F (7, 46) = 110,863, P < 0.0001; R2 adjusted = 0,447). The coefficients for the three predictors that affected the SII, age, eGFR, and NLR are shown in **Table 3**. The dependent variable was not affected by the other evaluated variables. The predictive equation for this model was: SII = 539,88 −4,32 × Age −3,59 × eGFR + 193,78 × NLR.

Table 1. Demographics of the study population in Barreiras (BA), 2019–2020

Variables	Participants (n = 61)		
	Median	Percentile 25	Percentile 75
Age (years)	58	51	65
Waist (cm)	95	89	102
BMI (kg/m^2)	27,1	25,2	30,8
Sex			
Male		27 (44,3%)	
Female		34 (55,7%)	
Ethnicity			
White		6 (9,8%)	
Not white		55 (90,2%)	
Alcohol consumption			
Yes		12 (19,7%)	
No		49 (80,3%)	
Hypertensive drugs			
None		2 (3,3%)	
1 medicine		19 (31,1%)	
2 medicines		20 (32,8%)	
3 medicines		11 (18%)	
4 or more medicines		9 (14,8%)	
Hemoglobin (g/dl)	14	12,7	15,25
Hematocrit (%)	41,9	39,4	45,3
Creatinine (mg/dl)	0,89	0,73	1,08
Urea (mg/dl)	29	23	34
NLR	1,6	1,18	2,07
IL6 (pg/ml)	2,24	1,53	3,56
Ferritin (ng/ml)	154	99,65	207
Vitamin D (ng/ml)	25,5	21,75	29,7
hs-CRP (mg/l)	0,15	0,06	0,45
LDL (mg/dl)	107,5	90	140
eGFR (ml/min/1,73 m^2)	91,2	77,3	111,8
SII	371,2	249,04	504,56

BMI: body mass index; IL6: interleukin 6; hs-CRP: high sensitivity C-reactive protein; LDL: low-density lipoproteins; eGFR: estimated glomerular filtration rate; SII: systemic immune-inflammatory index.

As shown in **Figure 1**, the two groups (low-risk + intermediate-risk and high-risk + very-high-risk) were correlated with the SII. However, there was no correlation between the SII result and the Framingham risk score.

DISCUSSION

In this cross-sectional study, adult patients with hypertension in a hypertension care program at a primary healthcare facility in Brazil were evaluated for traditional cardiovascular risk factors and their inflammatory parameters. The SII, a simple ratio based on platelet, neutrophil, and lymphocyte counts, positively correlated with age, renal function, and NLR in adults with hypertension.

Inflammation plays an important role in vascular damage in arterial hypertension due to the increase in oxidative stress.[4] To this matter, many inflammatory biomarkers have been evaluated as surrogates to prevent undesired outcomes such as acute myocardial infarction and stroke. CRP, an acute-phase inflammatory protein, is associated with hypertension development when elevated.[14] The NLR, a simple ratio between the neutrophils and lymphocytes, also showed a good correlation when elevated to predict arterial hypertension development in a Chinese cohort.[4,15] Apart from the prediction role in hypertension development, the SII correlated with the development of left ventricle hypertrophy in hypertensive patients, showing the importance of inflammatory biomarkers in the prediction of hypertension and the development of structural damage once hypertension is installed.[16] In our sample, the NLR was positively associated with the SII in hypertensive patients, suggesting that when elevated, hypertension might be present in patients.

Traditional risk factors such as diabetes, obesity, dyslipidemia, aging, male sex, and smoking are usually related to poor CV outcomes in hypertensive patients.[2] In our sample, higher age was associated with a higher SII in hypertensive patients, but there was no correlation with sex. On the contrary, a South African study evaluated the accuracy of the SII to predict the new onset of essential hypertension.[17] Women with higher age had higher SII results and developed essential hypertension in a

Table 2. Relationship between inflammatory markers and the systemic immune- inflammatory index

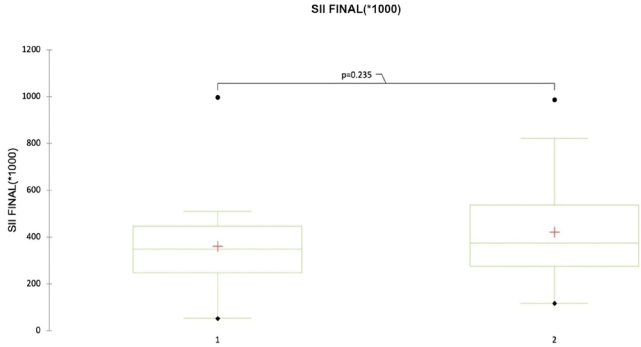
	Correlacion coefficient (p)
Age (years)	−0,076 (0,561)
BMI (kg/m^2)	0,01 (0,938)
LDL (mg/dl)	0,031 (0,813)
eGFR (mL/min/1,73 m^2)	−0,19 (0,143)
IL6 (pg/ml)	0,19 (0,166)
hs-CRP (mg/l)	−0,021 (0,873)
NLR	0,719* (< 0,001)

* Spearman correlation coefficient with P < 0.01; BMI: Body mass index; LDL: low-density lipoproteins; eGFR: estimated glomerular filtration rate; IL6: interleukin 6; hs-CRP: high-sensitivity C-reactive protein.

Table 3. Multivariate analysis of factors that influence the dependent variable Systemic inflammatory index

	B	Beta coefficient	t	p	95% CI for B	
					Inferior limit	Upper limit
(Constant)	539,88		2,07	0,04	14,52	1065,23
Age	−4,32	−0,26	−2,07	0,04	−8,53	−0,12
eGFR	−3,59	−0,4	−3,14	0,001	−5,9	−1,29
NLR	193,78	0,6	5,72	0,001	125,56	262

eGFR: Estimated glomerular filtration rate; NLR: neutrophil/lymphocyte ratio.



SII: systemic immune-inflammatory index; 1: low and intermediate risk; 2: high and very high risk; * Mann–Whitney U test.

Figure 1. Relationship between the SII and Framingham risk score in patients with hypertension.

higher proportion than men.[17] Our sample enrolled 56% women; the majority were over 50 years old and above ideal weight. Aging is also associated with increased in blood pressure. A cohort study conducted in the United States of America evaluated the onset of essential hypertension with aging and aldosterone sensitivity.[18] It was found that with higher age, the blood pressure levels are higher in patients with black ethnicity and in those with higher aldosterone sensitivity during the development of essential hypertension.[18] The RAASi is one of the main targets for controlling blood pressure. Continuous RAAS activation induces organ damage,[19] inflammation, and therefore, higher levels of SII. Most hypertensive individuals received an ACEi or ARB treatment strategy; however, we could not evaluate the rate of aldosterone inhibition because of a lack of financial support.

The CVD Framingham score was evaluated in our sample, and as it was shown, most of the patients had a high-risk CVD Framingham score.[12] In a recent elderly Chinese cohort, the SII was evaluated as a prediction tool for clinical outcomes in acute myocardial infarction patients who had undergone percutaneous coronary intervention. The SII showed an independent predictive value for in-hospital mortality, in-hospital major adverse cardiovascular and cerebrovascular events, and long-term mortality.[20] In our sample, the prevalence of acute myocardial infarction and stroke Arterial hypertension is associated with CVD, and the SII might be an efficient tool to predict future events.[5] The early detection and control of blood pressure values are still the main clinical tools to avoid unfavorable outcomes.[21,22]

There were some limitations to the study design and procedure. First, it was a single-center evaluation of patients in a hypertension care program. These patients may have had more information about their disease than the general population. Moreover, most participants used only two types of antihypertensive drugs with good achievement of the blood pressure goals, which reflects a less severe stage of hypertension. Owing to restrictions of the Brazilian public health system, a 24-hour arterial blood pressure monitoring device was not available to determine the range of blood pressure control. Adherence to drug treatment was evaluated, as was done in Brazil, using the self-report of the patient. However, using a single complete blood count to determine the ratio of neutrophils, lymphocytes, and platelets was revealed to be a good and inexpensive strategy to add information to the inflammatory status of patients. Usually, in the Brazilian Unified Public Health System, the requisition of hs-CRP and IL6 as screening tools is not permitted because of their high cost. This simple screening strategy could be adopted in low-income countries.

CONCLUSION

In summary, in this cross-sectional study, the SII was positively correlated with age and renal function in patients with hypertension. Traditional risk factors for CVD include the addition of SII and NLR to address inflammatory status.

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Association between the use of midazolam, fentanyl, propofol, ketamine, and dexmedetomidine and the incidence of delirium in elderly patients in intensive care units: a systematic review

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AUTHOR'S KEYWORDS:
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ICU.
Elderly.
Dexmedetomidine.
Propofol.
Midazolam.

ABSTRACT

BACKGROUND: Delirium is a common and serious complication among elderly patients in intensive care units (ICUs), and is often associated with increased morbidity and mortality rates. The choice of sedoanalgesic may influence the incidence of delirium; however, the evidence remains unclear, particularly in the elderly population.

OBJECTIVES: To evaluate the association between the use of different sedoanalgesics and the incidence of delirium in elderly ICU patients, based on data from randomized clinical trials.

DESIGN AND SETTING: This systematic review was conducted using data from randomized clinical trials performed in various ICU settings.

METHODS: A systematic search of the MEDLINE, Embase, and CENTRAL databases was performed in January 2024. The review included randomized clinical trials involving patients aged 60 years or older that examined the relationship between sedoanalgesics (midazolam, fentanyl, propofol, ketamine, and dexmedetomidine) and delirium incidence. Studies involving COVID-19 patients and non-randomized studies were excluded.

RESULTS: A total of 1,331 patients from six studies were included. The mean age of the patients ranged from 71 to 74.7 years. Four studies compared dexmedetomidine with propofol; two found no significant difference in delirium incidence, whereas two suggested a lower incidence with dexmedetomidine. The remaining studies compared propofol with ketamine and dexmedetomidine with midazolam and showed no significant differences in the incidence of delirium.

CONCLUSIONS: Dexmedetomidine may be associated with a lower incidence of delirium than propofol or midazolam in elderly ICU patients. However, further research is needed to confirm these findings and explore the factors contributing to delirium in this population.

SYSTEMATIC REVIEW REGISTRATION: Registered with PROSPERO, CRD42024575693, available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=575693.

INTRODUCTION

Delirium is a neuropsychiatric syndrome characterized by disturbances in cognition and consciousness, often observed in patients in intensive care units (ICUs), particularly among the elderly and those with prior cognitive impairment.[1,2] The management of symptoms such as pain and agitation in ICUs typically involves sedation and anesthesia, which, while aimed at patient comfort, can contribute to the onset of delirium.[3,4]

Midazolam, fentanyl, propofol, ketamine, and dexmedetomidine are among the most commonly used sedatives in Brazilian clinical practice, particularly in ICUs, due to their pharmacological properties suited for managing pain, agitation, and sedation in critically ill patients.[5,6] The preference for these medications is influenced by their availability, cost-effectiveness, and specific characteristics, such as rapid onset of action and ease of titration.[7] However, these agents are also associated with known adverse effects, including delirium, in certain clinical contexts.[8]

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agents are also associated with known adverse effects, including delirium, in certain clinical contexts.[8]

This condition is exacerbated in elderly patients undergoing procedures requiring sedation, which increases the risk of cognitive impairment and consequently extends the duration and severity of delirium. These factors are associated with higher mortality.[9,10] The presence of dementia or cognitive deficits in elderly individuals may further worsen patient orientation regarding their environment.[11]

Delirium is associated with longer hospital stays, increased mortality, and long-term cognitive decline.[12] Therefore, identifying sedatives and anesthetics that minimize the risk of delirium in this population is crucial for improving ICU care. The literature lacks a systematic review that specifically addresses this topic in the elderly population, despite it being the most affected by delirium. Therefore, this article reviewed randomized clinical trials to determine the relationship between various sedatives and the incidence of delirium in elderly ICU patients.

MATERIALS AND METHODS

General information

This study was a systematic review, and the manuscript was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines,[13] with data searches conducted in January 2024. This study was published on the PROSPERO platform (ID No. CRD42024575693). The MEDLINE, Embase, and CENTRAL databases were used to identify studies on the incidence of delirium related to the use of sedoanalgesics in elderly ICU patients. The keywords employed were: (delirium) AND (aged) AND (intensive care unit) AND (propofol) OR (fentanyl) OR (dexmedetomidine) OR (ketamine) OR (midazolam), with adaptations according to the specificities of each database.

Data selection and extraction

Article selection was conducted by two independent reviewers in two stages: an initial analysis of titles and abstracts, followed by full-text assessment. Discrepancies were resolved by consensus among all authors. The articles, unrestricted by language, were limited to publications published from 2000 onwards, to focus on recent data on sedoanalgesia in ICU settings. Only randomized clinical trials that examined patients aged 60 years or older using the Confusion Assessment Method for Intensive Care Units (CAM-ICU) to assess delirium were included. The choice of clinical trials is justified as they are the gold standard for investigating the relationship between delirium and the use of various sedoanalgesics, allowing for a rigorous analysis of the risks and safety of these drugs. The studied sedatives were midazolam, fentanyl, propofol, ketamine, and dexmedetomidine.

The exclusion criteria included articles that did not associate delirium with the use of specified sedoanalgesics, studies outside the ICU context, patients with COVID-19 or delirium tremens, cohorts, case reports, case-control studies, cross-sectional studies, reviews, and meta-analyses. These criteria aimed to eliminate potential confounding factors and ensure the relevance and accuracy of the analyzed data. It is important to note that the choice of inclusion and exclusion criteria preceded the search.

Data extraction was performed by two independent reviewers who collected information about the author, year, purpose, comparison, conclusion, type and location of the study, treatment interval, patient demographics, details of follow-up, intervention and control groups, drug dosing, incidence of delirium, odds ratio (OR), P-value, and sources of funding.

Methodological analysis

In the methodology adopted in the present study, the Cochrane Risk of Bias Tool (RoB 2.0)[14], which is a systematic approach for assessing bias in randomized clinical trials was used. The analysis focused on seven critical domains: the randomization process, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, addressing dropouts, selective reporting, and other potential sources of bias.

A thorough analysis was conducted on the adequacy of the random sequence generation process and allocation concealment to prevent predictability in participant selection. Lack of blinding and inadequate blinding of the outcome assessors were evaluated to mitigate the risk of performance and detection biases. Data integrity was rigorously verified, as was the selective reporting of outcomes.

The results of this bias assessment were communicated through an intuitive graph, in which the colored circles indicated the risk of bias in each domain per study, with green (low risk), yellow (uncertain risk), and red (high risk). This graph summarizes the risk profile of each study and aids in the critical interpretation of the results, ensuring a high standard of methodological rigor in the review.

Specifications

In this study, effect measures such as odds ratio (OR) and relative risk (RR) were employed to assess the association between the use of analgesics and the incidence of delirium in elderly ICU patients. These measures were selected to facilitate quantitative comparison between the intervention and control groups across the included studies. OR was predominantly used to determine the likelihood of delirium occurrence following the administration of sedatives, such as dexmedetomidine, propofol, ketamine, and midazolam, thereby enabling a clear interpretation of the effects of these medications on the studied outcome.

For each synthesis, we tabulated the characteristics of the interventions and compared them with those of the planned groups. The data were prepared for synthesis by handling the missing summary statistics and converting them when necessary. The results of individual studies are displayed in structured tables and visual tools, such as risk-of-bias charts, to facilitate comparison.

RESULTS

Study selection

After implementing the search strategy across the databases, 1325 articles were identified: 250 from MEDLINE, 769 from Embase, and 306 from CENTRAL. Of these, 114 were duplicates and were subsequently removed. Following the analysis of the studies, 1,205 of the 1,211 articles were excluded for not meeting the inclusion criteria or meeting the exclusion criteria. The remaining six articles were read in full, and ultimately, all 6[15–20] were selected for inclusion in this study. The reasons for excluding studies in the first stage of selection were drugs other than the five specified sedoanalgesics (which could introduce confounding bias in assessing the association between specific sedoanalgesic use and the occurrence of delirium), not using the CAM-ICU scale for delirium assessment, not associating the use of a specific sedoanalgesic with the occurrence of delirium, and not isolating the elderly population. These data are summarized in **Figure 1**.

Characteristics of the studies

The six included studies were randomized clinical trials. The details of the objectives, comparisons, conclusions, and designs of the studies are presented in **Table 1**. Four studies[16,17,19,20] compared dexmedetomidine with propofol. Another article[18] compared dexmedetomidine and midazolam, whereas another study[15] evaluated the use of ketamine versus propofol. No articles that compared the use of fentanyl with other sedoanalgesics or that met our inclusion criteria were found. Additionally, we did not find studies comparing dexmedetomidine with ketamine, propofol with midazolam, or ketamine with midazolam that met our inclusion criteria.

It is also noteworthy that among the six included studies, four received funding for their research, whereas the other two did not report any funding in their manuscripts.[15–20]

Demographic analysis

A total of 1,331 patients were evaluated in the six studies included in this review, comprising 561 men and 770 women. Additionally, three studies assessed patients over 60 years old, two studies examined patients over 65 years old, and one study focused on patients between 65 and 80 years of age.[15–20] The average age of the patients ranged from 71 to 74.7 years, although one of the studies did not report the average age of the participants.[15] The overall average age of the articles evaluated, considering the five studies that reported this value, was 72.37 years. No study has reported data on the median age of the patients. The selected studies were published between 2014 and 2023 and patient evaluations were conducted between 2009 and 2021. These studies were conducted in Thailand, China, Canada, and South Korea.

The average follow-up time was reported in three studies, with two of them noting a duration of five days, while the other reported a period of three days.[16,17,20] The follow-up time was limited to the period in which these patients were hospitalized in an ICU, and specifics on how delirium assessments were conducted during this follow-up are shown in **Table 2**.

Methodological analysis and risk of bias

The methodological analysis of the included studies indicated that most adhered to rigorous procedures for randomization and allocation concealment, as demonstrated by Siripoonyothai and Sindhvananda[15] and Shin et al.[20] However, there was a lack of clarity in the blinding of participants and assessors in some studies, including those by Siripoonyothai and Sindhvananda[15] and Shu et al.,[18] introducing uncertainty in this aspect (**Figure 2**).

Djaiani et al.[16] effectively managed allocation concealment, despite employing single blinding. Fang et al.[19] also presented deficiencies in detailing the blinding procedures, resulting in an uncertain risk. The analysis of randomized patients was consistently well-conducted, indicating appropriate handling of incomplete data. Shu et al.[18] demonstrated a low risk of bias in the blinding.

The study by Shin et al.[20] with its double-blind design and rigorous postoperative data collection procedures, effectively minimized performance and detection biases, although the absence of a pre-registered protocol leaves the risk of selective reporting uncertain. **Figure 2** highlights the predominance of a low bias risk across several critical categories, emphasizing the need for careful evaluation of the blinding of participants, personnel, and outcome assessors.

Sedoanalgesics and delirium

Four studies compared dexmedetomidine with propofol.[16,17,19,20] Two of these studies found no statistically significant differences in delirium rates between the groups, with P values of 0.0758 and 0.434 (95% confidence interval [95% CI]).[17,19] Shi et al.[17] compared 84 patients receiving dexmedetomidine (0.4–0.6 μg/[kg h]) with 80 patients receiving propofol (25–50 mg/[kg h]), reporting delirium incidences of 39.3% and 26.3%, respectively. Fang et al.[19] compared 54 patients on dexmedetomidine (0.2–0.7 μg/[kg h]) with 54 patients on propofol (0.3–4 mg/[kg h]), with delirium incidences of 3.7% and 9.2%, respectively.

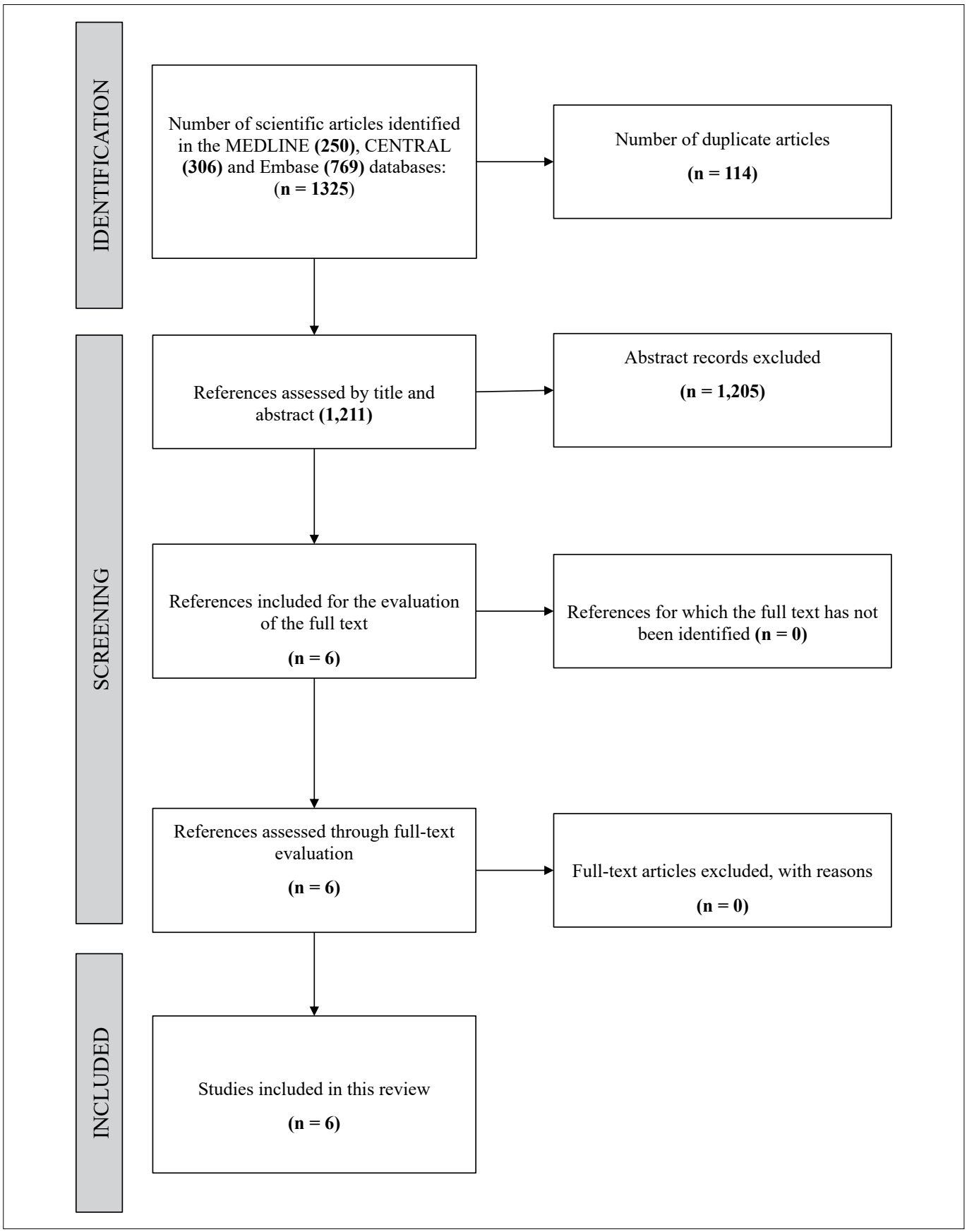

Figure 1. PRISMA flowchart.

Table 1. Characteristics and summary of the studies

Reference	Objective	Comparison	Conclusion	Study design
Siripoonyothai S et al.[15] Thailand	To compare postoperative delirium between ketamine and propofol during cardiac surgery with the use of extracorporeal circulation machine.	Postoperative delirium between groups that received ketamine and propofol.	Compared to propofol, ketamine resulted in fewer delirium events. However, the results are inconclusive.	Randomized clinical trial
Djaiani G et al.[16] Canada	Comparing dexmedetomidine and propofol regarding the incidence of postoperative delirium in elderly patients after cardiac surgery.	Postoperative delirium between sedation with dexmedetomidine and propofol.	Sedation with dexmedetomidine reduced the incidence, delayed the onset, and shortened the duration of postoperative delirium compared to propofol.	Randomized clinical trial
Shi C et al.[17] China	Investigating the effect of perioperative administration of dexmedetomidine on the occurrence and duration of postoperative delirium in elderly patients after cardiac surgery.	Postoperative occurrence of delirium between sedation with dexmedetomidine and propofol.	There was no significant difference in the incidence of delirium between the dexmedetomidine and propofol groups.	Randomized clinical trial
Shu A et al.[18] China	Investigating the influence of dexmedetomidine on delirium and hemodynamics in elderly patients under mechanical ventilation in the ICU.	Anti-delirium effects and hemodynamic influence between dexmedetomidine and midazolam.	Compared to midazolam, dexmedetomidine showed a lower incidence of delirium. However, there was no significant difference between the groups.	Randomized clinical trial
Fang H et al.[19] China	Assessing the sedative effect and safety of dexmedetomidine for postoperative mechanical ventilation in elderly patients.	Sedation effects and safety of dexmedetomidine compared to propofol.	It does not reduce the incidence of delirium or ICU length of stay.	Randomized clinical trial
Shin HJ et al.[20] South Korea	Evaluating the incidence of postoperative delirium in elderly patients undergoing lower limb orthopedic surgery under spinal anesthesia.	Postoperative occurrence of delirium between sedation with dexmedetomidine and propofol.	Dexmedetomidine showed a lower incidence of delirium than propofol.	Randomized clinical trial

Description: ICU, intensive care unit.

Table 2. Patient characteristics

Reference	Treatament (year)	Patients (n)	Men (n)	Women (n)	Population (year)	Mean Age (year ± SD)	Follow-up (day)	Follow-up details
Siripoonyothai S et al.[15]	2019–2020	64	35	29	> 65	NR	NR	Assessment of postoperative delirium within the first 24 hours in the ICU
Djaiani G et al.[16]	2011–2014	183	138	45	> 60	Intervention: 72,7 (6,4) Control: 72,4 (6,2)	5	Delirium assessment was conducted every 12 hours or as needed, using the CAM-ICU tool
Shi C et al.[17]	2009–2016	164	119	45	> 60	Intervention: 74,7 (7,2) Control: 74,2 (7,7)	5	Delirium assessment was performed twice daily until the fifth day post-surgery, utilizing the CAM-ICU assessment method
Shu A et al.[18]	2015–2016	80	52	28	> 60	Intervention: 73,4 (8,6) Control: 73,8 (7,9)	NR	Delirium assessment was conducted during the ICU stay
Fang H et al.[19]	2011–2012	108	62	46	65–80	Intervention: 73,7 (3,1) Control: 74,2 (4,2)	NR	Observation during mechanical ventilation and ICU admission
Shin HJ et al.[20]	2017–2021	732	155	577	> 65	Intervention: 71 (NR) Control: 72 (NR)	3	Delirium assessment using the confusion assessment method in the first three postoperative days

Description: NR, not reported; SD, standard deviation; CAM-ICU, Confusion Assessment Method for Intensive Care Units; ICU, intensive care unit.

Figure 2. Bias risk analysis.

In contrast, the other two studies found significant differences in delirium incidence.[16,20] Djaiani et al.[16] compared 91 patients on dexmedetomidine (0.4 μg/kg bolus, followed by 0.2–0.7 μg/[kg h]) with 92 patients on propofol (1.5–3 mg/[kg h]), reporting delirium incidences of 17.5% and 31.5%, respectively (P = 0.028, 95% CI, OR = 0.46, interval 0.23–0.92). Shin et al.[20] compared 366 patients on dexmedetomidine (1 μg/kg bolus, followed by 0.1–0.5 μg/[kg h]) with 366 patients on propofol (1–2 μg/ml infusion), with incidences of 3% and 6%, respectively (P = 0.036, 95% CI, OR = 0.42, interval 0.20–0.86).

Siripoonyothai and Sindhvananda[15] compared propofol with ketamine and found no significant difference in the incidence of delirium between the groups. The study involved 32 patients on propofol (1.5–6 mg/[kg h]) and 32 on ketamine (1 mg/[kg·h]), with delirium incidences of 56.25% and 31.25%, respectively (P = 0.47, 95% CI, OR = 2.11, interval 0.29–26.42).

Shu et al.[18] compared dexmedetomidine and midazolam and found no significant difference in the incidence of delirium. The study compared 40 patients on dexmedetomidine (1 μg/kg bolus, followed by 0.2–0.7 μg/[kg h]) with 40 patients on midazolam (0.05 mg/kg bolus, followed by 0.05–0.10 mg/[kg h]), reporting delirium incidences of 0% and 10%, respectively (P = 0.116, 95% CI). The odds ratios for this outcome have not been reported. The relevant data are summarized in **Tables 3** and **4**.

DISCUSSION

General considerations

The association between sedoanalgesia and the onset of delirium in ICU patients, particularly the elderly, is well documented; however, its multifactorial etiology complicates targeted intervention strategies.[21–25] Delirium incidence significantly increases

Table 3. Sedoanalgesia details

Reference	Intervention group	Control group	Intervention (n)	Control (n)	Dose – Intervention	Dose – Control
Siripoonyothai S et al.[15]	Propofol	Ketamine	32	32	Infusion of propofol ranging from 1.5–6 mg/(kg h)	Infusion of ketamine at 1 mg/(kg h)
Djaiani G et al.[16]	Dexmedetomidine	Propofol	91	92	Bolus of 0.4 µg/kg of dexmedetomidine followed by an infusion of 0.2–0.7 µg/(kg h).	Infusion of propofol ranging from 1.5–3 mg/(kg h)
Shi C et al.[17]	Dexmedetomidine	Propofol	84	80	Infusion of dexmedetomidine ranging from 0.4–0.6 µg/(kg h)	Infusion of propofol ranging from 25–50 mg/(kg h)
Shu A et al.[18]	Dexmedetomidine	Midazolam	40	40	Bolus of 1 µg/kg of dexmedetomidine followed by an infusion of 0.2–0.7 µg/(kg h)	Bolus of 0.05 mg/kg of midazolam followed by an infusion of 0.05–0.10 mg/(kg h)
Fang H et al.[19]	Dexmedetomidine	Propofol	54	54	Infusion of dexmedetomidine ranging from 0.2–0.7 µg/(kg h)	Infusion of propofol ranging from 0.3–4 mg/(kg h)
Shin HJ et al.[20]	Dexmedetomidine	Propofol	366	366	Bolus of 1 µg/kg of dexmedetomidine followed by an infusion of 0.1–0.5 µg/(kg h)	Continuous infusion of propofol adjusted to an effective concentration of 1–2 µg/ml

Table 4. Analysis of the incidence of delirium

Reference	Presence of delirium Intervention (n)	Presence of delirium Control (n)	Odds Ratio	P valor
Siripoonyothai S et al.[15]	18 of 32 patients (56,25%)	10 of 32 patients (31,25%)	2,11 (0,29–26,42)	0,47
Djaiani G et al.[16]	16 of 91 patients (17,5%)	29 of 92 patients (31,5%)	0,46 (0,23–0,92)	0,028
Shi C et al.[17]	33 of 84 patients (39,3%)	21 of 80 patients (26,3%)	NR	0,0758
Shu A et al.[18]	0 of 40 patients (0%)	4 of 40 patients (10%)	NR	0,116
Fang H et al.[19]	2 of 54 patients (3,7%)	5 of 54 patients (9,2%)	NR	0,434
Shin HJ et al.[20]	11 of 366 patients (3%)	24 of 366 patients (6%)	0,42 (0,20–0,86)	0,036

Description: NR, not reported.

with age, particularly post-65 years, reflecting the heightened vulnerability of this demographic to ICU-related stressors and pre-existing neuropsychiatric conditions.[26–29] Given this, our review focused exclusively on studies involving elderly patients to address the nuances of this high-risk group.

The choice of the diagnostic tool critically influences the consistency and reliability of delirium detection. The use of the CAM-ICU scale across all included studies ensured a standardized approach, although variations in assessment intervals were noted, ranging from twelve to twenty-four hours, or unspecified in some cases.[30–35] These discrepancies underline the need for uniform application protocols to enhance the comparability of study outcomes.

Dexmedetomidine versus propofol

In the comparative analysis between dexmedetomidine and propofol, our findings suggest that dexmedetomidine may provide a protective effect against delirium, which is supported by the significant results of two of the four studies reviewed.[16,20] Specifically, Djaiani et al.[16] and Shin et al.[20] reported a reduced incidence of delirium with dexmedetomidine, indicating its potential advantage in certain clinical scenarios, such as orthopedic surgery. The high methodological quality of these studies, as reflected in their RoB ratings, enhances the credibility of their results.

However, this protective effect was not observed uniformly across all studies. Shi et al.[17] and Fang et al.[19] found no significant differences in the incidence of delirium between dexmedetomidine and propofol, suggesting that variations in dosage and bolus administration may critically influence outcomes.

Although this review did not include placebo-controlled trials, existing evidence emphasizes the importance of administration techniques in maximizing the protective effects of dexmedetomidine and improving long-term cognitive outcomes.[36–40] Consequently, future research should focus on precise dosing and standardized administration to better define the role of dexmedetomidine in delirium prevention and provide clearer guidance for sedation practices in ICU settings, ultimately aiming to optimize patient outcomes.

Dexmedetomidine versus midazolam

Shu et al.[18] observed that although there was no statistically significant difference between the groups, the dexmedetomidine

group exhibited a descriptively lower incidence of delirium than the midazolam group. This lack of statistical significance may be attributed to the small sample size studied.[41–47] In contrast, the literature comparing these two drugs in both adult and elderly populations (without isolating the elderly) consistently shows that dexmedetomidine has a protective effect against delirium, while midazolam is associated with a higher incidence of this outcome.

Further supporting this, Pasin et al.[43] systematic review and meta-analysis of 14 randomized clinical trials involving 3,029 adult patients found that dexmedetomidine significantly reduced the occurrence of delirium, agitation, and confusion compared to the control groups (P = 0.03, 95% CI, RR = 0.68, interval 0.49–0.96). Although this meta-analysis did not exclusively focus on elderly patients, the evidence strongly suggests that dexmedetomidine may be beneficial in reducing these adverse outcomes.

Given the findings of Shu et al.[18] and the broader literature, it is evident that larger and more targeted studies specifically focusing on the elderly population are necessary. These studies should have sufficient sample sizes to reduce random errors and enhance the reliability of the conclusions.[48] Such research is crucial to fill the current gap in the literature and provide more precise guidance on the use of sedatives, such as dexmedetomidine, in elderly patients, ultimately leading to improved clinical outcomes in this vulnerable group.

Propofol versus ketamine

The comparison between propofol and ketamine, as explored by Siripoonyothai and Sindhvananda,[15] did not yield conclusive results owing to wide confidence intervals and potential sample size limitations. The observed trends suggest a higher incidence of delirium with propofol; however, the variability in the data underscores the need for more robust trials to definitively establish the comparative risks of these sedatives. Moreover, there is a lack of consensus on the impact of ketamine on delirium in both adult and elderly populations, as evidenced by Shurtleff et al.,[49] further emphasizing the need for comprehensive research to clarify its effects across different age groups.

Final considerations

The high heterogeneity across the included studies due to differences in population demographics, sedative regimens, and outcome measurements precluded a meta-analysis. However, despite these variations, the pooled data provided valuable insights into the relationship between sedoanalgesics and delirium. Notably, significant gaps in the literature were identified, including the absence of studies comparing fentanyl with other sedatives and the lack of research on drug combinations, such as propofol and midazolam, propofol and ketamine, or midazolam and ketamine. These deficiencies, particularly in older adults, underscore the urgent need for comprehensive studies to evaluate these factors. Such research is essential for developing more effective and tailored sedation strategies in ICU settings and for providing conclusive and detailed evidence regarding the comparative efficacy and safety profiles of these drugs.

Strengths and limitations

This review aimed to synthesize data from clinical trials available in the literature since 2000 on the incidence of delirium and its relationship with the use of sedoanalgesics in elderly ICU patients. The methodology used is detailed to allow for replication in this study. This review maintains a high scientific standard by adhering to all the Cochrane recommendations. The extraction of descriptive and statistical data enabled a broader assessment of the included studies.

The methodology, restricted to clinical trials focusing on the elderly, has limited the availability of relevant literature for analysis. To compensate for this limitation, literature on the impact of these drugs on the general adult population is included in the discussion. Although this may result in less specific conclusions for the elderly, the combined approach underscores the need for more research dedicated to this age group to avoid inappropriate generalizations between studies of different populations.

Additionally, the deliberate exclusion of studies comparing drug use with placebo aimed to maintain a focus on the comparative analysis of different pharmacological therapies employed in hospital settings. This decision seeks to better understand the current practices and therapeutic options available for sedoanalgesia among elderly populations.

This systematic review did not identify randomized clinical trials conducted in Brazil that met the inclusion criteria. Consequently, we also included studies conducted in other countries, such as Thailand, China, Canada, and South Korea, that explored strategies for sedoanalgesia in elderly patients in ICU settings and employed the same pharmacological agents widely used in Brazilian intensive care practice. This approach enabled the synthesis of relevant evidence for clinical practice despite contextual differences. Nevertheless, we highlight the need for future studies to evaluate sedoanalgesia protocols within the Brazilian context, considering local specificities, and complementing the international experience presented in this review regarding delirium outcomes in elderly patients.

CONCLUSION

This study highlights the complex relationship between sedative use and the occurrence of delirium in elderly ICU patients, emphasizing that advanced age is a significant risk factor for delirium. Despite the varying results, dexmedetomidine appears to be potentially more beneficial than propofol and midazolam. The limitations of the studies in the literature underscore the need for more

comprehensive and standardized future research. The variability in sedative dosages and administration methods further highlights the importance of additional clinical trials to establish optimized sedation practices that minimize the risk of delirium, thereby improving care and outcomes in this vulnerable population.

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Sleep quality and levels of stress, anxiety, and depression in patients treated with homeopathy: a prospective study in the Brazilian public healthcare service

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ABSTRACT

BACKGROUND: Chronic noncommunicable diseases (NCDs) have a multifactorial etiology and are associated with psychosocial factors, such as stress, anxiety, and depression. Sleep quality also influences general health and is associated with obesity and NCDs. Homeopathy, as a medical specialty, is effective in managing these conditions because of its comprehensive approach to individuals.

OBJECTIVE: To evaluate the influence of homeopathic treatment on sleep quality and levels of stress, anxiety, and depression.

DESIGN AND SETTING: Observational, longitudinal, and prospective study on individuals over 18 years of age with homeopathic medical follow-up for 6 months in the public healthcare service of Guarulhos, São Paulo.

METHODS: Participants were evaluated initially (T0) and after 3 (T1) and 6 months (T2) using validated questionnaires (Pittsburgh Sleep Quality Index and the Depression Anxiety and Stress Scale), following all ethical precepts. The scores were compared over time and correlated with each other ($P < 0.05$).

RESULTS: The mean patient age was 49 years. Initially, 81% of the participants had sleep disorders and severe or extremely severe levels of stress (33.78%), anxiety (28.38%), and depression (27.03%). A total of 26 patients were present at the three evaluation points, which were included as the participants of the study. Homeopathic treatment significantly improved sleep quality and reduced stress, anxiety, and depression. Sleep quality and anxiety were strongly ($r = 0.53$, $P = 0.005$) and weakly ($r = 0.25$, $P = 0.021$) correlated with stress, respectively.

CONCLUSION: In the short term, homeopathic treatment had a positive impact on the sample, suggesting that this therapy can be used to prevent NCDs.

INTRODUCTION

Currently, the main causes of mortality and high healthcare costs worldwide are chronic noncommunicable diseases (NCDs), which are characterized by multiple etiologies, many risk factors, long latency periods, prolonged courses, non-infectious origins, deficiencies, and functional disabilities.[1,2]

According to the World Health Organization (WHO), NCDs, including cardiovascular diseases, neoplasms, chronic respiratory diseases, and diabetes mellitus, are the main causes of mortality and high healthcare costs globally.[3] Factors such as unhealthy lifestyles, diet, insufficient physical activity, tobacco and alcohol consumption, and psychosocial factors, including high levels of anxiety, stress, and depression, are crucial determinants in the pathogenesis of these diseases.[1,4]

Sleep quality is fundamental to general health and is directly associated with the incidence of obesity and several chronic diseases.[5] Inadequate sleep can aggravate mental health conditions like stress and depression, creating a vicious cycle that worsens NCDs.[6] Improving sleep quality and reducing symptoms of stress, anxiety, and depression are essential for the prevention and control of NCDs.[5,6]

Homeopathy, a medical specialty with a comprehensive approach to the individual, considers the complexity and individual needs of each patient and is particularly effective in managing multifactorial conditions such as NCDs. It addresses all physical, emotional, mental, and behavioral signs and symptoms with the aim of promoting the integral state of balance of the organism.[7,8] Thus, it contributes to the prevention and control of NCDs and can consequently help

reduce mortality and healthcare costs associated with these diseases. Furthermore, the homeopathic approach is recognized and legitimized by the National Policy on Integrative and Complementary Practices (PNPIC) as a viable and accessible option for the general population and is offered in Brazilian public healthcare services.[9]

Considering the above, the objective of this study was to evaluate the influence of homeopathic treatment on the quality of sleep and levels of stress, anxiety, and depression in patients treated by the public healthcare service in the city of Guarulhos, São Paulo.

METHODS

This was an observational, longitudinal, and prospective study carried out with patients over 18 years of age, regardless of gender, who began homeopathic medical follow-up from June 21, 2022, to January 31, 2023, in two healthcare services in the city of Guarulhos. Convenience sampling was performed based on the inclusion criteria.

In addition to routine homeopathic appointments, which consisted of homeopathic anamnesis, diagnosis of the situation presented by the individual, prescription of homeopathic medicine, and guidance regarding lifestyle habits, specific and validated questionnaires were also applied for the studied variables in the first appointment and in the follow-up appointments at 3 and 6 months after the initial assessment.

Only patients treated by the same homeopathic doctor in the two healthcare services in the city that offered homeopathic care were considered for inclusion in the study. This doctor was the main study researcher who conducted the questionnaires at all times during the evaluation. The individuals had homeopathic medical follow-up appointments for 6 months, with an assessment of their evolution at three time points: T0, time zero (first appointment); T1, time one (3 months of follow-up); and T2, time two (6 months of follow-up).

For sleep analysis, the Pittsburgh Sleep Quality Index (PSQI) was applied.[10–12] This questionnaire consists of 19 items grouped into seven components, each scored on a scale from 0–3. The scores of the seven components were added together to obtain an overall PSQI score ranging from 0 to 21. Scores of 0–4 indicate good sleep quality, 5–10 indicate poor sleep quality, and > 10 indicate sleep disorders.

The patient's emotional state was assessed using the Depression Anxiety and Stress Scale, short version of 21 items (Depression Anxiety and Stress Scale: DASS-21).[13] The DASS-21 is composed of a set of three Likert-type subscales (depression, anxiety, and stress). Each subscale consists of seven items designed to assess the emotional states regarding depression, anxiety, and stress. Individuals were asked to answer questions based on the week prior to the assessment. Four response possibilities of severity or frequency were provided, organized on a scale of 0–3 points, with the results obtained by adding up the responses to the items that make up each of the three subscales.[14,15] According to the final score per subscale, an individual's level of stress, anxiety, and depression was assessed at that particular moment, as shown in **Table 1**.

It is worth mentioning that at T1 and T2, patients were asked whether they used any other medication and whether they sought out any form of treatment or other therapies due to issues related to anxiety, stress, discouragement, sadness, or problems with sleep during the study period, with the aim of ensuring that there had not been any stimulus of this nature since the beginning of the evaluation. If positive, the individual was excluded from the final analysis.

Individuals took part in the research after signing a Free and Informed Consent Form containing all study information in a clear and detailed manner. Data collection began only after approval from the Research Ethics Committee of Universidade Santo Amaro (Unisa) under Opinion 5.469.720.

Analysis of variance (ANOVA) was applied to compare the scores at the initial time (T0) and at 3 and 6 months after the start of the homeopathic treatment (T1 and T2, respectively), with reference to sleep quality and levels of stress, anxiety, and depression in the studied individuals. Pearson's correlation was performed to evaluate the degree and direction of the linear relationship between sleep quality and stress, depression, and anxiety scores, considering 0.05 or 5% for the rejection level of the null hypothesis.

RESULTS

Initially, 74 patients were evaluated, the majority of whom were women (89.19%) aged between 35 and 63 years (average 49 ± 13.97 years). At T0, 81% of patients had a change in their normal sleep pattern (poor sleep or sleep disorder), and a significant

Table 1. Score interpretation determined by each subscale after applying the Depression Anxiety and Stress Scale, short version of 21 items (DASS-21)

Score	Stress level
0–10	Normal (N)
11–18	Low (L)
19–26	Moderate (M)
27–34	Severe (S)
35–42	Extremely severe (ES)
Score	**Anxiety level**
0–6	Normal (N)
7–9	Low (L)
10–14	Moderate (M)
15–19	Severe (S)
20–42	Extremely severe (ES)
Score	**Depression level**
0–9	Normal (N)
10–12	Low (L)
13–20	Moderate (M)
21–27	Severe (S)
28–42	Extremely severe (ES)

proportion had severe or extremely severe levels of stress, anxiety, and depression (33,78%, 28,38% and 27,03%, respectively).

Of the 74 patients evaluated initially, 26 returned in 3 (T1) and 6 (T2) months (**Figure 1**), making these individuals the focus of our study.

In **Figure 2**, the scores obtained by applying the questionnaires at the first appointment, at 3 (T1) and 6 months (T2) after the start of the homeopathic treatment were compared regarding sleep quality and the levels of stress, anxiety, and depression in the 26 patients who were present at the time of the three assessments.

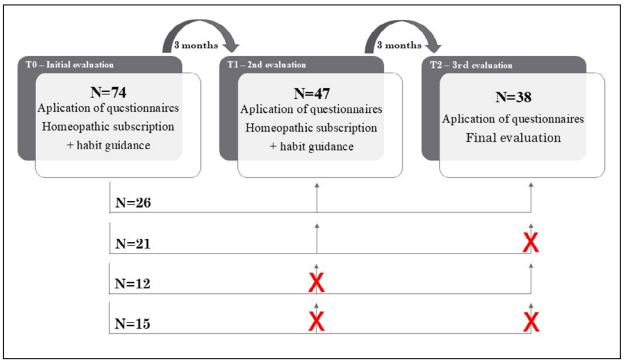
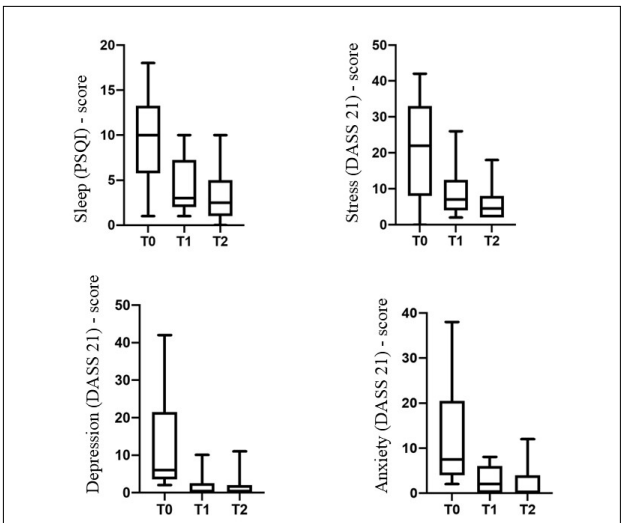


Figure 1. Sample loss during the observation of patients' evolution after the start of homeopathic treatment in the public healthcare service of Guarulhos (SP).



Comparison of sleep quality (PSQI; P < 0,001*#) and stress levels (P < 0,002*#), anxiety (P < 0,024*#) and depression (P < 0,035*#) between different evaluation moments (first appointment [T0] and after 3 months [T1] and 6 months [T2] of this) of individuals who started homeopathic treatment in the public healthcare service of Guarulhos (SP) from June 2022 to January 2023. ANOVA, statistical significance, P < 0.005. * Comparison between T0 and T1; # Comparison between T0 and T2. PSQI, Pittsburgh Sleep Quality Index; DASS21, Depression Anxiety and Stress Scale, short version of 21 items.

Figure 2. Positive impact of treatment on sleep quality, stress level, anxiety and depression.

Table 2 shows the correlation of sleep quality (poor or sleep disorder) with stress, anxiety, and depression levels after 6 months of homeopathic treatment (T2). There was a strong positive Pearson's Correlation (r = 0,53/P = 0,005*) between sleep changes and anxiety, and a weak correlation (r = 0.25/P = 0.021*) between changes in sleep disorders and stress level.

DISCUSSION

The importance of sleep duration and quality of health is widely evidenced in studies that have found an association between poor sleep quality and the appearance of cardiovascular diseases (CVDs) and metabolic, respiratory, mental, and musculoskeletal diseases.[16] While some studies have identified the impacts of morbidities on sleep quality,[17,18] others suggest that sleep deficiency and disorders can develop pathological processes and lead to diseases. Evidence in this regard is consistent with that of CVDs.[16,19,20]

In this study, the observation of poor sleep or sleep disorders among the patients during their first appointment was noteworthy, and this finding was a risk factor for NCDs in the studied population. During the initial assessment, a significant proportion of the individuals experienced severe or extremely severe levels of stress, anxiety, and depression. Because these conditions are involved in the pathogenesis and incidence of NCDs,[21] especially those related to CVDs, it is presupposed that this situation is another risk factor for NCDs in this sample.

In recent decades, epidemiological studies have demonstrated strong evidence of an association between depression and CVDs.[22] The cardiotoxic effects of depressive symptoms have been consistently observed, which is why it is important to invest in strategies to prevent this emotional state, in the same way that stressful situations must be tackled, as there is evidence that daily exposure to chronic stress or severe psychological trauma can also increase the risk of developing and dying from CVDs.[22,23]

Stress is associated with a greater risk of hypertension, acute myocardial infarction, arrhythmogenesis, and heart failure.[21,22]

Table 2. Correlation between sleep quality and levels of stress, depression, and anxiety of individuals attended by the public healthcare service in Guarulhos (SP) after 6 months of homeopathic treatment (T2)

Variable (score at T2)	Mean ± SD	Sleep quality (score at T2)	r	P
Level of depression	1,3 ± 0,9	3,6 ± 2,8	0,03	0,878
Level of anxiety	2,4 ± 2,1	3,6 ± 2,8	0,53	0,005*
Level of stress	6,2 ± 4,9	3,6 ± 2,8	0,25	0,021*

Pearson's Correlation Test. * Statistical significance P < 0.005.

This is because changes occur in the body in response to chronic stress experienced daily owing to biological mechanisms that may be responsible for elevated hypothalamic-pituitary-adrenal axis activity, reactivity of the autonomic nervous system, inflammation, oxidative stress, and endothelial dysfunction, which may be associated with the development of cerebrovascular diseases and CVDs.[22,23]

Likewise, anxiety or anxiety disorders can influence the onset or progression of CVDs, due, for example, to the fact that anxiety is associated with unhealthy behaviors, such as tobacco consumption, excessive alcohol intake, lower physical activity, and poor diet, which increase the risk of CVDs.[24] In the same way as chronic stress, the organism reacts to the stimulus caused by anxiety through the excessive activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, increasing the release of plasma catecholamines, resulting in endothelial damage, ultimately leading to atherosclerosis, coronary artery disease and possible acute coronary events, making it important to identify these risk factors and develop mechanisms for their prevention.[21–24]

The homeopathic approach to mental conditions is well documented in literature, which meets the need to use tools that help in the psycho-emotional balance of individuals, avoiding the development of situations that further compromise their health.[25] To exemplify the role of homeopathy in this context, we can mention the study carried out in 2008 that reports a series of clinical cases of depression treated exclusively with homeopathy at the Outpatient Clinic of Homeopathy and Depression of the public healthcare service in Jundiaí, São Paulo, showing a therapeutic response, with a reduction of more than 50% in depression scores in 93% of patients after seven weeks of treatment, on average, suggesting that homeopathy can be a therapeutic alternative in the treatment of depression.[24]

In 2010, Giorgi and collaborators[26] showed that homeopathic treatment resulted in a higher rate of anxiety reduction after 90 days of treatment compared to conventional anxiolytics, in addition to no side effects, which occurred with allopathic medicines traditionally used to control anxiety. Two groups were analyzed: one group was treated with diazepam (benzodiazepine) and the other with homeopathic medicine, with a greater reduction in anxiety in the group treated with homeopathy. Zepeda-Quiroz et al.[25] also showed an excellent response in the management of anxiety and depressive disorders with homeopathy, concluding that there is a comparable and even better effect than conventional treatment, with fewer undesirable reactions.

Considering these harmful effects arising from the treatment of anxiety and depression disorders through the use of conventional medications, Grimaldi-Bensouda et al.[27] concluded, after comparing the use of conventional psychotropic drugs, the regular use of homeopathic medicines alone, and the mixed use of these two types of medicine among patients seeking care for anxiety and depression disorders, that in addition to homeopathy with the possibility of helping with the rebound effect of these drugs, patients treated with homeopathy, exclusively or in combination, were less likely to use psychotropic drugs over 12 months compared to those treated conventionally, and the rate of clinical improvement was higher for the group treated exclusively with homeopathy than for those treated with conventional treatment.

In this study, comparing the scores obtained by applying the questionnaires at the first appointment and 3 and 6 months after the start of homeopathic treatment with regard to the quality of sleep and the levels of stress, anxiety, and depression, a statistically significant improvement was observed in these four variables after 6 months of homeopathic treatment (**Figure 2**).

Data of the correlation of sleep quality with the level of stress, anxiety, and depression (**Table 2**) show that both stress and anxiety, to a greater extent, interfere with the quality of sleep, which, in a way, also corroborates epidemiological studies that show that sleep disorders, particularly insomnia, affect approximately 50% of individuals with anxiety.[28]

It is important to highlight that the treatment was not only aimed at complaints regarding sleep and/or emotional state, as the choice of the most appropriate homeopathic medicine for each individual case followed the Law of Similars, which is one of the laws that rule homeopathy, considering the individual's totality of presented symptoms, which is another principle of medical rationality.

The results described here could be even more significant if the study time is longer and the number of individuals evaluated is greater. The absence of the 74 individuals initially assessed after six months may have compromised the representativeness of the sample and the robustness of the conclusions.

The fact that questionnaires can be considered long and may have made the consultation convenient for the patient and for the doctor who administered the questionnaires, and recall bias can all be seen as potential limitations of this study.

The homeopathic care offered in just two locations of the city (difficult to access for many residents) may have contributed significantly to absenteeism as well as economic conditions, both in terms of the patients' ability to travel to care locations and in the purchase of homeopathic medicines, representing a financial barrier that may have affected adherence to treatment and, consequently, the results of the study.

Due to these considerations, difficulties were observed in the municipality in relation to both geographic and economic accessibility. Furthermore, the centralization of homeopathic care in just two healthcare services in a large municipality (with an area of 319,19 km^2) and the non-availability of homeopathic medicines free of charge are still negative aspects of this scenario, which compromises and hinders the effectiveness of homeopathic treatment.[29,30]

Based on the acquired results, homeopathic treatment may help prevent risk factors for NCDs, as the improvement in sleep quality and levels of stress, anxiety, and depression was evident and significant after 6 months of individualized homeopathic medical follow-up in the studied population.

CONCLUSION

Homeopathic treatment had a positive impact on the studied population, with improvements in sleep quality and levels of stress, anxiety, and depression in a short period (3–6 months), suggesting that this therapy could be used as a prevention strategy for NCDs.

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Prognostic value of chemotherapy response score in advanced ovarian cancer: a single-center retrospective analysis

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ABSTRACT

BACKGROUND: The chemotherapy response score (CRS) is a histopathological tool used to assess the tumor response in patients with high-grade serous ovarian carcinoma (HGSC) undergoing neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS).

DESIGN AND SETTING: This single-center retrospective study was conducted at the Faculty of Medicine at Istanbul University. The study included patients treated between January 1, 2010, and December 31, 2017 at a tertiary care hospital specializing in gynecologic oncology.

OBJECTIVES: This study aimed to evaluate the prognostic significance of omental and adnexal CRS in predicting overall survival (OS) and disease-free survival (DFS) in patients with advanced HGSC undergoing NACT followed by IDS.

METHODS: Data from 79 patients with advanced HGSC treated with NACT followed by IDS between 2010 and 2017 were analyzed. CRS was applied to both omental and adnexal samples, and its association with OS and DFS was evaluated. Statistical analyses were performed using univariate and multivariate methods with a significance level of $P < 0.05$.

RESULTS: Omental CRS 1-2 was identified as an independent predictor of decreased OS (hazard ratio 2.69; 95% confidence interval 1.26–5.76, $P = 0.010$), whereas adnexal CRS 1-2 did not significantly impact DFS or OS in multivariate analysis. Patients with omental CRS 3 had superior outcomes, with a 5-year OS rate of 72%, compared to 30.8% in the CRS 1–2 group. The median DFS of the CRS 1–2 group was 19 months, whereas that of the CRS 3 group was 35 months ($P = 0.005$).

CONCLUSIONS: Omental CRS is a strong independent predictor of OS in patients with advanced HGSC, whereas adnexal CRS has limited prognostic value. CRS should be considered in clinical practice to guide treatment decisions, and further research is warranted to refine its use by using molecular and radiological markers.

INTRODUCTION

Although not the most common, ovarian cancer is the deadliest gynecological malignancy. The World Health Organization reports that approximately 225,500 new cases are diagnosed annually, and 140,200 deaths occur, making it the seventh most prevalent and eighth leading cause of cancer-related deaths among women globally.[1,2] Approximately 80% of cases are diagnosed at an advanced stage, with high-grade serous carcinoma (HGSC) being the most common histological type.[3,4]

Surgery, often combined with chemotherapy, either as neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) or primary debulking surgery (PDS) followed by adjuvant chemotherapy, remains the cornerstone of treatment for advanced-stage ovarian cancer. The use of NACT and IDS has increased in recent years because of favorable results from two randomized phase III trials, which showed similar disease-free survival (DFS) and overall survival (OS) with lower surgical morbidity and mortality rates compared to those undergoing PDS.[5,6]

Another advantage of NACT followed by IDS is that it can provide an opportunity for future prognostic risk assessment through histopathological evaluation of the tumor response to chemotherapy. Böhm et al.[7] developed the chemotherapy response score (CRS), which is a simple and reproducible scoring system based on post-therapy evaluation of the tumor architecture and microenvironment at the omental site. They demonstrated that CRS was significantly correlated with DFS, whereas the results for OS were mixed.

Böhm et al.[7] proposed a simplified three-tier system: CRS 1, minimal tumor response; CRS 2, moderate tumor response with easily identifiable residual neoplastic foci; and CRS 3, complete or near-complete response with no residual neoplastic cells or minimal irregularly scattered tumor cells up to 2 mm in maximum size. This three-tiered scoring system demonstrated a significant prognostic difference between the CRS 1–2 and CRS 3 groups and improved interobserver reproducibility. Consequently, the three-tiered CRS has been incorporated into the International Collaboration on Cancer Reporting (ICCR) and College of American Pathologists (CAP) guidelines for the histopathologic reporting of ovarian carcinoma.[7,8] Currently, the ESGO-ESMO-ESP consensus conference recommendations on ovarian cancer state that CRS performed during IDS on an omental (preferred) or adnexal specimen provides valuable prognostic information and is thus recommended.[9]

OBJECTIVE

This study aimed to validate the prognostic role of the CRS system in a cohort of patients from a clinic that has been an ESGO-accredited advanced ovarian cancer surgery center since 2018.

METHODS

Study design

The study protocol was reviewed and approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee at Istanbul University (approval number: 2024/2413). All the patients provided informed consent for the use of their medical information upon admission. All surgeries were performed by gynecologic oncologists.

This study was a retrospective analysis, and the sample size was determined based on the available data from patients who met the inclusion criteria within the defined study period (January 1, 2010, to December 31, 2017). No prospective sample size calculations were performed. The retrospective nature of the study allowed us to include all eligible patients, which improved the generalizability of the findings to this patient population.

Study population

This study reviewed women with a postoperative histopathological diagnosis of advanced HGSC, treated between January 1, 2010, and December 31, 2017. Selection for NACT at our center was determined by a multidisciplinary tumor board after standardized preoperative staging using whole-abdomen magnetic resonance imaging and fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography. NACT was favored when complete or optimal cytoreduction was deemed unlikely based on objective imaging findings, including involvement or encasement of the superior mesenteric artery; multiple hepatic parenchymal metastases; involvement of the pancreatic head or body; infiltration of the hepatic hilum; extra-abdominal metastases (cerebral, pulmonary, osseous, or diffuse pleural carcinomatosis); or diffuse miliary carcinomatosis of the small-bowel serosa where resection would be expected to risk short-bowel syndrome. Patient-related factors also prompted NACT when medically unfit status was present, particularly Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 or significant comorbidities precluding extensive cytoreduction. Surgical pathology reports and/or clinical records were reviewed for each case to identify patients who received neoadjuvant platinum-based chemotherapy with carboplatin and paclitaxel. In this cohort, 141 women underwent NACT before undergoing IDS. Because the use of CRS has been validated and recommended only for HGSC, all other epithelial ovarian cancer histotypes were initially excluded from the present study. Patients with synchronous malignancies, incomplete clinicopathological records, and those who did not undergo optimal cytoreductive surgery were excluded. Women with platinum-refractory diseases were excluded from the study. The study sequence is illustrated in **Figure 1**.

Germline or somatic BRCA 1/2 status was not routinely obtained during the study period because of local reimbursement policies; therefore, genetic data were not systematically collected and were not included in the analyses.

Pathology review

The ICCR issued guidelines on reporting serous ovarian cancer, advising the inclusion of a 3-point scoring system described by Böhm et al.[7] as the standard for the assessment of tumor regression following NACT.

All available hematoxylin and eosin stained slides from the surgical specimens that were diagnosed as HGSC in the Pathology Department of Istanbul Faculty of Medicine were re-evaluated by three pathologists (S.Ö, A.B, S.B), including an expert gynecologic pathologist (S.Ö). Each slide representing the omentum and adnexa was scored independently by pathologists according to a three-tier system. The summary of the scoring system proposed by Böhm et al. is as follows: Score 1: No or minimal tumor response (mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci); Score 2: Partial tumor response (both tumor groups and regression-associated fibroinflammatory changes are easily identifiable); Score 3: Complete or near-complete response (mainly regression, with few irregularly scattered individual tumor cells or cell groups, all measuring < 2 mm, or no residual tumor identified).[7] The cases that did not receive the same score from all three pathologists were evaluated together, and a consensus was established for outcome analysis.

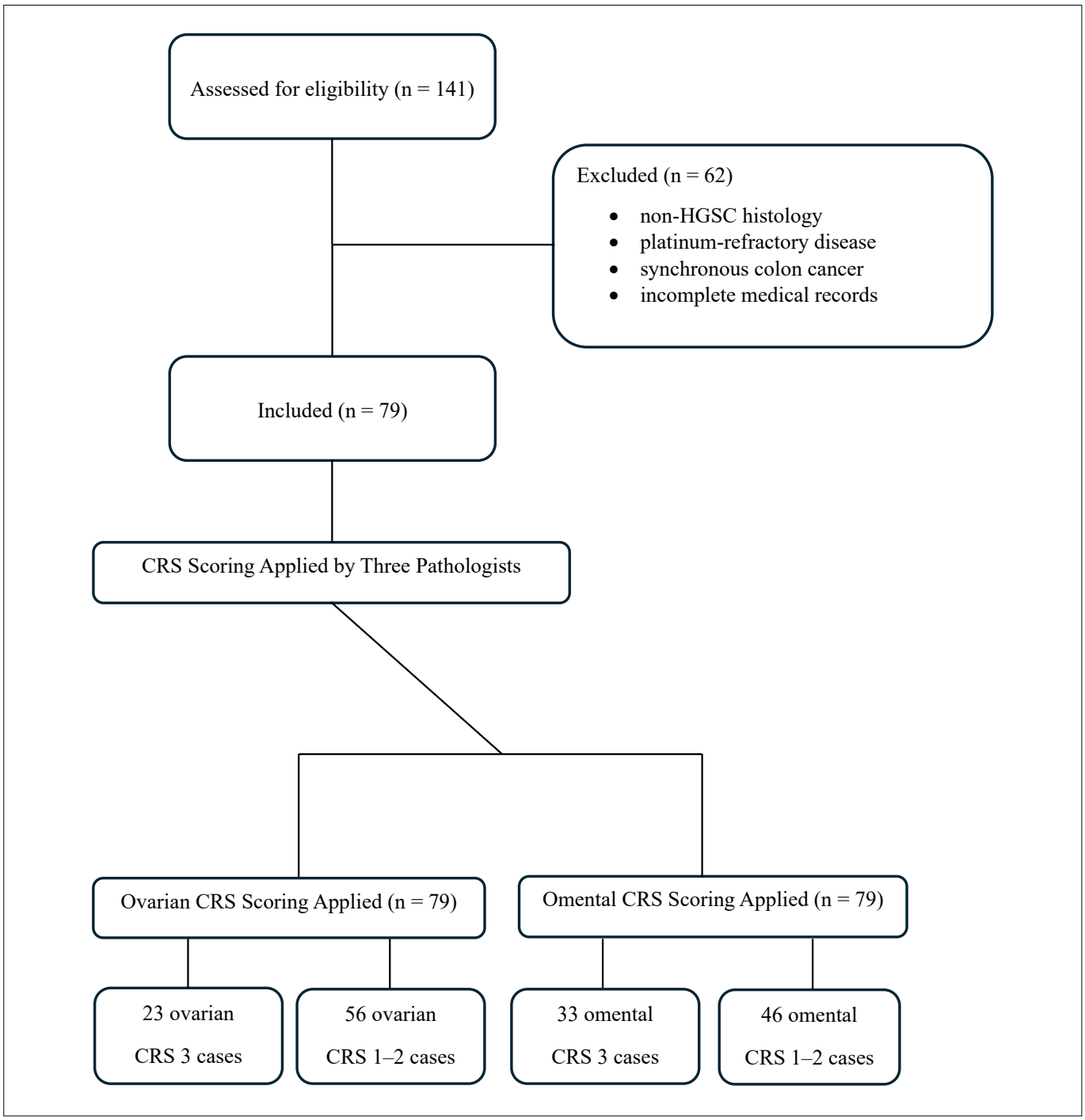

Figure 1. Flow diagram of the study.

Statistical analysis

Patient data, including age, disease stage, histology, CA-125 levels at diagnosis and completion of NACT, and residual tumors after IDS, were collected from computerized medical records. The level of CA-125 reduction attributable to NACT was defined as the difference between the highest pretreatment and pre-surgical CA-125 measurements. The survival status of patients was determined as alive or dead at the time of the last follow-up. This was confirmed by performing a Social Security Death Index search for all study participants with recorded deaths. After initial diagnosis, recurrence was defined as documentation of metastasis with serum CA-125 measurement and imaging techniques after a DFS ≥ 3 months. DFS was defined as the time from surgery to the first identification of recurrence by radiological

imaging and serum CA-125 measurement or death from any cause, whichever occurred first, or the date of the last contact for patients who remained alive without recurrent disease. OS was calculated as the period between the initial diagnosis of HGSC and the date of death or last contact. The surviving patients were censored at the last follow-up. Survival analysis was based on the Kaplan–Meier method, and the results were compared using a log-rank test. The chi-square test and Student's t-test for unpaired data were used for statistical analysis. Cox regression analysis was used to determine the factors affecting survival, presented as hazard ratios (HRs) and 95% confidence intervals (95% CI), unadjusted or adjusted for all factors. All variables with a p value < 0.05 in univariate analysis were included in the multivariate analysis. All statistical analyses were performed using SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

RESULTS

A total of 62 patients were excluded because of non-HGSC histology, platinum-refractory disease, synchronous colon cancer, or incomplete medical records. **Table 1** shows a comparison of the baseline characteristics of the 79 patients included in this study. Twenty-three adnexal CRS 3 cases were compared with 56 adnexal CRS 1–2 cases. Age, menopausal status, pre-NACT CA-125 levels, post-NACT CA-125 levels, percentage of CA-125 drop, stage, presence of ascites at surgery, number of NACT cycles, and recurrence rates were similar between the groups. The time to chemotherapy after IDS (47 days vs. 30 days, respectively) and median follow-up (72 months versus 48.50 months, respectively) were significantly longer in adnexal CRS 3 cases than in adnexal CRS 1–2 cases. Patients with adnexal CRS 3 were more likely to have a high omental CRS than that of those with adnexal CRS 1–2 (69.6% and 30.4%, respectively).

For the entire cohort, univariate analysis revealed that adnexa CRS 1-2 ($P = 0.016$) and Omental CRS 1–2 ($P = 0.007$) were significant predictors of decreased DFS. Multivariate analysis showed that none was determined to be an independent risk factor for decreased DFS (**Table 2**).

In the entire cohort, univariate analysis revealed that the presence of ascites ($P = 0.002$), adnexa CRS 1–2 ($P = 0.011$), and omental CRS 1–2 ($P < 0.001$) were significant factors for decreased OS. At the end of multivariate analysis, only omental CRS 1–2 (HR 2.69; 95% CI 1.26–5.76, $P = 0.010$) was identified as independent predictor of decreased OS as shown in **Table 3**.

Because only omental CRS was identified as an independent predictor of decreased OS, log-rank analysis was performed to assess the impact of omental CRS on survival. The median DFS for women with omental CRS 1–2 was 19 months (95% CI

Table 1. Baseline characteristics of the study cohort.

	Adnexal CRS 1–2 (n = 56)	Adnexal CRS 3 (n = 23)	P
Age, years (median)	60 (38–80)	58 (39–78)	0.927
Menopausal status			
Pre-menopause	16 (28.6%)	4 (17.4%)	0.299
Post-menopause	49 (71.4%)	19 (82.6%)	
Pre NACT CA 125 levels (median, IU/ml)	1192.50 (259–10858)	980 (270–8169)	0.553
Post NACT CA 125 levels (median, IU/ml)	32.50 (7–450)	29 (3–355)	0.524
Percent of CA 125 drop %, (median)	96.32 (71.76–99.53)	96.53 (81.08–99.86)	0.742
Stage			
Stage IIIC	47 (83.9%)	17 (73.9%)	0.35
Stage IV	9 (16.1%)	6 (16.1%)	
Presence of ascites at surgery, n			
Present	23 (41.1%)	8 (34.8%)	0.603
Absent	33 (58.9%)	15 (65.2%)	
NACT cycles			
3–4	23 (41.1%)	10 (43.5%)	0.844
> 4	33 (58.9%)	13 (56.5%)	
Time to chemotherapy after interval debulking surgery, days (median)	30 (15-75)	47 (24-95)	**0.001**
Omental CRS			
Score 1–2	39 (69.6%)	7 (30.4%)	**0.001**
Score 3	17 (30.4%)	16 (69.6%)	
Recurrence, N			
Present	43 (76.8%)	16 (69.6%)	0.503
Absent	13 (23.2%)	7 (30.4%)	
Median follow up, months	48.50 (15–104)	72 (24–129)	**0.014**

CA 125, cancer antigen 125; NACT, neoadjuvant chemotherapy; CRS, chemotherapy response score.

Table 2. Univariate and multivariate analyses for prognostic factors for disease-free survival in the entire cohort.

Variable	Univariate analysis HR 95% CI P	Multivariate analysis HR 95% CI P
Age	0.912	
Menopausal status (post-menopause vs. pre-menopause)	0.73	
Pre NACT CA 125 levels	0.443	
Post NACT CA 125 levels	0.564	
Percent of CA 125 drop	0.878	
Stage (IV vs. IIIC)	0.69	
Ascites (present vs. absent)	0.168	0.755
NACT cycles (> 4 vs. 3–4)	0.059	0.074
Time to chemotherapy after interval debulking surgery	0.079	0.46
Adnexa CRS (1–2 vs. 3)	**2.10 1.14–3.86 0.016**	0.096
Omental CRS (1–2 vs. 3)	**2.08 1.22–3.54 0.007**	0.112

HR, hazard ratio; CI, confidence interval; LN, lymph node.

Table 3. Univariate and multivariate analyses for prognostic factors for overall survival in the entire cohort.

Variable	Univariate analysis HR 95% CI P	Multivariate analysis HR 95% CI P
Age	0.992	
Menopausal status (post-menopause vs. pre-menopause)	0.756	
Pre NACT CA 125 levels	0.423	
Post NACT CA 125 levels	0.675	
Percent of CA 125 drop	0.363	
Stage (IV vs. IIIC)	0.69	
Ascites (present vs. absent)	**2.59 1.43–4.70 0.002**	1.86 1–3.48 0.05
NACT cycles (> 4 vs. 3–4)	0.153	0.198
Time to chemotherapy after interval debulking surgery	0.213	0.838
Adnexa CRS (1–2 vs. 3)	**2.62 1.24–5.53 0.011**	0.182
Omental CRS (1–2 vs. 3)	**3.56 1.77–7.16 < 0.001**	**2.69 1.26–5.76 0.01**

HR, hazard ratio; CI, confidence interval; LN, lymph node.

14.8–23.1, standard error [SE] 2.11) compared to 35 months (95% CI 13.1–56.8, SE 11.14) in the omental CRS 3 group (P = 0.005) (**Figure 2**). The 5-year DFS rate was higher in the omental CRS 3 group (38.5% in the omental CRS 3 group vs. 14.9% in the omental CRS 1–2 group). The median OS of the omental CRS 1–2 group was 46 months (95% CI 38.8–53.1, SE 3.67), while the median OS of the omental CRS 3 group was not yet reached (P < 0.001) (**Figure 3**). When the 5-year OS rates were examined; superior outcomes were observed in omental CRS 3 cases than in omental CRS 1–2 cases (72% versus 30.8%, respectively).

At the time of reporting, of the 33 women in the omental CRS 3 group, 12 (36,4%) had died, whereas 21 (63,6%) were alive. The corresponding figures were 35 (76,1%) and 11 (23,9%) in omental CRS Groups 1 and 2, respectively.

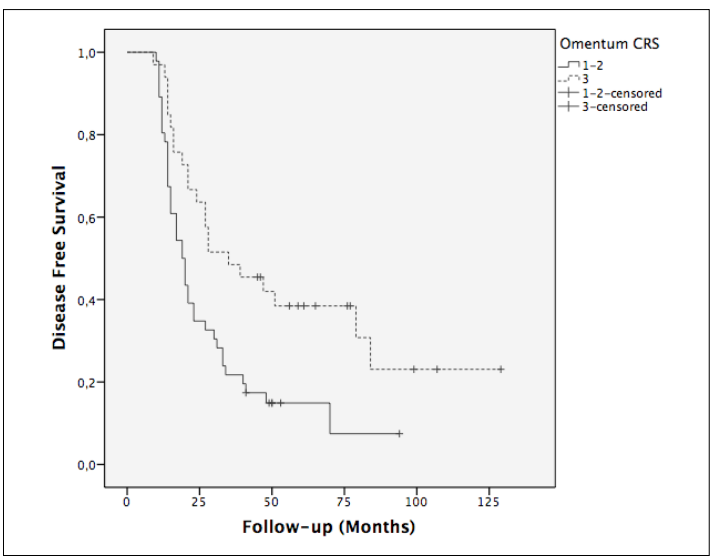

Figure 2. Kaplan–Meier curve showing disease-free survival based on omental CRS (1–2 versus 3).

DISCUSSION

In this study, we investigated the prognostic significance of CRS in patients with advanced-stage HGSC, with a particular focus on the differences in outcomes between adnexal and omental CRS. Our results demonstrated that omental CRS 1–2 was a significant independent predictor of decreased OS, whereas neither adnexal CRS 1–2 nor omental CRS 1–2 were independent predictors of decreased DFS in multivariate analysis. These findings reinforce the

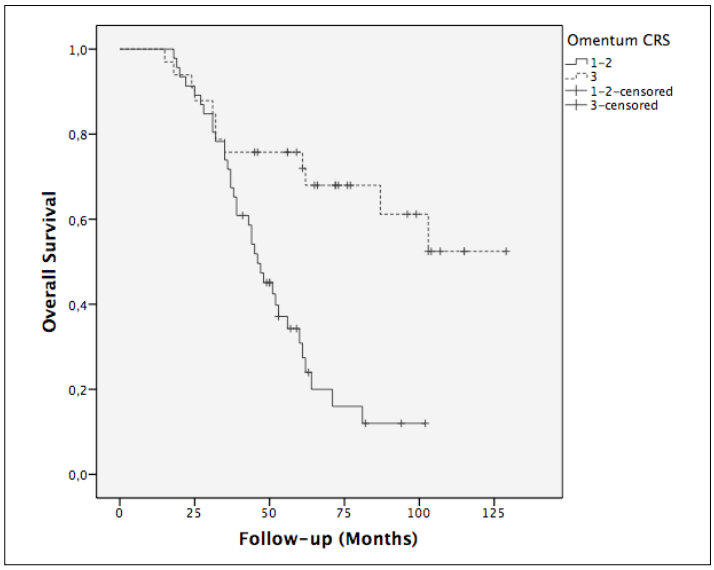

Figure 3. Kaplan–Meier curve showing overall survival based on omental CRS (1–2 versus 3).

importance of the omental CRS as a critical site for assessing chemotherapy response in HGSC.

The CRS system, initially developed and validated by Böhm et al.,[7] has been accepted as a reliable and reproducible marker for evaluating histopathologic response to NACT.[7] Although the importance of the CRS score is emphasized in the ESGO-ESMO-ESP consensus conference recommendations on ovarian cancer, the relationship between the CRS score and DFS and OS outcomes is inconsistent in studies in the literature (**Table 4**).[7,9–18] Our findings align with previous studies that established the prognostic value of CRS, particularly in the omentum, where higher CRS 3 is associated with significantly improved OS compared to that with CRS 1–2.[14–16,19] In line with the work of Santoro et al., we found that omental CRS 3 patients had superior survival outcomes, with a 5-year OS rate of 72%, compared to 30.8% in omental CRS 1–2 patients.[14]

One of the notable findings in our study was the absence of prognostic significance for adnexal CRS 1–2 in the multivariate

Table 4. Summary of studies evaluating CRS in relation to DFS and OS.

Study	Sample Size	Scoring System	Period of Enrollment	Results	HR, P
Böhm et al.[7]	62 (TC)	Six-tier omental and adnexal	2009–2014	A significantly improved DFS for mCRS 4–5 compared with mCRS 2–3 (Adjusting for age, stage, and residual disease) A significant OS benefit for mCRS 4–5	mCRS 2–3 vs. mCRS 4–5: Median survival, 11.3 vs. 32.1 months; aHR, 6.13; 95% CI, 2.13–17.68; P < 0.001 aHR, 24.97; 95% CI, 2.35–265.6; P < 0.01 P = 0.59 P = 0.12
	71 (VC)	Three-tier omental	1999–2012	Adnexal scores not associated with DFS or OS Improved DFS for mCRS3 compared with mCRS 1–2 Nonsignificant trend for OS	mCRS 1–2 vs. mCRS 3: median survival, 12 vs. 18 months; aHR, 3.60; 95% CI, 1.69–7.66; P < 0.001 mCRS 1–2 vs. 3: median survival, 28.4 vs. 45.1 months; aHR, 1.81; 95% CI, 0.79–4.14; P = 0.15
Lee et al.[10]	110	Three-tier omental and adnexal	2006–2014	İmproved DFS for mCRS3 compared with mCRS 1–2 No significant difference in OS between mCRS 1–2 and mCRS 3 Adnexal CRS showed no significant association with outcome	The median DFS of CRS 1–2 vs. CRS 3 14.5 vs. 18.6 months, P = 0.016 P = 0.902 P = 0.317
Coghlan et al.[11]	71	Three-tier omental	2010–2014	İmproved DFS for mCRS3 compared with mCRS 1–2 No significant association for OS	HR, 2; 95% CI, 1.06–3.78; P = 0.032; median DFS, 26 months (mCRS 3) vs 16 months (mCRS 1–2) mCRS 1–2 vs. 3: HR, 1.57; 95% CI, 0.68–3.65; P = 0.291

Continue...

Table 4. Continuation.

Study	Sample Size	Scoring System	Period of Enrollment	Results	HR, P
Ditzel et al.[12]	68 (omental n = 65) (adnexal n = 59)	Three-tier omental and adnexal	2005–2012	İmproved DFS for AT mCRS3 compared with AT mCRS 1–2 No significant association with OS between AT mCRS 1–2 and AT mCRS3 Adnexal CRS showed no significant association with DFS and OS	AT mCRS 1–2 vs. 3; HR, 0.526; 95% CI, 0.306–0.904; P = 0.020 Median DFS, 10.9 vs. 18.9 months AT mCRS 1–2 vs. 3; HR, 0.608; 95% CI, 0.319–1.16; P = 0.131 Median DFS, 39.4 vs. 53.6 months P = 0.062 P = 0.055
Michaan et al.[13]	132	Three-tier omental and adnexal	2009–2014	Significantly longer DFS for mCRS 3, with no significant OS difference A significantly longer DFS but not OS for patients with ovCRS 3 Significantly longer DFS for cCRS 3, with no significant OS difference	P < 0.01 Median DFS = 7.5, 12, and 17 months for ovCRS 1, 2, and 3, P = 0.012 P < 0.01
Santaro et al.[14]	161	Three-tier omental and adnexal	2014–2017	Worsened DFS with mCRS1 and ovCRS1-2, Compared with mCRS3 and ovCRS3 Worsened OS with mCRS1 compared with mCRS3	mCRS1 vs. mCRS3: HR, 2.17; 95% CI, 1.41–3.33; P = 0.0004 mCRS2 vs. mCRS3: HR, 2.34; 95% CI, 1.35–4.04; P = 0.002 ovCRS1 vs. ovCRS3: HR, 2.53; 95% CI, 1.50–4.24; P = 0.001 ovCRS2 vs. ovCRS3: HR, 1.90; 95% CI, 1.08–3.37; P = 0.03 mCRS1 vs. mCRS3: HR, 2.75; 95% CI, 1.29–5.86; P = 0.01
Böhm et al.[15]	80	Three-tier omental	2009–2015	İmproved DFS with mCRS3 compared with mCRS2 İmproved OS with mCRS3 compared with mCRS2	Median DFS 13 months (mCRS 2) and 27 months (mCRS 3); HR 0.39 (95% CI 0.21–0.7), P = 0.002 (Adjusted for age, stage, and debulking status) Median OS was 31 months (mCRS 2) and 66 months (mCRS 3); HR 0.17 (95% CI 0.07–0.44), P = 0.0002 (Adjusted for age, stage, and debulking status)
Zorzato et al.[16]	108	Three-tier omental	2007–2017	İmproved DFS with mCRS3 compared with mCRS1 İmproved OS with mCRS3 compared with mCRS1	HR 0.35; 95% CI, 0.2–0.61; P < 0.0001 HR 0.38; 95% CI, 0.18–0.82; P = 0.013

Continue...

Table 4. Continuation.

Study	Sample Size	Scoring System	Period of Enrollment	Results	HR, P
Lawson et al.[17]	158	Three-tier omental and adnexal	2013–2018	İmproved DFS with mCRS3 compared with mCRS 1–2 No association with OS between mCRS1-2 and mCRS3 İmproved DFS for ovCRS3 compared with ovCRS1-2 No association with OS between ovCRS1-2 and ovCRS3 İmproved DFS for cCRS3 compared with cCRS 1–2 No association with OS between cCRS 1–2 and cCRS3	HR 0.612, 95% CI: 0.378–0.989, P = 0.045 HR 0.96, 95% CI: 0.495–1.865, P = 0.91 HR 0.535, 95% CI: 0.297–0.963, P = 0.037 HR 0.734, 95% CI: 0.327–1.645, P = 0.45 HR 0.364, 95% CI: 0.148–0.896, P = 0.028 HR 0.66, 95% CI: 0.205–2.131, P = 0.49
Liontos et al.[18]	48	Three-tier omental and adnexal	2011–2016	Median DFS was associated with CRS at omentum CRS at omentum was not associated with OS Adnexal scores not associated with DFS or OS	Median DFS was: 10.3 months (mCRS 1) (95% CI 7.4–15.7), 14 months (mCRS 2) (95% CI 12.2–22.9), 18.7 months (mCRS 3) (95% CI 13.5–31.3), P = 0.003 Median OS was: 29.3 months (mCRS 1) (95% CI 10.9-NR), 32 months (mCRS 2) (95% CI 16.4–46.9) 42.3 months (mCRS 3) (95% CI 30.8-NR), P = 0.182 P = 0.115 P = 0.428

DFS, disease-free survival; OS, overall survival; CRS, chemotherapy response score; mCRS, omental chemotherapy response score; ovCRS, ovarian chemotherapy response score; cCRS, combined chemotherapy response score; HR, hazard ratio; TC, test cohort; VC, validation cohort; AT, after traiing.

analysis for DFS, which contrasts with some reports suggesting the relevance of adnexal CRS in predicting survival outcomes.[13,14,17,20] This discrepancy may stem from inherent challenges in scoring adnexal disease, as previously noted in the literature. The adnexal site is often less reproducible, and adnexal CRS has shown variable prognostic significance across studies.[21] Further research is needed to standardize the assessment of CRS in adnexal tissue and to determine its potential utility in guiding clinical decision-making.[19]

Our study further underscores the critical role of the omental CRS in predicting long-term survival. As demonstrated in a meta-analysis by Cohen et al.,[19] omental CRS 3 remains a strong independent predictor of both DFS and OS. In our cohort, the median OS for the omental CRS 1–2 group was 46 months (95% CI 38.8–53.1, SE 3.67), indicating a shorter survival compared to that of the omental CRS 3 group, for which the median OS was not yet reached. These results suggest that the extent of response to chemotherapy in the omentum can serve as a valuable surrogate for predicting treatment response and overall prognosis.

Despite the strengths of our study, including its well-characterized cohort and comprehensive follow-up data, some limitations must be acknowledged. The relatively small sample size may have limited the generalizability of our findings. Moreover, the exclusion of patients with platinum-refractory disease may have introduced selection bias, potentially underestimating the true prognostic significance of CRS. In addition, the absence of BRCA 1/2 data due to local reimbursement constraints during the study period precluded analysis of the potential influence of BRCA status on CRS distribution and survival outcomes.

CONCLUSION

Our study highlights the prognostic value of omental CRS in advanced epithelial ovarian cancer, particularly for predicting OS. The use of CRS, especially in omental tissues, should be further explored as a clinical tool to guide therapeutic decision-making and follow-up strategies. Future research should focus on refining the CRS system and integrating it with molecular and radiological markers to enhance its prognostic utility.

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Impact of thyroid volume on serum ionized calcium and PTH levels after total thyroidectomy

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ABSTRACT

BACKGROUND: The relationship between thyroid gland volume and hypoparathyroidism after total thyroidectomy remains controversial.

OBJECTIVE: To evaluate thyroid gland mass as a risk factor for hypoparathyroidism after total thyroidectomy.

DESIGN AND SETTING: A Retrospective cross-sectional observational study was conducted at Centro Universitário Lusíada (UNILUS), Santos/SP, Brazil.

METHODS: Patients undergoing total thyroidectomy between January 2022 and September 2023 were retrospectively evaluated for serum levels of ionized calcium and ultrasensitive parathyroid hormone (PTH), measured preoperatively and 30–60 days postoperatively, and thyroid mass, obtained by weighing the specimen.

RESULTS: A total of 174 patients were evaluated, with a predominance of women (89.7%), a median age of 50.5 years, and a median goiter volume of 36.3 mL. A reduction in both PTH and ionized calcium levels was observed in the postoperative period compared with the preoperative period ($P < 0.05$). No significant changes were observed in PTH levels and volume ($P = 0.481$). For calcium, there was a tendency towards an association between volume measurements and its change between the pre- and postoperative periods, which was marginally significant ($P = 0.051$).

CONCLUSION: There was a marginal association between volume and changes in pre- and postoperative ionized calcium levels, but no significant association with pre- and postoperative PTH measurements.

INTRODUCTION

Total thyroidectomy is the most common endocrine surgery. Postoperative hypocalcemia is the most common complication of total thyroidectomy. Its incidence varies from 30% to 60%, and most patients recover completely. It is not always associated with accompanying symptoms and, in most cases, resolves in less than 6 months. The incidence of transient and permanent hypocalcemia varies from 19% to 38% and 0% to 3%, respectively.[1]

The mechanisms include direct injury, devascularization, venous drainage obstruction, or inadvertent excision of the parathyroid glands. A systematic review identified predictors of transient and permanent hypocalcemia after total thyroidectomy. Independent clinical predictors of permanent hypocalcemia included reoperation for bleeding, identification of fewer than two parathyroid glands, Graves' disease, and larger thyroid volume on multivariate analysis.[2] However, in another meta-analysis, the significant predictors of transient hypocalcemia were younger age, female sex, parathyroid autotransplantation, inadvertent parathyroid excision, Graves' disease, thyroid cancer, central compartment clearance, severe preoperative vitamin D deficiency, and low postoperative 24-hour parathyroid hormone (PTH) levels.[3]

However, the effect of thyroid gland volume as a risk factor for hypoparathyroidism remains controversial. In a prospective review of 121 patients undergoing total thyroidectomy, the thyroid volume was calculated preoperatively using ultrasound and by weighing the surgical specimen. When analyzing the incidence of complications based on the quartiles of gland weight and volume, no significant difference was observed in the incidence of transient or permanent hypoparathyroidism.[4]

OBJECTIVES

This study aimed to evaluate thyroid gland mass as a risk factor for decreased ionized calcium and PTH levels following total thyroidectomy.

METHODS

This study was approved by the Institutional Review Board of Fundação Lusíada, Centro Universitário Lusíada (UNILUS) under number 857/2023, on August 4th, 2023. All patients who underwent total thyroidectomy between January 2022 and September 2023 were retrospectively evaluated by reviewing their medical records. The inclusion criteria were as follows: patients aged > 18 years who underwent total thyroidectomy. Exclusion criteria included any type of cervical clearance, altered calcium homeostasis, prior surgical or radiotherapy treatment in the cervical region, and incomplete medical records.

All patients underwent surgery by the same surgical team using a standardized technique. The following aspects were evaluated: biochemical monitoring of mineral homeostasis by measuring ionized calcium and ultrasensitive PTH levels, assessed preoperatively and between 30 and 60 days postoperatively, and the mass of the thyroid gland obtained by weighing the specimen after removal.

Statistical analyses were performed as follows: frequency distribution was used to describe categorical variables, and measures of central tendency (mean and median) and variability (range and standard deviation) were used for numerical variables. The Wilcoxon signed-rank test was used to assess the association between preoperative and postoperative measurements of numerical variables (PTH and ionized calcium). We calculated the difference between postoperative and preoperative measurements of ionized calcium and PTH levels, creating a categorical variable (increase or decrease), and the association between the numerical variable and this new categorical variable was evaluated using the non-parametric Mann–Whitney U test. The Shapiro-Wilk test was used to check the normality of the numerical data for variables (PTH, ionized calcium, and volume). A significant level of 5% was used for all statistical tests. The statistical software STATA version 18 (StataCorp LLC, College Station, Texas, United States) was used for all the statistical analyses.[5]

RESULTS

A total of 174 patients were evaluated, with a predominance of women (89.7%), a median age of 50.5 years, and a median goiter volume of 36.3 mL (**Table 1**).

When comparing preoperative and postoperative PTH measurements, it was noted that the postoperative measurements were lower, and this difference was statistically significant (P < 0.001). The same was observed for ionized calcium; although there was a slight reduction, the difference was statistically significant (P = 0.0004) (**Table 2**).

To assess the association between preoperative and postoperative measurements in relation to volume, we created a difference variable by subtracting preoperative measurements from postoperative measurements (**Table 3**).

Table 1. Distribution of the study population according to demographic and clinical variables (n = 174)

Variable	Category / Measures	Freq. (%) / Measures
Gender	Female	156 (89,7)
	Male	18 (10,3)
Age	Range	18 – 83
	Median	50,5
	Mean (SD)	50,8 (13,8)
Volume (cm)	Range	4,7 – 495
	Median	36,3
	Mean(SD)	49,0 (49,4)

SD = standard deviation.

Table 2. Association between preoperative and postoperative measurements of parathyroid hormone and ionized calcium (n = 174)

Variable	Measures	Pré	Post	P value
PTH	Range	15 – 105	5,1 – 85	< 0,001
	Median	44,3	39,6	
	Mean (SD)	46,3 (17,8)	41,1 (14,9)	
Ionized Calcium	Range	1,00 – 1,35	0,88 – 1,38	0,0004
	Median	1,23	1,22	
	Mean (SD)	1,23 (0,05)	1,22 (0,07)	

PTH = parathyroid hormone; SD = standard deviation; P value obtained using the paired Wilcoxon signed-rank test.

Table 3. Distribution of differences between postoperative and preoperative parathyroid hormone and ionized calcium levels

Variable	Measures	Measures		Difference (Post- minus pre-)
		Pre	Post	
PTH	Range	15 – 105	5,1 – 85	(-73,0) – 35,2
	Median	44,3	39,6	(-3,0)
	Mean (SD)	46,3 (17,8)	41,1 (14,9)	(-5,2) (13,5)
Ionized Calcium	Range	1,00 – 1,35	0,88 – 1,38	(-0,41) – 0,34
	Median	1,23	1,22	(-0,02)
	Mean (SD)	1,23 (0,05)	1,22 (0,07)	(-0,015) (0,072)

PTH = parathyroid hormone; SD = standard deviation.

An increase was considered when the difference was positive, that is, the postoperative measurement was greater than the preoperative measurement, and a decrease was considered when the difference was negative, or the postoperative measurement was lower than the preoperative measurement. The volumes were then compared in relation to the increase or decrease in pre- and postoperative values. It is observed that the volumes were larger when the postoperative PTH difference was greater than the preoperative, with a median volume of 37.7 cm compared to a median volume of 35.1 cm when the postoperative PTH was lower than the preoperative, but no significant difference was observed (P = 0.481) (**Table 4**).

The volumes were larger when the postoperative calcium difference was greater than the preoperative value, with a median volume of 40.4 mL compared with a median volume of 31.3 mL

when the postoperative ionized calcium was lower than the preoperative value. However, a tendency towards an association was observed between the volume and ionized calcium (post- and preoperative), which was marginally significant (P = 0.051) (**Table 5**).

Therefore, it was found that the preoperative and postoperative measurements were different, with a decrease in the postoperative values compared to the preoperative values for both PTH and ionized calcium (P < 0.05). However, no significant changes were observed in the increase or decrease in PTH levels or volume (P > 0.05). For calcium, there was a tendency towards an association between volume measurements and the decrease or increase between the preoperative and postoperative periods, which was marginally significant (P = 0.051).

DISCUSSION

Total thyroidectomy can lead to hypoparathyroidism, the most frequent complication, with an incidence of permanent hypoparathyroidism of 4.11% at 6 months postoperatively.[6] Low postoperative levels of PTH and the resulting hypocalcemia may be associated with the accidental removal of one or more glands or compromised blood supply. Postoperative hypocalcemia can present with serious complications and cause significant morbidity.[7]

Monitoring postoperative PTH and serum calcium levels is the best predictor for identifying hypoparathyroidism and treating the resulting symptom, hypocalcemia; however, there is no consensus on the timing, patient selection, and cutoff points for PTH levels.[7] A meta-analysis included 23 studies. Twelve significant risk factors for postoperative hypocalcemia were identified: hypoparathyroidism, OR = 5.58; total thyroidectomy, OR = 3.59; hypomagnesemia, OR = 2.85; preoperative vitamin D deficiency, OR = 2.32; female gender, OR = 1.49; thyroid malignancy, OR = 1.85; thyroiditis, OR = 1.48; sub-sternal multinodular goiter, OR = 1.70; parathyroidectomy, OR = 1.58; central compartment neck dissection, OR = 1.17; modified radical neck dissection, OR = 1.57; and central neck dissection, OR = 1.54.[8] Another metanalysis showed significant predictors of transient hypocalcemia: younger age, female gender, parathyroid autotransplantation, inadvertent parathyroid excision, Graves' disease, thyroid cancer, central compartment dissection, preoperative vitamin D deficiency, and low PTH levels 24 hours postoperatively.[3] None of these studies considered gland volume as a possible risk factor.

Table 4. Association between volume and differences in parathyroid hormone measurements (difference = post- minus pre)

Variable	Measures	Difference in PTH (Post-Pre)		P value
		Reduction	Increase	
Volume (cm)	n	112	62	0,481
	Range	4,7 – 280,0	9,3 – 495,0	
	Median	35,1	37,7	
	Mean (SD)	46,2 (37,8)	54,0 (65,4)	

SD = standard deviation; PTH = parathyroid hormone; P value obtained using the Mann-Whitney U test.

Table 5. Association between volume and differences in ionized calcium measurements (difference = post minus preoperative), excluding one case in which the postoperative measurement was equal to the preoperative measurement (n = 173)

Variable	Measures	Difference in ionized calcium (Post- minus pre-)		P value
		Reduction	Increase	
Volume (cm)	n	102	71	0,051
	Range	9 – 126,2	4,7 – 495	
	Median	31,3	40,4	
	Mean (SD)	42,0 (28,1)	59,6 (68,4)	

SD = standard deviation; P value obtained using the Mann-Whitney U test.

A total of 2,937 patients were evaluated for hypoparathyroidism. The rates of transient and permanent hypoparathyroidism were 25.20% and 2.69%, respectively. A large thyroid mass was designated in cases in which the gland volume represented a difficulty that interfered with the regular progress of the procedure. This was a subjective criterion based on the surgeon's perception and experience. The occurrence of transient hypoparathyroidism was independently linked to thyroid weight (P < 0.001).[9] In a group of 227 patients, 74 (32.6%) had goiters with a weight exceeding 250 g (massive goiter), and 153 (67.4%) had masses between 100 g and 250 g. Patients with massive goiters had higher rates of transient hypoparathyroidism (41.9% vs. 25.5%).[10]

Thyroid volume was calculated preoperatively using ultrasonography and, together with the final specimen weight, correlated with the development of postoperative complications in 131 patients undergoing total thyroidectomy. When analyzing the incidence of complications based on the quartiles of weight and glandular volume, no significant differences were observed in the incidence of transient or permanent hypoparathyroidism in any of the groups. No fewer parathyroid glands were visualized intraoperatively in patients with larger thyroid glands, nor was there an increased number of glands accidentally removed during surgery. In fact, a certain protective trend was observed regarding the number of visualized glands and gland size, and the correlation between thyroid volume and accidental gland removal, with no significant differences.[4]

There is controversy in the literature regarding the possible influence of thyroid gland masses on hypoparathyroidism after total thyroidectomy. In our study, the operation led to a decrease in ionized calcium levels, but no significant association was observed with the mass. Regarding PTH levels, the observed decrease in the PTH levels was not statistically significant.

CONCLUSION

There may have been an association between volume and changes in preoperative and postoperative ionized calcium measurements, although the obtained value (P = 0.051) was considered marginally significant. No significant association was observed between pre- and postoperative PTH measurements.

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Insights for the treatment of depression in the Brazilian Public Health System

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Dear Editor,

A recent article by Cleare et al.[1] provides valuable insights into the pharmacological management of treatment-resistant depression (TRD), particularly regarding the use of adjunctive agents. Over a 52-week follow-up period, the study found that participants treated with adjunctive quetiapine exhibited significantly lower depressive symptom severity, reduced healthcare costs, greater gains in Quality-Adjusted Life Years (QALYs), and no differences in discontinuation rates compared to those receiving lithium. These findings raise important considerations for the treatment of depressive episodes within the Brazilian Public Health System (Sistema Único de Saúde, SUS), especially in cases of TRD.

Taking the state of São Paulo as an example, which is the most populous in Brazil, with over 44 million inhabitants, representing approximately 20% of the country's population, the estimated prevalence of depression in primary care is around 25%.[2] Most of these patients receive treatment through the public health system, where certain medications are provided free of charge with a medical prescription. Available treatments for depressive episodes include selective serotonin reuptake inhibitors (fluoxetine and sertraline), tricyclic antidepressants (clomipramine, amitriptyline, nortriptyline, and imipramine), and, in some regions, the serotonin and norepinephrine reuptake inhibitor venlafaxine.

Regarding evidence-based adjunctive strategies,[3] only lithium, risperidone, and immediate-release methylphenidate are currently available. Quetiapine, along with other atypical antipsychotics, is included in the formulary solely for patients diagnosed with bipolar disorder or schizophrenia, consequently making its use in major depressive disorder inaccessible through the public system. Furthermore, given Brazil's socioeconomic landscape, many patients cannot afford the monthly cost of private prescriptions. This is particularly relevant considering that among primary care users, psychiatric diagnoses are more prevalent in individuals with lower income, unemployment, and limited access to education.[2]

In Latin America, Brazil has the highest prevalence of TRD, ultimately affecting nearly 40% of patients with depression, with higher rates observed in public healthcare settings compared to private services.[4] In addition, compared to non-resistant depressive episodes, TRD in Brazil imposes significantly greater costs on the public health system, thus requiring increased resource allocation, including higher hospitalization rates and multiple pharmacological trials, with pharmaceutical expenditures representing the largest proportion of total costs.[5]

Given this scenario and considering that quetiapine is among the most effective adjunctive treatments for TRD,[6] for mental health professionals, particularly those working in the public sector, to advocate for expanding treatment options is crucial. Doing so could improve response and remission rates, enhance patient quality of life, and potentially reduce the long-term financial burden on the healthcare system.

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São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

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São Paulo Medical Journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

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Acknowledgements and funding

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." Any financial support should be acknowledged, always with the funding agency name, and with the protocol number whenever possible. Donation of materials used in the research can and should be acknowledged too.

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At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

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To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

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The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

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Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

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All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

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- level of significance (usually 0.05 or lower);
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Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

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All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

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Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

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Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

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Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

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