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- Impact of a telemedicine center on reducing the carbon footprint for primary health care

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- Adverse reactions to etiological treatment in patients with Chagas disease in the Western Potiguar mesoregion of Brazil

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Organ donation in Brazil: individual autonomy versus family consent

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Brazil has the largest public transplantation system worldwide. Nevertheless, approximately 3,000 people die annually while on the organ waiting list, highlighting the difficulty of balancing the growing demand with the limited donation rate.[1]

The Brazilian Registry of Transplants (Registro Brasileiro de Transplantes – RBT), maintained by the Brazilian Association of Organ Transplantation (Associação Brasileira de Transplante de Órgãos – ABTO), is the primary tool for monitoring donation and transplant activities. In its 2024 report, the RBT found that the potential donor notification rate had reached 71 per million population (pmp), meeting the stipulated target (70 pmp). However, the effective donation rate remained below expectations (27% versus the target of 30%), primarily because of high family refusal (46%). Therefore, the rate of effective donors was 19.2 pmp, a rate lower than that recorded in 2023 (19.9 pmp) and below the projected target for 2024 (21 pmp).[1]

Authorization for organ removal intended for transplantation has consistently provoked intense debate, as it concerns sensitive issues rooted in society's core values and fundamental legal principles, such as human dignity, personality rights, and individual autonomy.[2]

Brazil's legislative evolution illustrates the difficulties in finding an adequate consent model. The first three laws regulating transplantation in Brazil, enacted in 1963, 1968, and 1992, adopted the informed consent model, in which organ removal depended on the explicit consent of the individual during their lifetime or, in its absence, on the authorization of their family members after death.[3–6]

To increase the number of donations and transplantations, Law No. 9,434/1997 was enacted, establishing the presumed consent model, according to which all citizens would be considered donors unless a contrary declaration was registered in official documents.[7,8]

However, the practical application of this measure proved counterproductive, as, instead of increasing the number of donations, it significantly raised refusal rates.[9] Given this scenario, the mandatory aspect was revoked in October 2000.[10] Subsequently, Law No. 10,211/2001 reinstated informed consent, attributing the final decision regarding donation exclusively to the family, even if the donor had expressed their decision during their lifetime.[11]

Mechanisms to reinforce individual autonomy in organ donation have been proposed. One example is the Electronic Authorization for Organ, Tissue, and Part of the Human Body Donation (Autorização Eletrônica de Doação de Órgãos, Tecidos e Partes do Corpo Humano – AEDO), regulated by Provision No. 149/2023 of the National Council of Justice (Conselho Nacional de Justiça – CNJ).[12] This instrument enables any citizen to register, during their lifetime, electronically and free of charge, the intention to donate organs, tissues, and body parts after death. The document is issued free of charge at notary offices, made accessible to authorized physicians, and may be revoked at any time, representing a symbolic and practical advance in registering an individual's will.

This scenario reinforces the importance of discussing new consent models. The Federal Constitution, in Article 199, states that "the law shall provide for the conditions and requirements that facilitate the removal of organs, tissues, and human substances for transplantation purposes."[2] Thus, the legislation regulating the topic has the duty to facilitate the donation process, which Law No. 9,434/1997, in its current form, does not do.[7]

The draft reform of the Civil Code proposed relevant changes in the direction of the constitutional mandate. The proposal amends Article 4 of Law No. 9,434/1997, establishing that "the removal of tissues, organs, and body parts from deceased persons, for transplantations or other therapeutic purposes, shall not require authorization from any family members when the deceased has determined in writing, or has recorded in any of their personal documents, explicit authorization for the donation."[13]

Furthermore, the draft provides for the amendment of Article 14 of the Civil Code, which states that "the gratuitous disposition of one's own body, in whole or in part, after death, is valid for scientific or altruistic purposes. Sole Paragraph. The act of disposition may be freely revoked at any time." In the draft, this article gains an additional paragraph: "§1º – If there is a written disposition by the individual themselves, family authorization is not required, and in its absence, it shall be given according to the order of legitimate succession."[14]

International experiences reinforce the fact that no single consent model can guarantee success. In Spain, where presumed consent has been in force since 1979, a significant increase in postmortem donations occurred only after the creation of the national network of hospital transplant coordinators in 1989.[15]

In various Latin American countries that have adopted presumed consent, there has been no significant effect on donation rates. In the United States, informed consent is associated with high donation rates owing to the strengthening of highly professionalized organ procurement organizations with clear goals.[16]

There are also alternative models that preserve the family's decision but offer additional incentives. One example is the prioritization, on waiting lists, of patients with first-degree relatives who donated organs after death. Thus, family members who must decide on the donation of their deceased relatives' organs would have an additional incentive to approve the donation. This measure, adopted in Israel, resulted in a significant increase in family authorizations.[17]

This debate reinforces the idea that organ donation legislation must align with societal values and effective public policies. Law No. 14,722/2023, which established the National Policy for Awareness and Incentive for Organ and Tissue Donation and Transplantation, emphasizes the importance of public discussion, education, and demystification of the topic.[18] Many family refusals stem from misconceptions, negative experiences in hospital care, or delays in organ procurement.

Therefore, the future of organ donation in Brazil requires not only legislative revisions but also strengthening of the National Transplant System, quality information, and societal engagement. The AEDO and reform of the Civil Code represent relevant advances, but only a balanced combination of respect for individual autonomy, care for families, and social awareness will consolidate the true culture of donation in the country.

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Knee and ankle biomechanics during recovery from primary, secondary, and bilateral anterior cruciate ligament injuries: a quasi-experimental study

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ABSTRACT

BACKGROUND: Anterior cruciate ligament (ACL) tears are common knee injuries with a known but vague association with secondary joint injuries. The extent to which these injuries are preventable remains unclear.

OBJECTIVES: This study aimed to assess the functional differences in knee and ankle dorsiflexion biomechanics with full loading on one leg and to understand whether it could be a key point as a progressive method in ACL reconstruction, considering both legs and three different groups.

DESIGN AND SETTING: A quasi-experimental study of Medical Centers in an outpatient clinic in Portugal

METHODS: The Y balance test (YBT) was used to evaluate and analyze the association between ankle dorsiflexion range of motion (DF-ROM) and knee flexion. DF-ROM and knee flexion were used to compare the deficits between the operated and uninvolved limbs in all three groups (ACL-I, ACL-II, and ACL-III).

RESULTS: Ankle DF-ROM and knee flexion assessed during the YBT were associated with higher knee flexion ROM, identifying individuals who were better prepared for the next phase of the guideline. The study results provide preliminary data for future studies that use prospective longitudinal research and involve large patient populations to establish prognostic biomechanical markers for determining long-term dynamic stability after ACL reconstruction.

CONCLUSIONS: In the three groups with a history of ACL injury, compensations and kinematic asymmetries in dorsal flexion and knee flexion were observed in the operated and control legs both at 6 and 8 weeks of treatment.

INTRODUCTION

Anterior cruciate ligament (ACL) tears are common knee injury with a known but vague association with secondary joint injuries, and the extent to which these injuries are preventable remains unclear.[1-3] ACL injury impairs neuromuscular function putting athletes with ACL injury at a high risk of ACL reinjury and functional asymmetries throughout the recovery process.[1-4] Biomechanical assessment of kinematic changes over time can elucidate responses to neuromuscular intervention and ACL reconstruction (ACLR).[3,5-7]

Patients with ACLR commonly adopt poor movement patterns that potentially place them at an increased risk of reinjury if left untreated.[8,9] Persistent intermember biomechanical asymmetries during walking have been reported at the time of return to physical activity.[4,9,10]

Available ACL rehabilitation protocols in the scientific literature has substantial heterogeneity.[11-19] Movement compensations following ACLR are commonly observed in patients and can be assessed with various techniques.[20,21] Asymmetric functional activities mechanics can persist for years after ACLR despite full recovery of strength and clinically assessed function.[19,22,23] Practice guidelines suggest that the increased risk of future ACL injuries may be attributable to changes in neuromuscular function and biomechanics, such as greater internal rotation of the hip and dynamic valgus of the knee.[23-25] Although asymmetric knee joint mechanics have been associated with the consequent development of post-traumatic osteoarthritis, current clinical interventions have not been successful in fully restoring normal kinematics.[4,25-31]

Several post-ACLR rehabilitation protocols have been proposed to improve muscle strength and knee stability through muscle-strengthening and joint proprioception exercises. The proposed

protocols are mainly based on the biological tissue healing and remodeling timeframes.[23,28]

With the increase in publications available to rehabilitation specialists, a functional and safe progression for athletes needs to be identified to make progress in their postoperative ACLR rehabilitation program, particularly in joint mobility and weight bearing, which need to be controlled in the post-rehabilitation period.[32-34]

This article presents a progression system between 6 and 8 weeks after ACLR, which can form an important aspect of the movement-based retraining process, providing structural and patient autonomy. Although the incidence of ACL injuries in athletes has increased exponentially, no differentiated concern regarding primary, recurrent, or bilateral injuries has been raised. Monitoring knee and ankle function and movement is crucial to ensure safe transition. Changes in movement patterns during weight-bearing are unclear. Therefore, these factors need to be examined in order to identify strategies for preventing secondary ACL injuries after ACLR.

This study presents a novel approach to understanding clinical outcomes, including the ACL, for the first time, and in cases of recurrence. In this study, we investigated this topic and the novelty of the relationship between knee and ankle kinematics at a stage when progressively more body load is applied. We hypothesized that most athletes would not be ready to reach load control in the unipodal tests 6 weeks postoperatively, regardless of whether it was the first knee injury, recurrence, or bilateral injury. Removing crutches prematurely in patients with knee conditions may exacerbate knee kinematic asymmetries; however, their effect remains uncertain.

OBJECTIVE

This study aimed to comprehensively assess deficits in functional movement patterns and dynamic control, as well as side-to-side asymmetries in athletes after ACL, and to compare them with athletes who have suffered a recurrence of ACL injury, as well as with athletes who have suffered bilateral ACL injury.

METHODS

Design and sample

This study was approved by the Bioethics Committee and registered under number NCT06050005 at clinicaltrials.gov. Furthermore, the Consolidated Statement for Reporting Trials (CONSORT) statement and checklists were considered.[35] All procedures followed the principles of the Declaration of Helsinki for Good Clinical Practice and were approved by our Institutional Ethics Committee (Process CE.CSJD/P1.23). The Ethics Committee for Health provided favorable opinions on the implementation of the doctoral project and showed itself available provided support to achieve the proposed research objectives.

This was a three-group quasi-experimental study. Participants were recruited from medical services. The same examiner conducted all tests, and all participants completed the informed consent form.

The testing was performed in a sports medicine laboratory. The sample size was calculated based on pilot data and previous literature.[8,36,37] With 11 participants in each group, we had 80% power ($\alpha = 0.05$) to detect a clinically relevant 50% improvement in knee and ankle-dorsiflexion biomechanics during functional tests. A priori power analysis calculations were based on sagittal plane knee biomechanics and indicated that 36 athletes were needed to detect a medium effect size (0.3) with $\beta = 0.20$ and $\alpha = 0.05$.

A total of 88 volunteers were selected to participate in the study and divided into three groups.

Eighty-eight active participants were identified to participate in this research study and met the inclusion criteria.

The ACL-I group (25.8 ± 9.1 years old) of both sexes (15 women and 29 men) corresponds to the group of individuals who had an ACL injury for the first time. The ACL-II group includes individuals who have re-injured the ACL in the same knee (27.1 ± 7.5 years old) of both sexes (9 women and 16 men). According to this clinical criterion, injury to the same knee will occur after at least 1 year. The ACL-III group includes individuals who had ACL injury bilaterally (30.4 ± 6.8 years old) of both sexes (five females and fourteen males), considering the current injury for the study, but the contralateral leg in the past had the same rehabilitation.

The athletes were aged between 18 and 45 years (median, 12.7 years), participated in sports for > 50 h a year before their first ACL injury, and wanted to return to their pre-injury activity levels. ACLR was performed by the same medical team of experienced orthopedic surgeons, and the athletes participated in postoperative rehabilitation at the same physiotherapy clinic. Strict enrolment criteria were applied to ensure a homogeneous entry level.

Participants were selected after obtaining informed consent and involved specific predefined inclusion and non-inclusion criteria as described below. The participants were nonsmokers, exercised regularly, monitored by a coach/teacher, and did not take any dietary supplements or medications.

The inclusion criteria were as follows: began physiotherapy in the preoperative context and continuation of recovery up to 2 weeks postoperatively; age ≥ 18 years; and participants with previous severe chondral defects were not included in the study, but meniscus repair or meniscectomy performed at the time of ACLR was tolerated.

The exclusion criteria were concomitant bilateral injury with several chondral defects/history of surgery or contralateral

dysfunction; meniscal suture; cartilaginous injury; injury to the medial collateral ligament, lateral collateral ligament, and posterior cruciate ligament; concomitant intra- and extra-articular plastic surgery; complex injury from any accident; complex tibial condyle fracture; rheumatoid arthritis; recent heart disease; intermittent claudication; neuropathies; and cognitive alterations.

Procedure

The eligible participants underwent an initial assessment. All the follow-up evaluations were performed by the same evaluator. The participants' age, sex, body mass index (BMI), injury history, ACL rehabilitation (i.e., self-reported duration), surgical details (i.e., self-reported graft type and meniscal procedures), and previous activity level were obtained at baseline.

For screening, each potential participant's non-weight-bearing dorsiflexion range of motion (DF-ROM) was assessed for both legs, with the participant lying supine on a treatment table. The examiner moved the ankle into plantar flexion and placed it in a subtalar-neutral position by palpation. They passively dorsiflexed the ankle while maintaining a subtalar-neutral position until the point of first resistance. Then, the examiner measured the angle formed by the shaft of the fibula and the lateral midline of the foot using a standard goniometer. This assessment was performed with the subtalar joint in a neutral position to avoid movement compensation at the subtalar and midtarsal joints, and to effectively evaluate talocrural joint motion. Subsequently, the participants were guided to perform knee flexion. If associated pain was present at any time, the ROM count was finalized. After the examiner recorded the ROM measurements, the participants were prepared for motion analysis data collection using the YBT (**Figure 1**).

The evaluation period was divided into two phases: phase I, 6 weeks postoperatively, and phase II, 8 weeks postoperatively. Each phase presents unique clinical considerations and challenges. The ACLR treatment in all athletes began on postoperative day 1. All individuals were provided as much weight as possible to tolerate pain with crutches on postoperative day 1. On the postoperative day 21 (3), the amount of weight bearing increased. Full weight-bearing began in phase I (6 weeks) and was progressively achieved until phase II (8 weeks). The kinematic analysis focused on the operated leg.

Statistical analysis

Statistical analyses were performed using the Prism software (GraphPad Software Inc. Version 10.2.0, Boston, Massachusetts, United States). Data were transferred to the IBM SPSS Statistics 27.0.01.0 package for Windows (Armonk, New York, United States) program and statistically evaluated. Before proceeding with the statistical analysis, controls were made regarding the absence of data entry errors and whether the parameters were within the expected range.

The outcome variables analyzed included the DF-ROM, knee flexion range of motion (ROM), and dynamic balance (anterior reach, posteromedial reach, and posterolateral reach). Noncategorical baseline and outcome data were tested for normal distribution using the Kolmogorov–Smirnov test. Results are expressed as frequencies or as means ± standard deviations (SDs). Group demographics were compared using a one-way analysis of variance (ANOVA). To determine differences between the three groups and time (phase I — pretest and phase II — posttest), a 3 × 2 repeated measures ANOVA was conducted, followed by post hoc comparison. The within-group factor (pretest to posttest) as the main effect of time and the between-group factor as the main effect of group were considered.

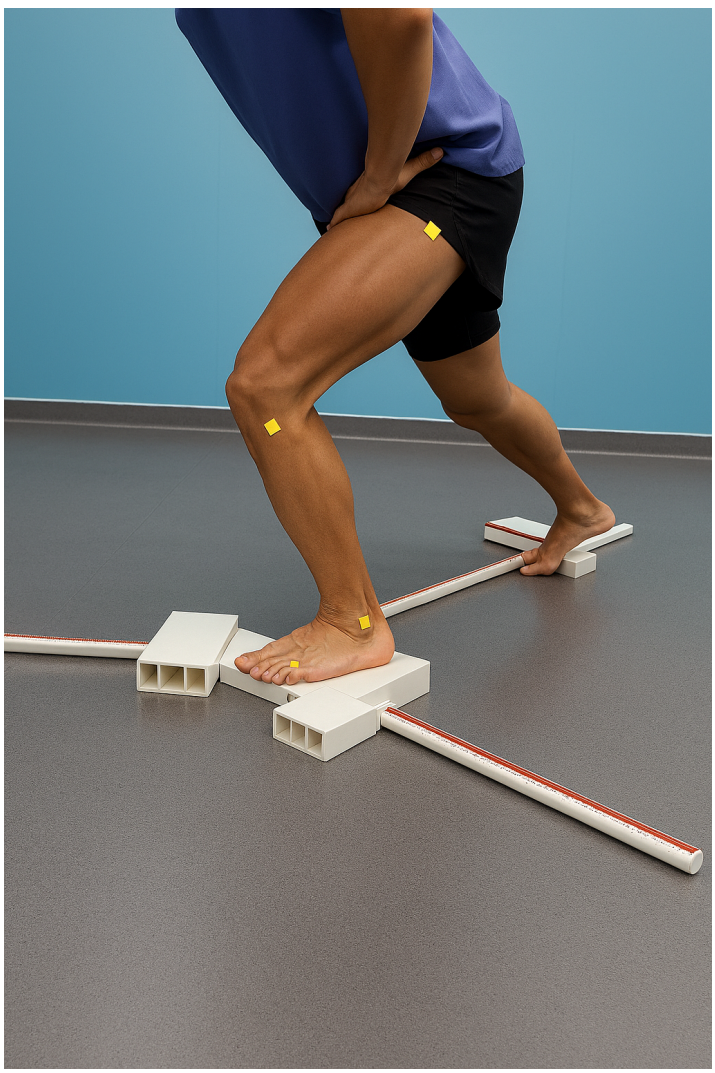

Figure 1. Experimental setup and bone references for range of motion calculations. Participants stand at the center of the equipment and push a plastic piece to the anterior, posteromedial, and posterolateral directions.

RESULTS

A total of 88 patients participated in functional performance tests. Forty-four patients who underwent primary ACL were initially included in this study (ACL — I group). A total of 25 patients were included in the ACL repair group with recurrent lesions (ACL — II group). The remaining 19 patients had bilateral ACL lesions that underwent reconstruction (ACL III group). **Table 1** presents demographic data. For the preoperative program, all participants were physically active, defined as 30 min of physical activity at least three times per week before surgery. The time from injury to surgery ranged from 2 weeks to 2 months (mean = 29.1 days, SD = 17.3, median = 33.5), and was significantly different between the groups (P < 0.001).

At baseline, no significant differences (P > 0.05) in the demographic data was observed among the three intervention groups (**Table 1**): age ([P = 0.173), mass (P = 0.192), height (P = 0.620), BMI (P = 0.551), and years of training before injury (P = 0.082]). The same was valid between the groups at baseline for any of the dependent variables of interest (P < 0.05), indicating that the groups were comparable in terms of their initial anthropometry.

The ankle DF-ROM and knee flexion for each group, along with means and SDs, are represented and related to the distance traveled during the YBT and are presented in **Table 2** for the ACLR leg and **Table 3** for the control leg.

Table 1. Basic data of the population studied

	ACL I group	ACL II group	ACL III group	P value
Age (years)	25.8 ± 9.1	27.1 ± 7.5	30.4 ± 6.9	0.173
Weight (kg)	74.0 ± 15.1	79.4 ± 18.0	68.0 ± 8.1	0.192
Height (cm)	176.0 ± 18.0	172.9 ± 14.8	171.0 ± 11.0	0.620
BMI (kg/m^2)	23.1 ± 2.8	24.8 ± 2.0	22.9 ± 1.8	0.551
Years of training before injury	11.1 ± 4.8	14.6 ± 5.9	17.5 ± 7.0	0.082

ACL = anterior cruciate ligament; BMI = body mass index.

Table 2. Means and standard deviations of dorsal flexion and knee flexion in the Y balance test

Variables ACLR leg	Group	Phase I Pre-test 6 weeks postoperatively Mean ± SD	Phase II Post-test 8 weeks postoperatively Mean ± SD	P value		
				Main effect of time	Main effect of group	Group × time interaction
DF-ROM ANTYBT	**ACL-I group**	40.7 ± 17.9	47.7 ± 12.3	F = 140.142 P < 0.001*	F = 43.233 P < 0.001*	F = 60.609 P < 0.001*
	ACL-II group	43.4 ± 10.1	45.4 ± 15.2			
	ACL-III group	18.1 ± 19.0	39.1 ± 13.8			
DF-ROM POSTLYBT	**ACL-I group**	24.0 ± 12.5	33.3 ± 14.0	F = 99.117 P < 0.001*	F = 20.487 P < 0.001*	F = 36.928 P < 0.001*
	ACL-II group	37.1 ± 17.0	38.2 ± 19.8			
	ACL-III group	30.1 ± 8.8	32.3 ± 8.8			
DF-ROM POSTMYBT	**ACL-I group**	32.8 ± 13.9	31.0 ± 9.5	F = 16.191 P < 0.001*	F = 2.987 P < 0.085	F = 8.222 P < 0.001*
	ACL-II group	27.7 ± 8.8	28.2 ± 9.6			
	ACL-III group	33.1 ± 17.6	35.1 ± 17.3			
KF-ROM ANTYBT	**ACL-I group**	51.8 ± 17.2	52.8 ± 20.3	F = 109.007 P < 0.001*	F = 38.411 P < 0.001*	F = 440.571 P < 0.001*
	ACL-II group	41.8 ± 20.3	50.1 ± 14.4			
	ACL-III group	40.8 ± 21,.2	42.1 ± 8.9			
KF-ROM POSTLYBT	**ACL-I group**	48.7 ± 30.1	59.0 ± 22.5	F = 75.120 P < 0.001*	F = 19.007 P < 0.001*	F = 23.007 P < 0.001*
	ACL-II group	58.8 ± 28.5	58.7 ± 13.1			
	ACL-III group	61.8 ± 7.7	62.2 ± 7.2			
KF-ROM POSTMYBT	**ACL-I group**	58.8 ± 14.4	64.9 ± 14.4	F = 28.142 P < 0.001*	F = 3.930 P < 0.062	F = 10.531 P < 0.001*
	ACL-II group	57.4 ± 14.8	63.7 ± 24.8			
	ACL-III group	57.5 ± 12.3	59.5 ± 10.3			

Values refer to the anterior cruciate ligament reconstructed leg; P < 0.05 indicates a statistically significant difference.
ACL = anterior cruciate ligament; ACLR = anterior cruciate ligament reconstruction; SD = standard deviation; ROM = range of motion; DF = dorsiflexion; KF = knee flexion; ANTYBT = anterior movement in Y balance test; POSMYBT = posteromedial movement in Y balance test; POSTLYBT = posterolateral movement in Y balance test.

Table 3. Means and standard deviations of dorsal flexion and knee flexion in the Y balance test

Variables Control leg	Group	Phase I Pretest 6 weeks postoperatively Mean ± SD	Phase II Posttest 8 weeks postoperatively Mean ± SD	P value		
				Main effect of time	Main effect of group	Group × time interaction
DF-ROM ANTYBT	**ACL-I group**	45.8 ± 11.4	48.6 ± 11.9	F = 74.553 P < 0.001*	F = 6.852 P < 0.004*	F = 14.248 P < 0.001*
	ACL-II group	46.4 ± 9.0	50.3 ± 17.7			
	ACL-III group	40.6 ± 16.8	41.0 ± 17.9			
DF-ROM POSTLYBT	**ACL-I group**	38.4 ± 9.3	35.9 ± 12.3	F = 10.232 P < 0.012	F = 14.032 P < 0.002*	F = 5.102 P < 0.0035*
	ACL-II group	40.6 ± 10.1	40.4 ± 15.2			
	ACL-III group	35.7 ± 15.3	35.7 ± 18.6			
DF-ROM POSTMYBT	**ACL-I group**	33.9 ± 10.6	37.6 ± 14.5	F = 42.743 P < 0.001*	F = 14.553 P < 0.001*	F = 8.383 P < 0.001*
	ACL-II group	43.8 ± 14.1	33.4 ± 14.2			
	ACL-III group	37.5 ± 17.0	37.7 ± 19.0			
KF-ROM ANTYBT	**ACL-I group**	52.7 ± 15.6	56.7 ± 18.1	F = 82.111 P < 0.001*	F = 43.288 P < 0.001*	F = 45.431 P < 0.001*
	ACL-II group	45.8 ± 10.8	53.7 ± 18.8			
	ACL-III group	39.7 ± 27.9	41.7 ± 13.9			
KF-ROM POSTLYBT	**ACL-I group**	54.8 ± 18.1	60.8 ± 10.3	F = 94.077 P < 0.001*	F = 10.084 P < 0.0047*	F = 12.248 P < 0.001*
	ACL-II group	59.4 ± 15.9	60.4 ± 7.9			
	ACL-III group	52.0 ± 17.9	63.0 ± 14.2			
KF-ROM POSTMYBT	**ACL-I group**	60.4 ± 14.8	65.7 ± 17.2	F = 102.825 P < 0.001*	F = 32.003 P < 0.001*	F = 37.561 P < 0.001*
	ACL-II group	53.9 ± 20.0	64.4 ± 13.1			
	ACL-III group	52.3 ± 17.0	60.7 ± 18.0			

The control values in groups I and II refer to the non-operated legs. Group III refers to legs with a history of anterior cruciate ligament injury; P < 0.05, statistically significant difference.

ACL = anterior cruciate ligament; SD = standard deviation; ROM = range of motion; DF = dorsiflexion; KF = knee flexion; ANTYBT = anterior movement in Y balance test; POSMYBT = posteromedial movement in Y balance test; POSTLYBT = posterolateral movement in Y balance test

Significant group × time interaction effects, main effect of time, and main effect of group were observed in all directions (P < 0.05). No significant between-group differences in the posteromedial direction of DF-ROM and knee flexion (ACLR leg) were observed. No significant effect of time on the DF-ROM in the posterolateral direction (control leg) was noted.

At anterior for DF-ROM and knee flexion at ACLR leg (P = 0.001), posterolateral for DF-ROM and knee flexion at ACLR leg (P = 0.001) and posteromedial for differences between phases and group × time interaction significant differences were found between ACL-I and other groups.

Additionally, there were significant differences in the anterior, posteromedial, and posterolateral directions for the DF-ROM and knee flexion for leg control.

DISCUSSION

This study assessed the functional differences with full loading on one leg and aimed to elucidate whether it could be a key factor as a progressive method in ACLR, considering the control leg and the difference in values between the legs and three groups.

Among the athletes in this study, the ACL-I group (n = 44) showed the best kinematic results for both dorsal ankle and knee flexion. At 6 weeks of assessment (phase I), the individuals were not yet ready for unipodal loading, and statistically significant differences were observed between the groups and control leg. The most commonly used criterion for progression in clinical practice is time from surgery, which is derived from the biological healing time. Meanwhile, injury and rehabilitation of a ligament results in a drastic change in its structure and physiology and creates a situation where ligament function is restored by the formation of scar tissue that is biologically and biomechanically inferior to the tissue it replaces.[18,38,39] These findings imply that most participants in our study group were not eligible for unipodal functional exercise. Despite satisfactory results between phases I and II, functional asymmetries still existed between the operated and control legs. Symmetrical exercise is a prerequisite for walking, running, and pivoting sports.[29,40,41] Anticipating recovery timings can be a risk factor for re-injury and can contribute to functional asymmetry at the end of recovery.

Full extension and weight bearing were achieved on the first postoperative day. Early postoperative assessments were performed at 6 and 8 weeks. The hallmark of this phase is enabling athletes to perform basic functional activities until they can tolerate more advanced activities. We consider this one of the positive effects of early rehabilitation and is consistent with the results of other studies.[42-44] Early accelerated rehabilitation characterized by joint mobilization and weight-bearing within 3 days postoperatively should be the mainstream approach in isolated ACL surgeries. When concomitant injuries (meniscal and cartilage) are present, the early rehabilitation phase should be adapted according to medical instructions.[18,34]

Based on this premise, a recent study has reported a compensatory pattern of decreased knee flexion and increased hip flexion angles in athletes after ACLR.[45] All of which could increase the risk of ACL injury. The reason for the reduction in knee flexion angle and dorsal flexion of the ankle remains unclear.[46-49] Some studies have suggested that altered activation or reduced strength of the quadriceps results in a decreased ability to flex the knee during demanding single-leg tasks, whereas others have suggested that the strength of the hamstrings can be reduced.[6,50]

In our study, the change in knee and ankle ROM was statistically significant, which, according to theory, is more protective against injury to the knee joint (i.e., increased flexion); however, we did not report patient outcomes or minimal clinically important differences.[12,16,51] Increasing plantar flexor extensibility and dorsiflexion ROM can help reduce the load on the ACL.[52,53]

Information regarding risk factors for ACL injury vary in the current literature.[51,53,54] Athletes after ACLR with asymmetric ROM in knee and ankle DF may be related to incorrect long-term recovery after ACLR, and loading timings must always be framed.[21,26,27]

In our study, patients who followed a partial-load regimen for up to 6 weeks postoperatively and progressively performed full-load exercises to be fully loaded at 8 weeks had better results. Deficits in amplitude and movement after an injury are well known. However, how these deficits correlate or can be predictors of the stages of evolution or lead to a new injury requires further exploration.

Interventions in a clinical population emphasize the difficulty of balancing the safety of athletes and testing to capture a representative population. Therefore, we implemented strict clinical criteria for study participation. This may also have biased our study cohort by selecting athletes who functioned at a higher baseline level. Adherence in our study was the fact that the athlete completed the 8 weeks of treatment and the pre/post biomechanical testing sessions in order to be included.

Asymmetries in the lower limbs may suggest an increased risk of ACL injury during these maneuvers, and suggesting the implementation of more position-specific ACL prevention programs may be reasonable, as the more dynamic movements associated with central players may develop specific muscles differently than those of wing players.

However, this study has some limitations. First, this study did not test the electromyographic signal characteristics of the patients' electromyographic signals, and strong conclusions were drawn regarding the pattern of muscle activity in patients with ACLR. Second, we investigated interventions in the general population of athletes, which could be a mistake because of the differences between sports. Lastly, patients with limb dominance were excluded from this study.

CONCLUSIONS

In the three groups with a history of ACL injury, compensations and kinematic asymmetries in dorsal flexion and knee flexion were noted in the operated and control legs both at 6 and 8 weeks of treatment.

Asymmetric performance on the YBT was considered valid for predicting the evaluation and control of the risk of lower limb injuries. This study provides new information on how clinical measurements of the DF-ROM and knee flexion are associated with biomechanical variables suggested as risk factors for ACL injury. Functional testing should be performed before treatment progression.

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Effects of music and conversation on pain and anxiety levels during transrectal ultrasound-guided prostate biopsy: a randomized-controlled prospective study

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ABSTRACT

BACKGROUND: Prostate biopsy is the recommended diagnostic test for prostate cancer in patients with abnormal findings on digital rectal examinations (DRE) or elevated PSA (prostate-specific antigen) levels. Biopsies can cause severe anxiety and pain.

OBJECTIVE: To evaluate the effects of music and conversation on pain and anxiety in patients undergoing transrectal ultrasound-guided prostate biopsy.

DESIGN AND SETTING: Prospective trial at a Tertiary University Hospital in Türkiye.

METHODS: A prospective randomized controlled study was conducted. Ninety patients who had abnormal findings on DRE and/or a PSA value greater than 2.5 ng/ml and were scheduled to undergo TRUS-PBx were randomly assigned to one of three groups (n = 30) via the sealed envelope randomization method: control, music, and conversation groups. VAS pain, VAS anxiety, and STAI scores were recorded before and after the procedure. Statistical analysis was performed using One-Way ANOVA and Kruskal–Wallis tests. Pairwise comparison tests were conducted for the parameters that yielded significant differences among the control, conversation, and music groups. For all statistical analyses, a P value < 0.05 was considered statistically significant.

RESULTS: Conversation reduced pain and anxiety significantly (P < 0.001 and P = 0.01 respectively). Post-Bx VAS pain and STAI-State scores were lower in the conversation group. Pairwise comparisons revealed significant differences between the music and conversation groups (VAS pain, P < 0.001; STAI-State, P = 0.006). However, pain and STAI-State scores were similar in both the groups (VAS pain P = 0.645; STAI-State P = 0.597).

CONCLUSIONS: The study demonstrated that listening to music had no significant effect on pain and anxiety in patients undergoing TRUS-PBx. Conversely, the findings showed that engaging patients in conversation significantly reduced pain and anxiety during the procedure.

CLINICAL TRIAL OR SYSTEMATIC REVIEW REGISTRATION: The trial is registered at clinicaltrials.gov (registration number: NCT07006779) and is accessible at https://clinicaltrials.gov/ct2/show/NCT07006779.

INTRODUCTION

Prostate cancer is one of the most common cancers affecting men. Prostate biopsy is the recommended diagnostic test for prostate cancer in patients with abnormal findings during digital rectal examination (DRE) or elevated prostate-specific antigen (PSA) levels.[1] Although transperineal prostate biopsy is increasing, standard transrectal ultrasound-guided prostate biopsy (TRUS-PBx) shows similar prostate cancer detection rates.[2] When the procedure is explained, patients with no prior experience are particularly susceptible to anxiety.[3] Moreover, increased anxiety during the procedure is associated with higher pain perception and irritation. Therefore, biopsy procedures can cause intense anxiety and severe pain for patients.[4]

Since the biopsy procedure is performed under local anesthesia, anxiolytic or sedative drugs are rarely administered.[5] Patients who experience severe pain during the intervention often avoid undergoing re-biopsy when necessary.[6] For these reasons, numerous studies and interventions have been conducted to reduce pain and anxiety in patients undergoing TRUS-PBx. A wide range of methods has been evaluated, from general anesthesia to combinations of local anesthesia with other techniques. Many nonpharmacological interventions, including distraction and anxiety-pain reduction techniques, have been investigated because of their practicality, accessibility, convenience, and minimal side effects.[7–10]

Music reduces pain, anxiety, and stress. Its effectiveness is attributed to its ability to divert patients' attention away from negative stimuli and create a calm environment.[11,12] The positive effects of music on patients undergoing TRUS-PBx have also been evaluated in several studies.[13–19]

Conversation is another effective distraction method that is free, easily accessible, and has no side effects. As anxiety levels increase, the pain experienced by patients also tends to increase. Consequently, reducing patients' anxiety through conversation can lower the pain level.[20] Reportedly, conversing with patients can reduce the anxiety and pain they experience.[20–26] However, there is limited research on the impact of conversation in reducing pain, anxiety, and stress, specifically in patients undergoing prostate biopsy.

This is the first prospective randomized controlled study to investigate the effects of listening to music or engaging in conversation on procedure-related anxiety and pain in patients undergoing TRUS-PBx.

OBJECTIVE

To evaluate the effects of music and conversation on pain and anxiety levels in patients undergoing TRUS-PBx.

METHODS

Study design and population

This prospective randomized controlled study was approved by the Local Clinical Research Ethics Committee (2017-KAEK-189-2021.05.05-08). The clinical trials. gov registration number for the trial is NCT07006779. Patients included in the study were those who presented to the Yozgat Bozok University Hospital Urology Clinic between June 2021 and October 2021, had abnormal findings on DRE and/or had a PSA value greater than 2.5 ng/ml and were scheduled to undergo TRUS-PBx. Sample sizes were calculated using the program GPower v.3.1.9.4 (Franz Faul, University of Kiel) with an alpha value of 0.05, 95% confidence interval (95% CI) power, and 0.19 effect size. Ninety patients were randomly assigned to one of three groups (n = 30) using the sealed-envelope randomization method: control, music, and conversation groups. An experienced urologist generated a randomized allocation sequence, enrolled the participants, and assigned them to the interventions. An experienced urologist performed all procedures.

Inclusion and exclusion criteria

Patients with psychiatric disorders, those who declined to participate, and those who were unable or unwilling to complete the questionnaires were excluded. Additionally, patients with hearing or perceptual impairments, continuous analgesic use, history of prior prostate biopsy, or prilocaine allergy were excluded. Patients for whom the biopsy procedure could not be completed for any reason were excluded. Informed consent was obtained from all the participants.

Data collection and definitions

Patients' sociodemographic data such as age, height, weight, and body mass index were documented. Medication and medical histories were recorded. The International Prostate Symptom Score (IPSS), PSA levels, and prostate volumes of all patients were recorded before the procedure. The blood pressure and heart rate were measured before and after the procedure.

The patients completed the State-Trait Anxiety Inventory (STAI) test. Low scores indicate low anxiety levels, whereas high scores reflect higher anxiety levels. Also, anxiety and pain levels were assessed using a visual analog scale (VAS), where a score of "0" indicated "no pain or anxiety," and a score of "10" represented "the most severe pain or anxiety."

Prophylactic ciprofloxacin was administered to patients 1 day before the procedure. The procedure room was designed to minimize external disturbances (e.g., sound or noise). Prior to biopsy, the patients received detailed information according to their assigned groups. In the music group, patient-selected music was played throughout the procedure. In the conversation group, discussions based on patients' interests were initiated and continued during the procedure. In the control group, no additional interactions beyond the informational briefings were provided.

The biopsy procedure was performed with patients in the lateral decubitus position with their lower extremities flexed. Rectal povidone-iodine was used for local cleaning. Lidocaine gel was applied rectally in all patients. After placing the rectal ultrasound probe, a periprostatic nerve block was performed by injecting 5 ml of 2% prilocaine solution. Twelve core biopsies were collected: six from each lobe.

All patients in the allocated groups underwent TRUS-PBx as described previously. After the procedure, the patients were asked whether they would be willing to undergo the procedure again if necessary. Responses were categorized as "positive," "negative," or "abstained."

Primary and secondary outcomes

The primary outcome of the study was to determine whether listening to music or engaging patients in conversation during the procedure reduced their anxiety and pain levels. The secondary outcome was to determine which was better for decreasing anxiety and/or pain levels: listening to music or engaging in conversation.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics version 26.0 (Armonk, New York). Nominal data were analyzed using the Chi-square test. Parametric numerical data were evaluated using the One-Way ANOVA variance, whereas non-parametric data were analyzed using the Kruskal–Wallis test. Pairwise comparisons were performed to identify significant differences among the control, conversation, and music groups. Pre- and post-procedure comparisons were also performed within each group. For all analyses, a P value < 0.05 was considered statistically significant.

RESULTS

Between June 2021 and October 2021, 101 patients at Yozgat Bozok University Training and Research Hospital Urology Clinic, were assessed for eligibility; however, 10 patients were not eligible and one declined to participate. Thus, 90 patients were randomly assigned to three groups (n = 30 each). Mean age and BMI were not significantly different among the groups (P = 0.339 and P = 0.383, respectively). Additionally, the mean IPSS, PSA value, and prostate volume were statistically similar among the three groups (P = 0.591, P = 0.582, and P = 0.262, respectively). The patient demographic data are shown in **Table 1**.

Hemodynamic parameters, such as systolic and diastolic blood pressure and heart rate measured before biopsy, showed no significant differences among the three groups (P = 0.619, P = 0.684, and P = 0.723, respectively). Additionally, the pre-procedure VAS anxiety (P = 0.299), STAI (P = 0.560), STAI-State (P = 0.850), and STAI-Trait (P = 0.515) scores were similar across the groups (**Table 2**).

No statistically significant differences were found in the post-biopsy blood pressure or heart rate among the three groups (P = 0.284 and P = 0.355, respectively). The scores of VAS pain, VAS anxiety, and the STAI-State recorded after the biopsy procedure were significantly lower in the conversation group (P < 0.001, P < 001and P = 0.010, respectively).

Statistically significant decreases in STAI-State scores, which were recorded before and after the biopsy, were observed only in the conversation group, whereas the scores increased in the other groups (P < 0.001) (**Table 3**).

Pairwise analysis showed that the conversation group differed significantly in post-biopsy VAS pain score, STAI-State score, and STAI score when compared to those of both the music and control groups. However, listening to music did not lead to a significant reduction compared to that in the control group (**Table 4**).

The patient opinion ("positive," "negative," or "abstained") on the repetition of the procedure was similar among the three groups.

DISCUSSION

Previous studies evaluating different methods of reducing pain and anxiety during prostate biopsy reported varied outcomes. Some participants observed a significant reduction in anxiety scores, others in pain scores, whereas others in both scores. Conversely, certain methods have been shown to be ineffective in alleviating pain or anxiety during prostate biopsy. This study evaluated the effects

Table 1. The demographic data of patients

Variables	Total (M ± SD) (n = 90)	Control (M ± SD) (n = 30)	Music (M ± SD) (n = 30)	Conversation (M ± SD) (n = 30)	P value
Age ± SD, years	65.32 ± 7.47	64.5 ± 7.37	66.96 ± 7.9	64.5 ± 7.08	0.339
BMI ± SD, kg/m²	28.66 ± 3.18	29.29 ± 3.29	28.08 ± 3.03	28.61 ± 3.21	0.383
IPSS ± SD	17.58 ± 8.25	16.5 ± 8.84	17.53 ± 8.09	18.7 ± 7.91	0.591
PSA ± SD, ng/mL	13.4 ± 19.62	9.71 ± 6.7	18.43 ± 28.11	12.07 ± 17.45	0.582
Prostate volume ± SD, cc	68.69 ± 36.4	64.05 ± 42.06	70.2 ± 26.33	71.83±39.60	0.262

M, mean; SD, standard deviation; BMI, body mass index; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.

Table 2. Comparison of pre-biopsy variables between the groups

Variables	Total (M ± SD) (n = 90)	Control (M ± SD) (n = 30)	Music (M ± SD) (n = 30)	Conversation (M ± SD) (n = 30)	P value
Pre-Bx Systolic Blood Pressure ± SD, mmHg	117.33 ± 15.96	117.5 ± 19.03	116.17 ± 14.72	118.33 ± 14.16	0.618
Pre-Bx Diastolic Blood Pressure ± SD, mmHg	70.75 ± 11.36	73.1 ± 14.31	69.5 ± 10.2	69.67 ± 8.9	0.684
Pre-Bx heart rate ± SD, bpm	80.64 ± 6.83	80.53 ± 8.06	80.1 ± 5.25	81.3 ± 7.06	0.723
Pre-Bx STAI ± SD	73.8 ± 16.77	71.63 ± 16.2	74.27 ± 18.63	75.5 ± 15.67	0.56
Pre-Bx STAI-State ± SD	34.1 ± 9.41	33.63 ± 8.93	34.2 ± 11.06	34.47 ± 8.34	0.85
Pre-Bx STAI-Trait ± SD	39.49 ± 9.88	37.9 ± 8.77	39.73 ± 10.62	40.83 ± 10.26	0.514
Pre-Bx Anxiety (VAS) ± SD	3.2 ± 1.7	3.03 ± 1.73	3 ± 1.23	3.57 ± 2.03	0.299

M, mean; SD, standard deviation; bx, biopsy; STAI, State-Trait Anxiety Inventory; VAS, visual analog scale; bpm, beats per minute.

Table 3. Comparison of post-bx variables between the groups

Variables	Total (M ± SD) (n = 90)	Control (M ± SD) (n = 30)	Music (M ± SD) (n = 30)	Conversation (M ± SD) (n = 30)	P value
Post-Bx Systolic Blood Pressure ± SD, mmHg	115.11 ± 15.51	112.83 ± 17.8	115.17 ± 14.05	117.3 ± 14.61	0.284
Post-Bx Diastolic Blood Pressure ± SD, mmHg	68.77 ± 10.2	69.83 ± 10.87	68.5 ± 9.66	68 ± 10.31	0.767
Post-Bx heart rate ± SD, bpm	80.36 ± 4.83	81.13 ± 4.09	79.37 ± 4.68	80.57 ± 5.59	0.355
Post-Bx STAI ± SD	74.54 ± 15.9	77.77 ± 16.28	76.5 ± 16.99	69.37 ± 13.4	0.066
Post-Bx STAI-State ± SD	35.33 ± 9.54	37.87 ± 8.93	36.87 ± 11.33	31.27 ± 6.72	**0.010**
Post-Bx STAI-Trait ± SD	38.95 ± 8.89	39.57 ± 8.93	39.2 ± 9.58	38.1 ± 8.35	0.879
Post Bx-Pre Bx STAI-State changes ± SD	1.23 ± 8.36	4.23 ± 5.21	2.66 ± 11.18	−3.2 ± 5.52	**< 0.001**
Post-Bx Anxiety (VAS) ± SD	1.03 ± 1.34	1.17 ± 1.98	1.13 ± 0.73	0.8 ± 0.96	0.101
Post-Bx Pain(VAS) ± SD	2.58 ± 1.79	3.3 ± 2.1	3.1 ± 1.18	1.37 ± 1.3	**< 0.001**

M, mean; SD, standard deviation; bx, biopsy; STAI, State-Trait Anxiety Inventory; VAS, visual analog scale; bpm, beats per minute.

Table 4. Pairwise comparisons of groups

Post-Bx STAI-State				
Groups	**Test Statistic**	**Std. Error**	**Std. Test Statistic**	**Sig.**
Conversation-Music	15.56	6.73	2.31	**0.02**
Conversation-Control	19.13	6.73	2.84	**0.004**
Music-Control	3.57	6.73	0.52	**0.596**
Post-Bx pain				
Groups	**Test Statistic**	**Std. Error**	**Std. Test Statistic**	**Sig.**
Conversation-Control	27.33	6.58	4.15	**< 0.001**
Conversation-Music	30.36	6.58	4.61	**< 0.001**
Control-Music	−3.03	6.58	−0.46	**0.645**
Differences between pre and post-bx STAI-State				
Groups	**Test Statistic**	**Std. Error**	**Std. Test Statistic**	**Sig.**
Conversation-Music	18.41	6.72	2.73	0.006
Conversation-Control	29.43	6.72	4.37	**< 0.001**
Music-Control	11.01	6.72	1.63	0.101

Bx, biopsy; STAI, State-Trait Anxiety Inventory.

of music, a method that has been explored in previous studies, and conversation, which has rarely been studied–on anxiety and pain in patients undergoing prostate biopsies. The findings revealed that listening to music did not reduce anxiety or pain; however, engaging the patient in conversations significantly reduced both.

Various techniques have been used to alleviate pain and anxiety during prostate biopsy. For instance, diaphragmatic breathing during TRUS-PBx significantly reduced anxiety, whereas hypnotherapy effectively reduced both pain and anxiety.[7,10] The use of nitrous oxide (N_2O) during TRUS-PBx had no impact on anxiety, but caused a slight reduction in pain levels.[27] Similarly, patients who received video-based education before TRUS-PBx experienced lower anxiety levels than did those who only received verbal information. The use of augmented reality glasses during the procedure has also been shown to reduce pain.[8,9] The results of this study revealed that conversion to TRUS-PBx significantly reduced both pain and anxiety, highlighting the potential of this simple, cost-effective, and accessible method for improving patient experience during prostate biopsy.

The effects of music have been investigated in several studies. A randomized controlled trial demonstrated that music had no significant difference in VAS and STAI scores compared to the control group.[18] Two studies reported that music decreased the STAI-state state and VAS pain scores of patients undergoing TRUS-PBx.[17,19] There are also studies in the literature showing that music only reduces STAI-State or VAS anxiety levels in patients undergoing TRUS-PBx and does not change pain level.[14–16] The influence of listening to music during prostate biopsy is controversial; however, the findings of this study revealed that music has no effect on VAS pain, VAS anxiety, and STAI score.

The effect of music on hemodynamic parameters remains controversial. Two studies demonstrated no significant difference between the music and control groups.[18,19] However, in other studies, significant differences were found in some hemodynamic parameters.[13–15,17] The outcome of this study showed no significant difference in the hemodynamics of the patients.

The controversial findings in literature may depend on various factors such as the type of music chosen, use of headphones, volume level of music, and other variables. Reportedly, music can produce different clinical effects depending on its tempo.[28]

In some studies, patient satisfaction and willingness to repeat the procedure were reported to be higher in the music group.[17,19] However, in this study, there was no significant difference between the music and conversation groups. This may be attributed to the fact that this variable was recorded by using three categorical options instead of a continuous scale.

Packiam et al. indicated that crying or verbal distractions may be more effective than music. However, there is a lack of data on the effects of conversing with patients on pain and anxiety during prostate biopsy.[18] Some studies have evaluated the impact of conversation and verbal distractions on pain and anxiety in other contexts. For example, pregnant women experience less pain during labor with distraction techniques such as conversation.[23] The effect of conversation was compared with lidocaine/prilocaine cream in

patients undergoing peripheral venous catheterization, and pain was found to be significantly lower in the conversation group.[22] In another study, hand-holding combined with conversation was reported to be more effective than midazolam in reducing preoperative anxiety.[20] Verbal distraction during burn dressing procedures was observed to alleviate anxiety but did not reduce pain.[29] Similarly, a survey revealed that more patients preferred conversation as a distraction over receiving procedural information before venipuncture.[21] Studies conducted with children have also shown that verbal distraction provided by parents significantly reduced pain during invasive procedures.[25] This study is consistent with current data and demonstrated that engaging patients in conversation significantly reduced both pain and anxiety during TRUS-PBx. However, some studies have reported that conversation is ineffective in alleviating pain and anxiety. For example, conversation does not reduce pain in burn patients during rehabilitation or in patients presenting to the emergency department with acute pain.[26–30]

The success of doctor-patient conversations depends on the selection of topics that the patient finds engaging and captivating. In this study, patients engaged in conversations about their interests and actively participated. During these conversations, the patients appeared to forget the procedure and distanced themselves from the pain and anxiety.

Although the study was planned as a prospective randomized controlled trial, it has limitations; due to the design, it was not a double-blind study. The pain level was assessed only before and after the procedure, whereas it should be assessed at each step of the process. The study was conducted at a single center with a relatively small sample size. In addition, the music was provided as ambient background music and not through headphones.

CONCLUSIONS

This study demonstrated that listening to music has no significant effect on pain or anxiety in patients undergoing TRUS-PBx. Conversely, the findings showed that engaging patients in conversation significantly reduced pain and anxiety during the procedure. Distracting patients via conversation during the biopsy procedure increases patient comfort. However, further studies with larger sample sizes are necessary to validate and expand on these findings.

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The Psychological Inflexibility in Pain Scale (PIPS) in Brazilian patients with chronic cancer pain: translation, cross-cultural adaptation, and validation study

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ABSTRACT

BACKGROUND: The Psychological Inflexibility in Pain Scale (PIPS) was developed to measure avoidance and cognitive fusion.

OBJECTIVES: To translate, cross-culturally adapt, and analyze the measurement properties of the Psychological Inflexibility in Pain Scale (PIPS) in Brazilian patients with chronic cancer pain.

METHODS: Questionnaire translation, cross-cultural adaptation, and validation studies were conducted in two hospitals in northeastern Brazil. The measurement properties tested included structural validity, construct validity, reliability, and internal consistency. The following assessment instruments were used in addition to the PIPS: Pain Catastrophizing Scale (PCS), Barthel Index, Edmonton Symptom Assessment Scale (ESAS), and Hospital Anxiety and Depression Scale (HADS).

RESULTS: The study sample consisted of 122 patients, most of whom were women (65.6%) with a mean age of 49 years. Most patients had uterine cancer (23%) and leukemia (9.8%). We identified problems in the two-dimensional structure of the PIPS by presenting three inadequate fit indices. Adequate reliability was observed in both domains. Regarding the avoidance domain, there was a correlation with a magnitude > 0.30 with the depression domain of the HADS, and correlations with a magnitude < 0.30 with the anxiety domain of the HADS, the PCS domains, and the Barthel Index. The cognitive fusion domain did not correlate with any of these scales ($P > 0.05$). No ceiling or floor effects were observed.

CONCLUSION: The Brazilian version of the PIPS is reliable; however, the instrument does not have a valid internal structure and the cognitive fusion domain is not a valid construct.

INTRODUCTION

Cancer pain affects approximately half of patients with cancer at different stages of the disease: 50.7% at any stage, 55% during treatment, and 66.4% in terminal, advanced, or metastasized stages. Even after the cancer has been cured, pain is still present in 39.3% of patients.[1] To assess this pain, one-dimensional scales such as the Visual Analog Scale, Numerical Pain Scale, and Wong-Baker Faces Pain Rating Scale are commonly used.[2] However, it is crucial also to consider the factors that can intensify or alleviate pain, such as physical, psychological and social aspects, for a broader understanding of the cancer pain phenomenon.[3]

The Psychological Inflexibility in Pain Scale (PIPS) is a valuable tool based on acceptance and commitment to therapy. Psychologically flexible individuals can pursue their goals and values despite experiencing pain. The PIPS was developed to measure inflexibility in patients with chronic pain, regardless of comorbidities, by assessing two distinct domains: avoidance and cognitive fusion.[4]

This scale has already been validated in several languages and cultures, including Spanish, German, Persian, Japanese and Chinese.[5–9] The Chinese version of the PIPS was adapted for 389 patients with cancer, demonstrating adequate psychometric properties.[8] Thus, its use for pain management in patients with cancer can contribute significantly to the treatment of these individuals.

Therefore, considering the importance of psychological inflexibility in chronic pain, conducting an adaptation study of the PIPS into Brazilian Portuguese is justifiable since this still needs to

be done. This study aimed to translate, culturally adapt, and evaluate the measurement properties of the PIPS for Brazilian patients with chronic cancer pain.

METHODS

Study design

A study was carried out to translate, cross-culturally adapt, and validate an evaluation scale based on the guidelines of the Consensus-based Standards for selecting health Measurement Instruments (COSMIN)[10] and the Guidelines for cross-cultural adaptation of self-report measures.[11] Permission to use the instrument was granted via e-mail (Dr. Rikard K. Wicksell).

The study was conducted at the Maranhão Oncology Hospital and Aldenora Bello Hospital in São Luís, Northeast Brazil. The University Research Ethics Committee approved this study (approval no. 5.232.253).

Sample

The sample size was calculated based on the COSMIN guidelines: seven times the number of items in the questionnaire, if this value is not less than 100. Given that the PIPS contains 12 items, the minimum sample size was 100 patients.[10]

The inclusion criteria for the study were as follows: cancer pain for at least 3 months; age 18 years or older, both sexes, ability to read and understand Brazilian Portuguese, diagnosis of cancer confirmed by biopsy, and awareness of cancer diagnosis.

The following patients were excluded from the study: those diagnosed with severe cognitive or psychiatric disorders, those who could not complete the questionnaires, and those without pain when filling in the questionnaires.

Translation and cross-cultural adaptation

The process of translation and cross-cultural adaptation of the PIPS followed the criteria of Beaton et al.[11] as described below.

1. Translation: Two independent translators with Portuguese as their mother tongue and fluency in English translated the PIPS into Brazilian Portuguese. One translator was from the health field. Each translator then produced a translation report.
2. Synthesis of translations: The two translators held discussions and revisions until they reached a single version of the PIPS by consensus under the observation of one of the researchers.
3. Back translation: Two translators translated the questionnaire back into their original language without prior knowledge of the original version. These translators have English as their mother tongue but are fluent in Brazilian Portuguese and are not from the health field.
4. Analysis by a committee of experts: This committee included four translators, three physiotherapists, and one physician. This group reviewed all translated and back-translated versions to correct possible discrepancies and arrived at the final version of the questionnaire.
5. Testing the pre-final version: The pre-final version was administered to 30 patients with cancer. This phase aimed to establish the degree of understanding of the items in the pre-final version of the PIPS. If the comprehension of each item was greater than 80%, the pre-final version was defined as the final version. If an item had less than 80% comprehension, these items were modified and tested on a new sample of 30 participants.
6. Final version: After all the stages, the research coordinator approved the final version of the PIPS in Brazilian Portuguese.

INSTRUMENTS

Initially, sociodemographic data and clinical characteristics of the patients were collected, including primary diagnosis, presence of comorbidities, date of diagnosis, presence of metastasis, length of treatment, and signs and symptoms. Subsequently, the evaluation scales were applied.

Psychological Inflexibility in Pain Scale (PIPS)

The PIPS was developed by Wicksell et al.[12] and has 12 items containing seven response options: 1. never true; 2. very rarely true; 3. seldom true; 4. sometimes true; 5. often true; 6. almost always true; and 7. always true. The PIPS has two domains: avoidance (items 1, 2, 4, 5, 7, 8, 10, and 11), and cognitive fusion (items 3, 6, 9, and 12). The avoidance domain relates to the patient's tendency to engage in certain behaviors to avoid pain and suffering, whereas the cognitive fusion domain assesses the frequency with which each individual manifests an action in the face of these thoughts as if they were true. The scores for the avoidance and cognitive fusion domains ranged from 8 to 56 and 4 to 28, respectively.

Pain Catastrophizing Scale (PCS)

The PCS consists of 13 items that assess pain catastrophizing behavior. It consists of three subscales: hopelessness, magnification, and rumination. Patients were required to answer items according to their thoughts and feelings when experiencing pain. The items were classified on a 5-point scale, divided into not at all (score 0) to all the time (score 4).[13] Thus, the total score for domain rumination ranged from 0 to 16, magnification ranged from 0 to 12, and helplessness ranged from 0 to 24 points. Higher scores indicated greater catastrophizing. The PCS was validated in Brazil for patients with chronic pain by Sehn et al.[14]

Hospital Anxiety and Depression Scale (HADS)

The HADS consists of 14 items, seven of which are used to assess anxiety and seven to measure depression and was validated for

Brazil by Botega et al.[15] Each item is scored on a scale from 0 to 3, with a total of 21 points for each scale. The higher the score, the greater the signs of anxiety or depression.

Barthel Index

The Barthel Index was validated for Brazil by Barros et al.,[16] composed of 10 items that assess patients' level of functional independence in daily activities, with scores ranging from 0 to 100. Higher scores indicated greater functional independence.

Edmonton Symptom Assessment System (ESAS)

The ESAS assesses pain, activity, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. For each symptom, it is possible to sign a scale ranging from 0 to 10, where zero represents the absence of the symptom and 10 describes the symptom in its strongest manifestation. This scale was validated in Brazil by Monteiro et al.[17] In this study, the ESAS was used only to characterize the sample.

Statistical analysis

Sociodemographic data were described as means and standard deviations (quantitative data) or absolute numbers and percentages (qualitative data). The internal consistency of each domain was calculated using Cronbach's alpha, considering a range between 0.7 and 0.95 to be adequate values.[18]

Reliability was assessed using a test-retest model. The intraclass correlation coefficient (ICC), 95% confidence interval (95% CI), standard error of measurement (SEM), and minimum detectable difference (MDD) were used to assess the reliability of the scores for each domain of the PIPS. ICC values greater than or equal to 0.75 was acceptable.[19]

Structural validity was analyzed using confirmatory factor analysis considering the original proposal of two domains and 12 items.[12] We used the software R Studio (Boston), with lavaan and SemPlot packages, and with the implementation of a polychoric matrix and the robust diagonally weighted least squares extraction method.[20,21] The following cutoff values were considered adequate for the fit indices: chi-square/degree of freedom (DF) < 3; comparative fit index (CFI) and Tucker-Lewis index (TLI) > 0.9; and root mean square error of approximation (RMSEA) and standardized root mean squared residual (SRMR) < 0.08.[22,23] Factor loadings were considered adequate when ≥ 0.4.[24] We used modification indices (MI) to analyze the model, considering a value > 10 as the cutoff point for identifying a problem in the model.[25]

For construct validity using correlations between instruments, the normality of the data was initially checked using the Kolmogorov–Smirnov test. Subsequently, Spearman's correlation coefficient (ρ) was used to determine the magnitude of the correlation between the PIPS and other measurement instruments. Interpretation of the magnitude of the correlations followed the following criteria: correlations with instruments measuring similar constructs should be ≥ 0.5; correlations with instruments measuring related but different constructs should be between 0.3 and 0.5; and correlations with instruments measuring unrelated constructs should be < 0.3.[10] This study hypothesizes that the domains of the PIPS show a significant correlation magnitude of < 0.3.

The effects of the floor and ceiling were also evaluated in this study. These effects occurred when more than 15% of the study participants (more than 15%) reached the minimum or maximum total score on the questionnaire, indicating a problem in assessing the instrument's responsiveness.

Internal consistency, reliability, and correlations were analyzed using SPSS statistical software (version 17.0, Chicago), and a 5% significance level was adopted.

RESULTS

Cross-cultural adaptation

It was unnecessary to adapt any terms or expressions to Portuguese during the translation. The pre-final version of the PIPS was administered to 30 patients with cancer-related pain. Only one patient (3.33%) needed help in understanding items 2 and 10 of the PIPS. Therefore, there was acceptable comprehension of the PIPS items (> 80%).

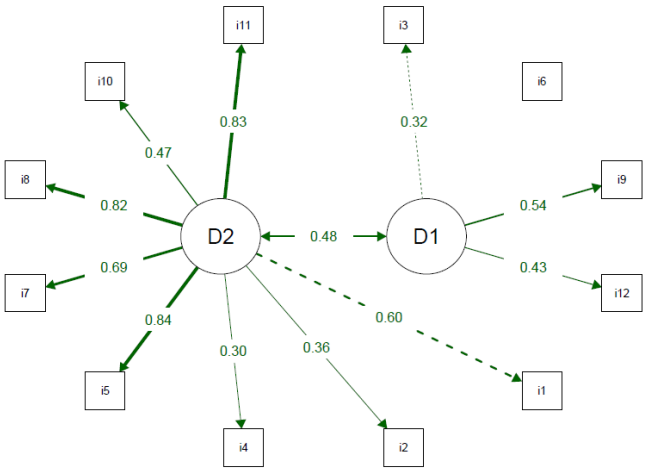
Structural validity

We identified problems with the two-dimensional structure proposed for creating the PIPS. Three fit indices were inadequate (TLI = 0.88, RMSEA = 0.102, SRMR = 0.101), whereas two were adequate (chi-square/DF = 2.2 and CFI = 0.903). The two-dimensional structure also showed inadequate factor loadings (less than 0.4) for items 3 (factor loading = 0.32) and 6 (factor loading = 0.09) of the cognitive fusion domain, and for items 2 (factor loading = 0.36) and 4 (factor loading = 0.30) of the avoidance domain, as shown in **Figure 1.**

Using MI, we investigated the model's problems, identifying that item 6 was consistently related to the avoidance domain (MI = 14.408), items 6 and 12 presented redundancy in the patients' response pattern (MI = 13.502), and items 3 and 6 presented redundancy in the patients' response pattern (MI = 10.99).

Characterization of the sample

The sample consisted of 122 patients, most of whom were women (65.6%) with an average age of approximately 49 years, were married (50.8%), and had completed elementary school (46.7%). Regarding the type of cancer, most were uterine cancer (23%) or leukemia (9.8%). Among the participants' characteristics, there



D1: cognitive fusion domain; D2, Avoidance domain. The thicker the line, the greater is the factorial load. The dotted lines indicate the first item in the domain.

Figure 1. Path diagram of the two-dimensional structure of the Psychological Inflexibility in Pain Scale (PIPS).

was a predominance of cases without metastasis (80.3%) and receiving curative care (95.9%). Other information are described in **Table 1** and **Table 2.**

Reliability and internal consistency

As shown in **Table 3**, we observed adequate test-retest reliability and internal consistency values, with an ICC of 0.8 for the cognitive fusion domain and 0.95 for the avoidance domain. Internal consistency was also acceptable, with Cronbach's alpha of 0.7 and 0.74 for the cognitive fusion and avoidance domains, respectively.

Construct validity via hypothesis testing

Regarding the avoidance domain of the PIPS, there was a correlation with a magnitude > 0.3 with the depression domain of the HADS and correlations with a magnitude < 0.3 with the anxiety domain of the HADS, the domains of the PCS, and the Barthel index (**Table 4**). Unexpectedly, the cognitive fusion domain of the PIPS did not correlate with the instruments used in this study ($P > 0.05$).

Floor and ceiling effects

We did not observe ceiling or floor effects, as in the no-PIPS domain, there were more than 15% maximum or minimum responses. For the cognitive fusion domain, none of the participants reached the minimum score (4 points) and 17 patients (13.9%) reached the maximum score (28 points); for the avoidance domain, one participant (0.8%) reached the minimum score (8 points), and no participant reached the maximum score (56 points).

Table 1. Personal and social characteristics of the patients included in the study (n = 122)

Variables	Number (%)
Sex	
Male	42 (34.4%)
Female	80 (65.6%)
Marital status	
Married	62 (50.8%)
Divorced	7 (5.7%)
Single	50 (41%)
Widowed	3 (2.5%)
Scholarity	
Primary education	12 (9.8%)
Basic education	57 (46.7%)
High school	40 (32.8%)
Higher education	13 (10.7%)
Type of cancer	
Uterus	28 (23%)
Leukemia	12 (9.8%)
Lymphoma	9 (7.4%)
Breast	8 (6.6%)
Pancreas	8 (6.6%)
Stomach	8 (6.6%)
Lung	5 (4.1%)
Ovary	5 (4.1%)
Multiple myeloma	5 (4.1%)
Penis	4 (3.3%)
Liver	3 (1.9%)
Bones	2 (1.6%)
Vulva	2 (1.6%)
Others	23 (18.9%)
Metastasis	
Yes	24 (19.7%)
No	98 (80.3%)
Type of treatment	
Curative	117 (95.9%)
Palliative	5 (4.1%)
Treatment modality	
Chemotherapy	49 (40.2%)
Surgery	26 (21.3%)
Surgery and medication	12 (9.8%)
Surgery and chemotherapy	10 (8.2%)
Medication	10 (8.2%)
Chemotherapy and radiotherapy	5 (4.1%)
Radiotherapy	5 (4.1%)
Surgery, chemotherapy and radiotherapy	2 (1.6%)
Surgery, chemotherapy and medication	2 (1.6%)
Surgery and radiotherapy	1 (0.8%)

DISCUSSION

Satisfactory test-retest reliability and internal consistency values were observed, ensuring score stability in the PIPS assessments conducted on different days. However, the two-dimensional internal structure of the PIPS proved inadequate, indicating that the scale items did not accurately reflect the intended domains. Finally, the avoidance domain was a valid construct, whereas the cognitive fusion domain showed no correlation with any of the instruments evaluated in the study.

Regarding reliability, we found acceptable ICC values, i.e., 0.8 and 0.95 for the cognitive fusion and avoidance domains, respectively. A Spanish study identified relatively higher reliability values, with an ICC of 0.97 for both domains, in which patients with fibromyalgia were investigated.[7] Similarly, a Chinese study also found higher values, with an ICC of 0.98 for the avoidance domain and 0.97 for cognitive fusion. The Chinese version assessed patients with chronic cancer-related pain.[8] Notably, all the versions mentioned, including the present study, had ICC values within the acceptable range, that is, greater than 0.75.

Regarding internal consistency, Cronbach's alpha values for the avoidance and cognitive fusion domains were 0.74 and 0.7, respectively. The Chinese study obtained a satisfactory Cronbach's alpha (0.74 for cognitive fusion and 0.88 for avoidance).[8] Similar to previous studies, the present study

Table 2. Descriptive analysis and scores of the questionnaires and scales used in the study

Variables	Mean (standard deviation)
Age (years)	49.52 (15.43)
ESAS (score, 0–10)	
Pain	6.68 (2.98)
Fatigue	2.87 (3.3)
Nausea	2.48 (3.19)
Sadness	4.31 (3.67)
Anxiety	4.69 (3.82)
Drowsiness	4.12 (3.79)
Lack of appetite	3.27 (3.4)
Shortness of breath	1.35 (2.48)
Lack of well-being	3.14 (3.25)
Barthel index (score, 0–100)	77.13 (29.02)
HADS (score, 0–21)	
Anxiety	7.26 (4.49)
Depression	6.68 (4.12)
PCS	
Helplessness (score, 0–24)	8.48 (5.79)
Magnification (score, 0–12)	6.56 (4.7)
Rumination (score, 0–16)	9.69 (4.04)
PIPS	
Cognitive fusion (score, 4–28)	23.19 (3.71)
Avoidance (score, 8–56)	34.76 (9.99)

ESAS, Edmonton Symptom Assessment Scale; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PIPS, Psychological Inflexibility in Pain Scale.

Table 4. Correlation between the domains of the Psychological Inflexibility in Pain Scale (PIPS) and other scales

Variables	Cognitive fusion		Avoidance	
	ρ	P	ρ	P
Barthel index	0.056	0.551	−0.196	0.035*
HADS				
Anxiety	0.116	0.205	0.237	0.009*
Depression	0.018	0.846	0.358	0.001*
PCS				
Helplessness	0.084	0.355	0.205	0.023*
Magnification	0.081	0.377	0.275	0.002*
Rumination	0.113	0.216	0.297	0.001*

HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale.
* Significant correlation (P < 0.05, Spearman correlation coefficient).

Table 3. Test-retest reliability and internal consistency of the Psychological Inflexibility in Pain Scale (PIPS)

Measures	Domains	
	Cognitive fusion	Avoidance
Test, mean (standard deviation)	23.05 (3.26)	37.12 (9.34)
Retest, mean (standard deviation)	23.48 (3.56)	38.28 (8.83)
ICC	0.8	0.95
95% CI of ICC	0.68 to 0.88	0.92 to 0.97
SEM, score (%)	1.54 (6.62%)	2.03 (5.39%)
MDD, score (%)	4.27 (18.35%)	5.63 (14.94%)
Cronbach's alpha	0.7	0.74

ICC, Intraclass correlation coefficient; CI, Confidence interval; SEM, Standard error of measurement; MDD, Minimum detectable difference.

showed adequate internal consistency values for the avoidance domain, with Cronbach's alpha coefficient ranging from 0.89 to 0.95.[5–7,9,12,26] However, in the cognitive fusion domain, internal consistency proved to be inadequate in most versions, with Cronbach's alpha coefficient below 0.7 in the original, German, Spanish, and Japanese versions.[5–7,27]

We partially confirmed the hypotheses of this study in terms of construct validity. The avoidance domain showed the expected correlations with anxiety, depression, catastrophizing, and functional independence. However, we identified a problem with the other PIPS domains, as we did not recognize the cognitive fusion construct as valid, given that there was no correlation with the tools used.

We observed that most validation studies on the PIPS correlated with the total score of the instrument and did not separate it by the domains of avoidance and cognitive fusion. The Chinese version of the PIPS with patients with cancer found correlation between the total PIPS score and the Acceptance and Action Questionnaire ($\rho = 0.54$) and the Chronic Pain Acceptance Questionnaire ($\rho = -0.41$).[8]

Part of the construct validity was related to the internal structure of the PIPS. In this sense, some studies conducted factor analysis and did not find adequate fit indices to support the structure with two domains and 12 items. The original study[27] showed residuals in the model that were higher than satisfactory. The Japanese study found inadequate fit indices, and it was only possible to fit the model after adding eight correlations between PIPS items.[6] The Greek study also found inadequate fit indices for the two-dimensional structure of the instrument,[28] similar to the results of the present study.

Contrastingly, the Spanish version found an adequate internal structure but used principal component analysis as a method, which is unsuitable for instruments with a reflective model.[7] The Chinese study also found an adequate two-dimensional structure but used an extraction method that was not very suitable for factor analysis of instruments with ordinal categorical responses.[8]

From clinical and research perspectives, the PIPS should be used with caution. Based on the results obtained and those of previous studies, the cognitive fusion construct appears problematic and requires confirmation or correction in studies with robust statistical methodologies.

The limitations of this study include the heterogeneity of the cancer types in the sample and the inclusion of a significant proportion of patients without metastasis or in palliative care conditions, typically associated with more severe pain. Additionally, our sample was recruited from a hospital-based oncology service; thus, the evaluative capacity of the PIPS may differ in outpatient or home-based care settings.

CONCLUSION

The Brazilian version of the PIPS is reliable. However, the two-dimensional structure (cognitive fusion and avoidance domains) does not have a valid internal structure, and the cognitive fusion domain is not a valid construct when analyzed via hypothesis testing.

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Cut-off point for diagnosing thoraco-lumbo-pelvic rotation range hypomobility through the leg lateral reach test in chronic low back pain: a cross-sectional study

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ABSTRACT

BACKGROUND: Studies have proposed using the leg lateral reach test (LLRT). However, they did not establish a cut-off point for testing.

OBJECTIVE: To establish a cut-off point for the thoraco-lumbo-pelvic rotation range using the LLRT in patients with chronic low back pain.

DESIGN AND SETTING: Cross-sectional study conducted in Buriticupu, Maranhão, Brazil.

METHODS: In the chronic low back pain group (LBPG, n = 35), we included patients aged 18 to 59 years, of both sexes, with scores ≤ 4 on the Baecke Habitual Physical Activity Questionnaire, body mass indeces ≤ 26 kg/m^2, disability levels ≥ 3 on the Roland-Morris Disability Questionnaire, and pain levels ≥ 3 on the Numeric Pain Rating Scale. In the healthy control group (HCG, n = 35), the patients had the same characteristics (except for pain and disability). We used receiver operating characteristic curves to check the rate of true versus false positives in different LLRT ranges of motion and found the best LLRT cut-off point using the following mathematical model: $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$.

RESULTS: The sample was mainly composed of females (HCG = 65.71%; LBPG = 82.85%, P = 0.101), and 68.42% of the characteristics (13 of 19 comparisons between groups) showed a significant difference (P ≤ 0.05), with an effect size ranging from moderate to large (Cohen's d ≥ 0.5). The cut-off value for ideal sensitivity and specificity was ≤ 82.85 cm.

CONCLUSION: Patients with chronic low back pain and an LLRT range ≤ 82.85 cm have hypomobility regarding thoraco-lumbo-pelvic rotation range.

INTRODUCTION

Chronic low back pain is a phenomenon related to pain amplification in the nervous system and is often classified as nonspecific low back pain.[1] Among 354 medical conditions surveyed in 195 countries, low back pain was the leading cause of lost productivity worldwide and the leading cause of years lived with disability in 126 countries, indicating that low back pain remains poorly understood and undervalued.[2]

In routine clinical assessment, some patients with chronic low back pain have hypomobility of the spine because of stiffness of the postural muscles, making movements that require trunk rotation in activities of daily living difficult.[3] Therefore, it is necessary to evaluate thoraco-lumbo-pelvic mobility before, during, and after longitudinal treatment, as it indicates the prognosis of patients through low-cost observation during physical examination.[3]

Thoraco-lumbo-pelvic mobility can be measured using the leg lateral reach test (LLRT). It was developed by Kim et al.[4] in healthy patients and adapted by Pontes-Silva et al. for patients with chronic low back pain.[3] In the test, the patient lies in the supine position, and the rater places a ruler perpendicular to the contralateral knee and measures the maximum distance that the tip of the patient's foot reaches during thoraco-lumbo-pelvic rotation.[3,4]

The LLRT is reliable and inexpensive;[3,4] however, it does not have a cut-off point to diagnose adequate thoraco-lumbo-pelvic mobility, making it just another test whose evaluation generates data that cannot predict prognoses.[5]

OBJECTIVE

Under the hypothesis that healthy individuals undergoing the LLRT generate a cut-off point for diagnosing thoraco-lumbo-pelvic hypomobility, this study aimed to establish a cut-off point for the thoraco-lumbo-pelvic rotation range through the LLRT in patients with chronic low back pain.

METHODS

Design and ethical aspects

This was a cross-sectional study following the Standards for Reporting Diagnostic Accuracy.[6] Patients signed an informed consent form before participation. All procedures were approved by the Human Research Ethics Committee of the Universidade Federal do Maranhão (UFMA) (report number: 2.892.673; January 2, 2019).

Context

We publicized the research in the university press and on social networks, including Facebook, WhatsApp, and Instagram (Meta Platforms, Inc., Menlo Park, California, United States) for 12 months (January 2020 to January 2021). Interested parties who contacted the researchers were invited to participate in the recruitment screening. All participants received a verbal explanation of the research procedures and freely agreed to participate in the study. We collected the variables in a private, bright room, with a temperature of 23°C and without external noise, in the city of Buriticupu, Maranhão, Brazil.

Study size and sampling

We calculated the a priori sample size using G*Power[7] with a critical t = 1.6675723,[8] $\delta = 2.5115915$, $\alpha = 0.05$, and $\beta = 0.80$.[9] As such, the sample required 70 patients divided into two independent and balanced groups (n = 35 + n = 35) whose main prognoses (pain and disability) required a significant difference ($P < 0.5$)[10] and size of moderate effect (d value ≥ 0.6).[11,12]

Patients and inclusion criteria

In the chronic low back pain group (LBPG), we included patients aged 18 to 59 years, of both sexes, who scored ≤ 4 on the Baecke Habitual Physical Activity Questionnaire,[3,13] with body mass indexes (BMIs) ≤ 26 kg/m^2,[14] reports of low back pain for ≥ 90 days,[3] disability levels ≥ 3[15] on the Roland-Morris Disability Questionnaire (RMDQ),[16] and pain levels ≥ 3[15] points on the Numeric Pain Rating Scale (NPRS).[17] In the healthy control group (HCG), patients had the same characteristics except for disability and pain.

We excluded patients with low back pain attributed to a specific or identifiable cause, such as a history of back surgery or vertebral fractures; spondylosis and spondylolisthesis; presence of radiculopathy or disc herniation confirmed by imaging and physical examination (i.e., changes in sensation, reflexes, or muscle strength); history of physical therapy for low back pain in the past 90 days or medication in the past 7 days; medical diagnosis of cancer, rheumatologic, neurologic, psychiatric, cardiovascular, or metabolic diseases; and pregnancy.[15]

Assessments and variables

We measured the iliospinale distance (from the medial malleolus to the anterior superior iliac spine),[18] weight, height, waist circumference, waist-to-height ratio,[19] BMI,[14] C-index,[20] pain,[17] disability,[16] and physical activity.[13] In addition, patients answered the Pain Self-Efficacy Questionnaire (PSEQ).[21] All physical examinations and subjective assessments were performed by an independent researcher experienced in the assessment and treatment of chronic low back pain.

The NPRS quantifies pain intensity using a sequence of 11 values (0 = no pain; 10 = the worst pain imaginable). Pain intensity was assessed at rest and after movements performed in the LLRT. This scale has been previously validated for this sample.[17]

The RMDQ was previously validated using a similar sample. This questionnaire is used to measure disabilities in individuals with low back pain. It consists of 24 items describing situations experienced by individuals with low back pain, with scores ranging from 0 to 24 points. The higher the score, the greater the disability.[16]

The PSEQ consists of 10 items that assess how confident a patient feels in certain situations. Each item has six options with their respective values in ascending order from "not at all confident" to "completely confident." The scores range from 0 to 60, with higher scores indicating higher levels of self-efficacy.[21]

The Baecke Habitual Physical Activity Questionnaire was also previously validated for this sample and was used to assess the patients' habitual physical activities.[13] The instrument uses the domains of work, sport, and leisure to quantify the level of physical activity. The score for each domain ranges from 1 to 5 points, with low scores corresponding to less active patients.[22]

Leg Lateral Reach Test

The LLRT measures thoraco-lumbo-pelvic mobility. The patient lies supine on the floor, and the evaluator uses a millimeter ruler perpendicular to the opposite knee on the side being tested to measure the maximum distance that the tip of the foot can reach. Patients moved their feet as far as possible without lifting their shoulders off the floor, rotating only the thoraco-lumbo-pelvic region.[3,4] Patients performed three repetitions on each side (right and left); we then calculated the average individual reach distances.

Statistical analyses

We used SPSS software (IBM Corp., SPSS Inc., Armonk, New York, United States, version 17) with an alpha set at 0.05 in all analyses[23] and checked the distribution of variables using Shapiro-Wilk and Kolmogorov-Smirnov histograms. Categorical variables were compared using Fisher's exact and chi-squared tests, and quantitative variables were compared using Student's t-test for unpaired samples (HCG vs. LBPG). Finally, we describe the comparisons in terms of mean, standard deviation, difference between means, confidence interval of the difference (95% CI), and effect size, calculated and classified by Cohen's d: ≤ 0.2 small effect, 0.5 moderate effect, and ≥ 0.8 large effect (https://www.psychometrica.de/effect_size.html).[24]

We used the receiver operating characteristic (ROC) curve to determine the rate of true positives versus false positives at different ranges of motion in the LLRT and found the LLRT cut-off point using the following mathematical model:[25] $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$. The values corresponding to sensitivity and specificity were closest to the point (0,1), which is considered the cut-off point that best differentiates patients with thoraco-lumbo-pelvic hypomobility from healthy individuals. Furthermore, we used the Youden *J* index (sensitivity + specificity - 1) to indicate the performance of the identified cut-off point (1 = perfect test; 0 = no diagnostic value)[26] and the positive (sensitivity/[1 – specificity]) and negative (= [1 – sensitivity]/specificity) likelihood ratios (http://getthediagnosis.org/calculator.htm).[27]

Finally, we used logistic regression models adjusted for stature, BMI, iliospinale distance, and waist-to-height ratio to consider the potential influence of these anthropometric variables on the outcome of thoraco-lumbo-pelvic rotation range hypomobility.

RESULTS

The sample consisted of 70 patients divided into two groups (HCG, n = 35; LBPG, n = 35), and was mostly female (HCG = 65.71%; LBPG = 82.85%, P = 0.101), and their characteristics are described in **Table 1**.

Table 2 shows the comparisons of all clinical characteristics of the groups, in which 68.42% of the analyses (13 comparisons) showed a significant difference (P ≤ 0.05) and effect sizes ranging from moderate to large (Cohen's d ≥ 0.5).

According to the ROC curve analysis, the cut-off values that produced ideal sensitivity and specificity were ≤ 82.85 cm during LLRT (sensitivity = 0.97, specificity = 0.31). The area under the curve, Youden's J index, and positive and negative likelihood ratios are presented in **Table 3** and **Figure 1**.

The logistic regression model results showed that the effect of the LLRT remained statistically significant after adjustment (P < 0.05), with an estimated odds ratio (OR) of approximately 0.5. The following anthropometric variables were not significantly associated with thoraco-lumbo-pelvic rotation range hypomobility: height (P = 0.700923, OR = 0.024421), BMI (P = 0.231799, OR = 0.752938), waist-to-height ratio (P = 0.875384, OR = 11.758806), or iliospinale distance (P = 0.646721, OR = 0.927256). Therefore, these findings suggest that anthropometric variables do not confound the association between the LLRT and thoraco-lumbo-pelvic rotation range hypomobility.

DISCUSSION

Main results synthesis

Our study confirmed the hypothesis and established a cut-off point for the diagnosis of thoraco-lumbo-pelvic rotation range hypomobility in patients with chronic low back pain (LLRT ≤ 82.85 cm). Additionally, the main outcomes (pain and disability) showed a significant difference (P ≤ 0.05) and an effect size ranging from moderate to large (Cohen's d ≥ 0.5) according to the a priori sampling requirement.

Study strengths

This is the first study to propose a cut-off point for the LLRT. Sensitivity and specificity values showed that the LLRT has an excellent ability to diagnose thoraco-lumbo-pelvic rotational range hypomobility in patients with chronic low back pain. However, we recommend that researchers and clinicians observe the biomechanical and anthropometric characteristics of patients undergoing LLRT and compare them with those of our sample, because they are known to be associated with lumbar function.[28]

Kim et al. found excellent reliability for the LLRT in a healthy sample with a mean reach of 73.19 cm, but they did not mention the need for a cut-off point for the LLRT.[4] In addition, the authors did not publish subsequent articles using the test itself.[4] Our results confirm the significant difference and large effect size (P < 0.001, d ≥ 0.5) between healthy patients and patients with chronic low back pain undergoing the LLRT, highlighting the importance of this point omitted by the pioneers (i.e., Kim et al.).[4]

The second article on the LLRT was published by Pontes-Silva et al. using a sample with chronic low back pain.[3] They also found excellent reliability and a similar mean range (73.29 cm), but they omitted the validation of a cut-off point for the diagnosis of thoraco-lumbo-pelvic rotation range hypomobility.[3] Our study has a sample similar to the recent one in all clinical and anthropometric variables; therefore, our cut-off point (≤ 82.85 cm) is in agreement with the previously tested reliability.[3]

Clinical applicability of outcomes obtained

Translating scientific findings into clinical practice is one of the greatest challenges in research, as reproducing methods

Table 1. Characteristics of study participants: Healthy control group (n = 35) and chronic low back pain group (n = 35)

Variables	Groups	Minimum	Maximum	Mean	SD
Age (years)	HCG	19.00	41.00	26.91	5.31
	LBPG	18.00	50.00	31.54	8.84
Waist (cm)	HCG	63.00	90.00	75.09	7.37
	LBPG	62.00	114.00	79.93	13.64
Weight (kg)	HCG	53.10	91.14	68.64	9.32
	LBPG	45.80	134.70	68.38	19.23
Height (m)	HCG	1.50	1.90	1.68	0.09
	LBPG	1.50	1.80	1.61	0.08
Body mass index (kg/m^2)	HCG	19.00	33.70	24.29	3.37
	LBPG	17.50	46.60	26.03	6.43
Waist-to-height ratio	HCG	0.40	0.50	0.45	0.05
	LBPG	0.40	0.70	0.49	0.08
Conicity index (score)	HCG	0.90	1.20	1.08	0.08
	LBPG	0.90	1.30	1.14	0.09
Pain chronicity (months)	HCG	0.00	0.00	0.00	0.00
	LBPG	3.00	180.00	58.77	46.89
Iliospinale distance Right (cm)	HCG	80.00	96.00	87.80	4.42
	LBPG	74.50	95.00	83.65	5.24
Iliospinale distance Left (cm)	HCG	80.00	96.00	87.91	4.49
	LBPG	74.30	95.00	83.39	5.30
Pain level (NPRS)					
Rest	HCG	0.00	0.00	0.00	0.00
	LBPG	3.00	10.00	5.34	1.89
Movement	HCG	0.00	0.00	0.00	0.00
	LBPG	3.00	10.00	5.83	1.85
Disability (RMDQ)	HCG	0.00	0.00	0.00	0.00
	LBPG	3.00	23.00	8.40	4.42
Self-Efficacy (PSEQ)	HCG	0.00	60.00	60	0.00
	LBPG	11.00	60.00	38.57	14.19
Leg Lateral Reach Test (cm)					
Right	HCG	82.70	110.70	92.59	6.66
	LBPG	24.30	106.30	73.34	18.70
Left	HCG	67.30	109.30	94.35	7.88
	LBPG	42.70	99.30	74.39	17.23
Physical activity level (Baecke)					
Occupational	HCG	1.80	3.80	2.53	0.46
	LBPG	1.80	3.80	2.61	0.41
Sport	HCG	1.00	3.80	2.06	0.70
	LBPG	1.00	3.80	1.98	0.75
Leisure	HCG	1.50	3.50	2.11	0.54
	LBPG	1.30	3.50	2.04	0.53

SD = standard deviation; HCG = healthy control group; LBPG = low back pain; cm: centimeters; NPRS = Numeric Pain Rating Scale; RMDQ = Roland-Morris Disability Questionnaire; PSEQ = Pain Self-Efficacy Questionnaire.

Table 2. Comparisons between groups: Healthy control group (n = 35) and chronic low back pain group (n = 35)

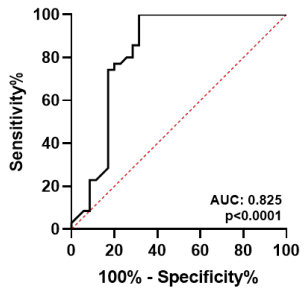
Variables	Groups	MD	95% CI	P value	Cohen's d
Age (years)	HCG LBPG	−4.63	−8.10, −1.15	0.010*	0.635#
Waist (cm)	HCG LBPG	−4.84	−10.07, 0.39	0.069	0.441
Weight (kg)	HCG LBPG	0.26	−6.95, 7.47	0.943	0.017
Height (m)	HCG LBPG	0.07	0.02, 0.11	0.002*	0.822#
Body mass index (kg/m^2)	HCG LBPG	−1.74	−4.19, 0.71	0.160	0.339
Waist-to-height ratio	HCG LBPG	−0.05	−0.08, −0.01	0.006*	0.600#
Conicity index (Score)	HCG LBPG	−0.06	−0.10, −0.02	0.005*	0.705#
Pain chronicity (months)	HCG LBPG	−58.77	−74.59, −42.95	<0.001*	1.773#
Iliospinale distance R (cm)	HCG LBPG	4.15	1.84, 6.46	0.001*	0.856#
Iliospinale distance L (cm)	HCG LBPG	4.52	2.17, 6.86	<0.001*	0.920#
Pain level (NPRS)					
Rest	HCG LBPG	−5.34	−5.98, −4.70	<0.001*	3.996#
Movement	HCG LBPG	−5.82	−5.20, −6.45	<0.001*	4.457#
Disability (RMDQ)	HCG LBPG	−8.40	−9.99, −6.80	<0.001*	2.402#
Self-Efficacy (PSEQ)	HCG LBPG	21.43	16.64, 26.22	<0.001*	2.136#
Leg Lateral Reach Test (cm)					
Right	HCG LBPG	19.25	12.55, 25.94	<0.001*	1.371#
Left	HCG LBPG	19.96	13.57, 26.35	<0.001*	1.490#
Physical activity level (Baecke)					
Occupational	HCG LBPG	−0.09	−0.30, 0.12	0.402	0.184
Sport	HCG LBPG	0.08	−0.26, 0.43	0.645	0.110
Leisure	HCG LBPG	0.07	-0.18, 0.33	0.578	0.131

MD = mean difference; CI = confidence interval; HCG = healthy control group; LBPG = low back pain; NPRS = Numeric Pain Rating Scale; RMDQ = Roland-Morris Disability Questionnaire; PSEQ = Pain Self-Efficacy Questionnaire. *Significant difference (t-test, P ≤ 0.05). #Moderate effect size (Cohen's d ≥ 0.5).

Table 3. Cut-off value, sensitivity, and specificity of thoraco-lumbar-pelvic mobility (cm) based on the leg lateral reach test; cm: centimeter

Variable	Cutt-off	Sensitivity	Specificity	AUC 95% CI	Youden Index	Positive Likelihood	Negative Likelihood
LLRT (cm)	≤ 82.85 (cm)	0.97	0.31	0.826 (0.717, 0.934)	0.66	1.41	0.10

AUC = area under the curve; CI = confidence interval; LLRT = leg lateral reach test.



AUC = area under the curve of the leg lateral reach test.

Figure 1. Receiver Operating Characteristic (ROC) curve.

tested in laboratories with the infrastructure to do so is not feasible for most healthcare professionals. Thus, the LLRT has excellent discriminatory power to diagnose thoraco-lumbo-pelvic rotation hypomobility in patients with chronic low back pain and presents itself as an assessment tool with potential for application because it is simple, fast, accessible, and does not require a large physical space (which may even be used for home care).[3,4]

Practice guidelines for the management of musculoskeletal pain recommend thorough physical examination and outcome measures to monitor prognosis.[29] Therefore, considering that patients with chronic low back pain may present with asymmetries in trunk rotation and decreased spinal flexibility,[30] the inclusion of the LLRT in clinical and experimental settings may guide therapeutic approaches to bilaterally compare and monitor the mobility of thoraco-lumbo-pelvic rotation in this population.[4]

The low specificity of the LLRT results in a high rate of false positives, indicating that individuals without true hypomobility may be incorrectly identified as having hypomobility. In clinical decision-making, this can lead to overtreatment, unnecessary interventions, or the misallocation of resources. Although the LLRT may be useful as an initial screening tool owing to its sensitivity and ease of application, its results should be interpreted with caution.

Therefore, to optimize its use, the LLRT should not be used in isolation. It is best employed in combination with other diagnostic tools such as more specific physical tests, imaging when indicated, or clinical judgment based on patient history and presentation. This multimodal approach balances the tradeoffs between sensitivity and specificity, improves diagnostic accuracy, and ensures appropriate clinical decisions.

Limitations and prospects for new studies

We are aware that the biostatistics of such studies are based on measures of central tendency to describe and/or infer the analyzed results. As such, we emphasize that the distance achieved in the LLRT may be influenced by stature and length of the low limb, taking into account the biological individuality of the patients (i.e., individual patient data).[31] Therefore, before using the cut-off point established in this study, we suggest that clinicians and scientists check whether there is a significant difference (> 5%) between their patients and those in our sample for the aforementioned characteristics.

Although the LLRT showed high sensitivity (97%), which is favorable for identifying at-risk individuals, its specificity was low (31%), indicating a high false positive rate. These results suggest that, while the test effectively rules out individuals without reduced thoraco-lumbo-pelvic mobility, it may also incorrectly classify many individuals as positive, even when they are not clinically impaired. This reduces its usefulness for confirming a diagnosis.

Several factors may account for the low specificity observed in this study. For example, LLRT performance may overlap between individuals with and without functional impairments, especially in heterogeneous populations. This overlap could result from variability in physical activity levels, compensation strategies, or differences in trunk and low limb biomechanics. In addition, anthropometric characteristics, such as stature, leg length, and pelvic width, may influence the reach distance during the LLRT and potentially bias the classification threshold.

Future studies should stratify the cut-off points based on height or other anthropometric measures. This would increase specificity without substantially compromising sensitivity, provided that robust samples were used. In addition, combining the LLRT with other functional tests or clinical indicators could improve overall diagnostic accuracy. Despite these limitations, the high area under the ROC curve (area under the curve = 0.826) and low negative likelihood ratio indicate that the LLRT holds promise as a screening tool for ruling out clinically significant dysfunction, but not as a standalone diagnostic measure.

CONCLUSION

Patients with chronic low back pain and an LLRT range ≤ 82.85 cm have hypomobility in the thoraco-lumbo-pelvic rotation range.

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Brazilian version of the Cognitive Risk Profile for Pain Scale: translation, cross-cultural adaptation, and validation

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COSMIN.
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ABSTRACT

OBJECTIVES: To translate, cross-culturally adapt, and validate the Cognitive Risk Profile for Pain (CRPP) scale for Brazilians with chronic pain.

METHODS: We conducted a questionnaire-based validation study. Patients (males and females) with pain in any part of the body for > 3 months were included (n = 191). The participants were assessed using the CRPP scale, the Numeric Pain Rating Scale (NPRS), the Hospital Anxiety and Depression Scale (HADS), the Pain-Related Catastrophizing Thoughts Scale (PCTS), and the Brunel Mood Scale (BRUMS). After the translation, cross-cultural adaptation, and validation of the CRPP scale, we tested for ceiling or floor effects, construct validity, reliability, and internal consistency. Finally, the second application of the CRPP scale was used to measure test-retest reliability.

RESULTS: Most participants were female, over 36 years of age, overweight, physically active, and had an average pain history of approximately 41 months. No ceiling or floor effects are observed. Nine domains of the CRPP scale correlated with the NPRS score, two domains of the HADS and PCTS, and six domains of the BRUMS. All CRPP domains demonstrated adequate reliability and internal consistency.

CONCLUSION: The Brazilian version of the CRPP scale demonstrated adequate measurement properties in patients with chronic pain.

INTRODUCTION

Chronic pain affects approximately 116 million adults and costs approximately $635 billion annually in medical treatment and lost worker productivity.[1] It is a major public health problem. The prevalence of chronic pain is continuously investigated.[2] The multidimensional aspect of pain and the difficulties in adequately measuring and characterizing pain are recognized. Instruments that allow the accurate and consistent measurement of chronic pain are warranted. The cognitive risk profile for pain, as reported by the patient, is also necessary.[3]

Although assessment of the cognitive risk profile for pain is important in assessment routines, it is complex and challenging to elucidate in patients with chronic pain. The constructs included in the cognitive risk profile of pain are difficult to measure. For example, the philosophical beliefs about pain, denial that mood affects pain, denial that pain affects mood, perception of blame, inadequate support, disability entitlement, desire for medical breakthrough, skepticism of a multidisciplinary approach, and conviction of hopelessness.[4]

Cook and DeGood[4] developed the Cognitive Risk Profile for Pain Scale (CRPP), which showed adequate internal consistency and construct validity in an American population. To date, the CRPP scale has not been adapted for the Brazilian population according to international recommendations[5–7] preventing its use in research and routine clinical assessments. Therefore, this study aimed to translate, cross-culturally adapt, and validate the CRPP scale for Brazilian patients with chronic pain.

METHODS

Study design and ethical aspects

A questionnaire validation study was conducted according to the guidelines for the process of cross-cultural adaptation of self-report measures[3] and the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN).[6]

Data collection for this study was conducted online using the free Google Forms platform (Mountain View, California) and disseminated through social networks and physical therapy clinics. This study was approved by the Research Ethics Committee of Universidade Ceuma (report no. 4.555.379).

Translation and cross-cultural adaptation

Permission to adapt the questionnaire into Brazilian Portuguese was granted by email from one of the authors (Dr. Andrew J. Cook).[4] The process of translation and cross-cultural adaptation of the CRPP scale into Brazilian Portuguese followed the recommendations of Beaton et al.[3] and was developed in five phases: translation and cross-cultural adaptation, synthesis of translations, back-translation of the questionnaire, analysis, and testing of the final version of the CRPP scale cross-culturally adapted into Brazilian Portuguese.

Translation: Two independent translators (a physiotherapist with 10 years of experience in the field and an English teacher with 20 years of experience in translation without technical knowledge in the health field), native speakers of Brazilian Portuguese fluent in English, translated the original version of the CRPP scale into Brazilian Portuguese.

Synthesis of translations: After discussions and revisions, two translators, under the supervision of one of the researchers, independently synthesized two versions of the translated questionnaire, which were discussed to produce a single version in a consensual manner.

Back-translation: Two independent translators (with no technical knowledge of health issues) and native and fluent Portuguese speakers translated the Portuguese version of the CRPP scale back into English without prior knowledge of the original version of the questionnaire.

Analysis by a committee of experts: Four specialists in the field of rehabilitation, together with the four translators involved in the project, reviewed all translated and back-translated versions to correct any discrepancies and arrived at the pre-final version of the CRPP scale in a form agreed upon by all members of the committee.

Pre-final version test: The pre-final version of the CRPP scale was administered to 30 individuals with chronic pain whose first language was Brazilian Portuguese. Participants read and completed the questionnaire, and at the end of completion, they indicated their understanding of the pre-final version of the CRPP scale by checking a box with "Yes" or "No" answers for each item in the questionnaire. If the items were not understood by more than 20% of the participants, they were reformulated and retested with a new sample of 30 participants until the desired level of understanding was reached.

Sampling and participants

The sample size was calculated according to the COSMIN recommendation of at least 100 participants.[7] The following inclusion criteria were considered: patients of both sexes; age 18 years or older; pain for more than three months in any part of the body; participants receiving treatment for pain, whether medical, pharmacological, physiotherapeutic or psychotherapeutic; literate. The exclusion criteria were as follows: diagnosis of severe cognitive or psychiatric illness, and non-Brazilian participants.

After defining the final version of the CRPP scale, the following measurement properties were evaluated: construct validity and test-retest reliability. This was accomplished by administering CRPP twice, one week apart. First, the CRPP scale and the following instruments were used to validate the construct: Numeric Pain Rating Scale (NPRS),[8] Hospital Anxiety and Depression Scale (HADS),[9] Pain-Related Catastrophizing Thoughts Scale (PCTS),[10] Brunel Mood Scale (BRUMS).[11] In the second application, the CRPP scale was administered to measure test-retest reliability.

Cognitive Risk Profile for Pain scale (CRPP)

The CRPP scale is a self-report instrument designed to aid clinical risk assessment and treatment planning for patients with chronic pain. It consists of 53 items with 6 response options: 1 – I strongly agree; 2 – I somewhat agree; 3 – I somewhat agree; 4 – I somewhat disagree; 5 – I partially disagree; 6 – I strongly disagree. However, several items have reverse scores (1 = 6; 2 = 5; 3 = 4; 4 = 3; 5 = 2; 6 = 1), namely: items 2–5, 7, 11–14, 16–18, 23, 24, 26, 28–30, 32, 35–43, 45–48, 51–53.

CRPP has nine domains: philosophic beliefs about pain (items 16, 17, 29, 30, 35, and 45); denial that mood affects pain (items 8, 19, 25, 31, and 53); denial that pain affects mood (items 10, 21, 33, 34, 49, and 50); perception of blame (items 9, 12, 23, 24, and 48); inadequate support (items 6, 11, 37, 39, 41, and 43); disability entitlement (items 13, 26, 32, 42, 47, and 51); desire for medical breakthrough (items 2, 5, 28, 36, 40, 46, and 52); skepticism of multidisciplinary approach (items 1, 15, 20, 22, 27, and 44); conviction of hopelessness (items 3, 4, 7, 14, 18, and 38).

For each domain, the average of the responses was calculated, generating scores ranging from one to six. High values indicate greater cognitive risk.[4] The Brazilian version of the CRPP scale is available at https://questionariosbrasil.blogspot.com/.

Others scales

NPRS measures pain intensity using a series of 11 numbers (from 0 to 10), with 0 representing "no pain" and 10 representing "maximum imaginable pain." This instrument was validated in Portuguese.[8]

The HADS measures symptoms of anxiety and depression using 14 items (seven items for anxiety and seven items for depression). To calculate a score for each domain, the answered items were added together, resulting in a score varying from 0 to 21. Higher scores indicated more severe symptoms. This instrument was previously validated in Brazil.[9]

The PCTS measures catastrophic thinking with 9 items. To calculate the total score, all items were added and divided by the number of items answered, resulting in a score varying from 0 to 5. Higher scores indicated greater catastrophizing. This instrument was previously validated in Brazil.[10]

The BRUMS assesses mood using 24 items grouped into six domains: anger, confusion, depression, fatigue, tension, and vigor. Each domain contains four items. The sum of the responses for each subscale yielded a score ranging from 0 to 16. Higher scores indicated a worse mood. This instrument was previously validated in Brazil.[11]

Statistical analysis

Descriptive statistics were performed, and the variables are presented as means and standard deviations, or absolute and relative frequencies. SPSS software (version 17.0, Chicago) was used to analyze the descriptive statistics, reliability, internal consistency, and construct validity.

Internal consistency was calculated using Cronbach's alpha to determine whether redundant or heterogeneous items were present in the questionnaire. Cronbach's alpha > 0.7 was considered adequate.[6] Reliability was assessed based on a test-retest model using the intraclass correlation coefficient (ICC). An ICC > 0.75 was considered adequate.[12] In addition, we calculated the standard error of measurement (SEM) and minimum detectable change (MDC).[13]

For construct validity, the Spearman correlation coefficient (rho) was used to determine the magnitude of the correlation between the CRPP scale and other instruments. Since there is no instrument with a similar construct used in Brazil, our hypothesis is that correlations with instruments measuring related but different constructs should vary between 0.3 and 0.5.[13] Ceiling and floor effects were evaluated in this study. By definition, these effects occur when more than 15% of the study participants reach the minimum or maximum questionnaire scores.[13]

RESULTS

Two adjustments were made to the Brazilian version of the CRPP scale: in item 9, the term "medical care" was changed to "care provided by health team care"; in item 39, the term "insurance providers" was expanded to "insurance providers, health insurance, and/or public health system". The preliminary version of the CRPP scale was administered to 30 patients with chronic pain. Item 12 was understood by 28 participants (93.33%). All other 52 items were understood by 100% of the respondents.

The study sample comprised 191 participants. Most participants were female, over 36 years old, overweight, physically active, and did not use tobacco or alcohol. The most common pain locations were the lumbar spine, cervical spine, knees, and shoulders. The mean duration of pain was slightly longer than 41 months (**Table 1**). Among the data obtained, the variables anxiety and depression of the HADS and vigor and mental confusion of the BRUMS presented the highest means as well as the highest standard deviations of the entire sample (**Table 2**).

The nine domains of the CRPP scale correlated with the NPRS score, anxiety, and depression domains of the HADS, PCTS, and six domains of the BRUMS. A significant correlation was observed with magnitudes varying from 0.145 to 0.658 (**Table 3**).

The reliability and internal consistency were assessed using a subsample (n = 57). Adequate reliability was demonstrated for all the CRPP scale domains, with ICC values ranging from 0.786 to

Table 1. Participant characteristics (n = 191)

Variables	Mean (± SD) or Number (%)
Sex (female)	128 (67%)
Age (years)	36.56 (12.27)
Body mass (kg)	72.16 (15.63)
Stature (m)	1.64 (0.09)
Body mass index (kg/m^2)	26.40 (4.81)
Marital status	
Single	104 (54.5%)
Married	72 (37.7%)
Divorced	13 (6.8%)
Widowed	2 (1%)
Education level	
Incomplete primary education	5 (2.6%)
Complete primary education	6 (3.1%)
Incomplete secondary education	5 (2.6%)
Complete secondary education	20 (10.5%)
Incomplete undergraduate degree	42 (22%)
Complete undergraduate degree	36 (18.8%)
Incomplete post-graduation	19 (9.9%)
Complete post-graduation	58 (30.5%)
Physical activity (yes)	138 (72.3%)
Smoker	
Yes	2 (1%)
No	186 (97.4%)
Ex-smoker	3 (1.6%)
Alcoholism	
No	90 (47.1%)
Rarely	75 (39.3%)
Once/week	24 (12.6%)
Daily	2 (1%)
Pain time (months)	41.72 (62.36)
Main body pain sites	
Low back	90 (47.1%)
Neck	26 (13.6%)
Knee	22 (11.5%)
Shoulder	18 (9.4%)
Head	7 (3.7%)
Foot	7 (3.7%)
Hip	5 (2.6%)
Leg	4 (2.1%)
Others	12 (6.3%)

0.942. The Cronbach's alpha values were also adequate (0.714–0.922) (**Table 4**). No ceiling or floor effects were observed.

DISCUSSION

This is the first study to translate, cross-culturally adapt, and validate the CRPP scale for Brazilians with chronic pain according to international recommendations.[5–7] Our results showed adequate construct validity, reliability, and internal consistency when applied to patients with chronic pain.

In terms of construct validity, the nine domains of the CRPP scale[4] were correlated with pain,[8] anxiety,[9] depression,[9] catastrophizing thoughts,[10] tension, anger, vigor, fatigue, and mental confusion[11] in instruments previously validated in the same population. Therefore, the CRPP scale can be used to measure philosophical beliefs about pain, denial that mood affects pain, perception of blame, inadequate support, disability entitlement, desire for medical breakthrough, skepticism of a multidisciplinary approach, and conviction of hopelessness in the assessment routine.[4]

In terms of reliability and internal consistency, our results indicated that each of the nine domains of the CRPP scale[4] achieved reliable scores within the errors inherent in prospective assessments. These reliability and internal consistency results allow healthcare professionals to compare the prognoses of their patients over the treatment period, as measurements at different times are supported by ICC, internal consistency, SEM, and MDC.

These findings have significant clinical and scientific implications. As such, the minor adjustments made to items 9 and 39 of the Brazilian version of the CRPP scale demonstrate the need for cultural adaptation beyond translation, particularly in healthcare systems with different structures and terminologies. These adaptations ensured greater clarity and relevance for the Brazilian respondents, which is crucial for the valid application of self-report instruments in diverse sociocultural contexts.

Additionally, the level of comprehension of 52 out of 53 items by all participants indicated a strong validity. This confirmed that the instrument is accessible to Brazilian patients with chronic pain. This is particularly relevant in clinical settings where tools must be easily understood to ensure accurate self-reporting.

Table 2. Instrument scores (n = 191)

Instrument	Mean (SD)
Numeric Pain Rating Scale (score, 0–10)	6.12 (2.31)
Hospital Anxiety and Depression Scale (score, 0-21)	
Anxiety	9.05 (4.65)
Depression	6.61 (3.88)
Pain-Related Catastrophizing Thoughts Scale (score, 0–5)	1.78 (1.31)
Brunel Mood Scale (score, 0–16)	
Tension	5.95 (2.44)
Depression	5.83 (3.84)
Anger	5.76 (3.83)
Vigor	6.52 (2.78)
Fatigue	4.92 (2.28)
Mental confusion	6.41 (3.15)
Cognitive Risk Profile for Pain Scale (score, 1–6)	
D1	4.27 (0.91)
D2	2.7 (1.06)
D3	3.02 (1.25)
D4	2.74 (1.03)
D5	3.25 (0.97)
D6	2.48 (1.32)
D7	4.26 (0.87)
D8	1.71 (0.6)
D9	3.14 (1.27)

D1, philosophic beliefs about pain; D2, denial that mood affects pain; D3, denial that pain affects mood; D4, perception of blame; D5, inadequate support; D6, disability entitlement; D7, desire for medical breakthrough; D8, skepticism of multidisciplinary approach; D9, conviction of hopelessness.

Table 3. Correlation between the domains of the Cognitive Risk Profile for Pain scale (CRPP) and other instruments (n = 191)

Instruments	CRPP								
	D1	D2	D3	D4	D5	D6	D7	D8	D9
NPRS	0.240*	0.041	0.331*	0.117	0.263*	0.293*	0.055	0.051	0.345*
HADS									
Anxiety	0.232*	0.074	0.428*	0.308*	0.360*	0.239*	0.211*	0.270*	0.439*
Depression	0.196*	0.053	0.359*	0.265*	0.342*	0.231*	0.148*	0.274*	0.412*
PCTS	0.376*	0.003	0.497*	0.304*	0.360*	0.232*	0.317*	0.658*	0.596*
Brunel Mood Scale									
Tension	0.212*	0.044	0.291*	0.255*	0.296*	0.154*	0.108	0.163*	0.275*
Depression	0.260*	0.075	0.431*	0.271*	0.369*	0.225*	0.136	0.246*	0.478*
Anger	0.262*	0.062	0.413*	0.268*	0.321*	0.154*	0.178*	0.260*	0.472*
Vigor	0.230*	0.153*	0.382*	0.274*	0.331*	0.204*	0.206*	0.145*	0.441*
Fatigue	0.260*	0.098	0.332*	0.232*	0.320*	0.160*	0.151*	0.087	0.350*
Mental confusion	0.163*	0.092	0.366*	0.229*	0.243*	0.120	0.136	0.159*	0.385*

NPRS, Numeric Pain Rating Scale; HADS, Hospital Anxiety and Depression Scale; PCTS, Pain-Related Catastrophizing Thoughts Scale; D1, philosophic beliefs about pain; D2, denial that mood affects pain; D3, denial that pain affects mood; D4, perception of blame; D5, inadequate support; D6, disability entitlement; D7, desire for medical breakthrough; D8, skepticism of multidisciplinary approach; D9, conviction of hopelessness.

Table 4. Reliability and internal consistency of the Cognitive Risk Profile for Pain scale (CRPP) (n = 57)

Domain	Test	Retest	ICC	95% CI	SEM	MDC	α
D1	4.44 (0.86)	4.4 (0.84)	0.856	0.756, 0.915	0.32	0.89	0.781
D2	2.72 (0.99)	2.68 (1.07)	0.856	0.755, 0.915	0.39	1.08	0.852
D3	2.93 (1.23)	2.98 (1.21)	0.93	0.882, 0.959	0.32	0.89	0.919
D4	2.83 (1.19)	2.89 (1.12)	0.87	0.779, 0.923	0.42	1.15	0.778
D5	3.17 (1.02)	3.07 (0.97)	0.898	0.827, 0.94	0.33	0.91	0.714
D6	2.52 (1.3)	2.41 (1.27)	0.907	0.842, 0.945	0.39	1.09	0.913
D7	4.28 (0.89)	4.37 (1.02)	0.882	0.8, 0.931	0.33	0.92	0.844
D8	1.75 (0.65)	1.84 (0.63)	0.786	0.637, 0.874	0.3	0.82	0.795
D9	3.54 (1.29)	3.64 (1.39)	0.942	0.901, 0.966	0.32	0.89	0.922

D1, philosophic beliefs about pain; D2, denial that mood affects pain; D3, denial that pain affects mood; D4, perception of blame; D5, inadequate support; D6, disability entitlement; D7, desire for medical breakthrough; D8, skepticism of multidisciplinary approach; D9, conviction of hopelessness; ICC, intraclass correlation coefficient; SEM, standard error of measurement; MDC, minimum detectable change; α, Cronbach's alpha.

This study has one key limitation. We only performed the analysis on a sample of Brazilian participants. To further validate the CRPP scale for chronic pain, new studies testing the CRPP scale in different languages and in different countries are warranted. Other measurement properties, such as structural validity and responsiveness, should also be considered.

CONCLUSION

The Brazilian version of the CRPP scale showed adequate measurement validity in patients with chronic pain. This version of the CRPP scale can help health professionals working with Brazilians to identify maladaptive pain beliefs and coping strategies, thus enabling more personalized interventions. It can also serve as a valuable outcome measure in multidisciplinary pain management programs, helping monitor cognitive and behavioral progress over time. From a research perspective, having a culturally adapted CRPP scale allows for cross-cultural comparisons and longitudinal studies to examine how pain beliefs and behaviors evolve in response to different treatments.

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Impact of a telemedicine center on reducing the carbon footprint for primary health care: a multicenter retrospective cohort study

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ABSTRACT

BACKGROUND: Telemedicine can promote access to specialized care and avoid travel to referral centers.

OBJECTIVES: To present the environmental impacts and the positive results for the sustainability of the Brazilian public health system after the implementation of the TeleNordeste Project developed by hospital BP – A Beneficência Portuguesa de São Paulo.

DESIGN AND SETTING: A retrospective cohort study was developed in three states in the Brazilian Northeast, Alagoas, Maranhão, and Piauí.

METHODS: This study was conducted between August 2022 and December 2023. All patients participating in telemedicine care were selected for this type of care by Primary Health Care (PHC) doctors according to the need for clinical discussion. The variables analyzed were the total distance and time (round trip) saved by telemedicine care, the amount of carbon emissions not released into the environment, gasoline costs, resolution of care through teleconsultation, and evaluation of the Net Promoter Score.

RESULTS: In total, 25,194 consultations were conducted via telemedicine, requiring in-person referral in 775 tele-interconsultations, representing a resolution rate of 96.92%. It saved approximately 10,737,287 miles (17,279,988.6 km) and 264,302 hours for patients and the municipal health department, and reduced carbon dioxide (CO_2) emissions according to Environmental Protection Agency (EPA) parameters, estimated at 4,294,915 kg, saving US$ 1,660,068.89 (R$ 8,532,754.09) on gasoline.

CONCLUSION: To our knowledge, in Brazil, this study is one of the first to present results on the impact of telemedicine on reducing carbon emissions in relation to the movement of patients to reference centers in healthcare networks and the resolution of care provided in health units in the context of the PROADI-SUS TeleNordeste Project developed by BP and promotes reflection on the potential benefits of telemedicine according to current evidence.

INTRODUCTION

Globally, health services are the centers of operations for healthcare and assistance, saving lives and promoting well-being; however, the current structure of these services involves the production of high amounts of carbon dioxide (CO_2) through the use of significant resources and equipment that consume a lot of energy and harm the environment and public health.[1–4] Recent evidence estimates that healthcare systems represent approximately 4.4% of CO_2 emissions worldwide, with higher percentages in industrialized countries.[3–7] Recognition of this issue is beginning to gain prominence in the global scientific community through the science of sustainability in healthcare, which analyzes various dimensions of resource consumption and environmental emissions associated with healthcare activities. This emerging field of knowledge presents tools and metrics to quantify the unintended consequences of healthcare related to service provision, evaluate effective alternatives that improve patient care and safety, and simultaneously consider the sustainability of health systems.[2]

Considering the ethical principle of non-maleficence,[8] health professionals are committed to not causing harm,[6] and in this way, health systems should lead the way towards greater sustainability and preservation of the environment and well-being of the population with proposals for alternatives for reducing CO_2 emissions and maintaining quality of care.[1] Telemedicine saw a rapid expansion of its use with the COVID-19 pandemic, enabling care to be maintained

with less patient exposure.[9] Since this period, it has had a positive impact on global healthcare, promoting greater access for many patients, especially for residents of distant areas of health centers, by reducing travel.[3]

In this context, the hospital BP – A Beneficência Portuguesa de São Paulo, recognized as a hospital of excellence by the Brazilian Ministry of Health, through the Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde (PROADI-SUS) has developed TeleNordeste Project, providing specialized consultations to several municipalities, in the Brazilian Northeast, to promote access to specialized care for users of the SUS and to avoid travel to reference centers with significant distances on a continental country like Brazil. Therefore, meeting the purpose of improving access to specialized assistance is associated with reducing CO_2 emissions and their environmental impacts.[10]

This study aimed to present the environmental impacts and the positive results for the sustainability of the public health system, SUS, benefiting users and managers of the locations served after the implementation of the TeleNordeste Project developed by the hospital BP – A Beneficência Portuguesa de São Paulo.

METHODS

Study design

A retrospective cohort study was conducted to analyze the environmental impacts of teleconsultations conducted through BP's TeleNordeste Project. This study followed the guidelines of the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) for cohort studies.[11]

Location and period of study

This research was developed by the hospital BP – A Beneficência Portuguesa de São Paulo through the PROADI-SUS in partnership with the Ministry of Health, with the implementation of the Specialized Medical Assistance Project in the Northeast region of Brazil by means of Telemedicine, TeleNordeste from BP, registered with NUP 25000.170151/2021-65.

The project was implemented in 360 municipalities in three states in the Brazilian Northeast: Alagoas (90), Maranhão (134), and Piauí (136), with the proposal to carry out tele-interconsultations from August 2022 to December 2023. Synchronous tele-interconsultations were offered with specialist doctors, connecting doctors from different BP specialties, Primary Health Care (PHC) teams, and patients from the territories served in the same virtual environment synchronously, enabling discussions about clinical conditions dedicated to the management of the patient's longitudinal care.[10] Schedules of tele-interconsultations were carried out through the Bookings platform by PHC, and virtual meetings were carried out through the Teams platform, both from BP's institutional Microsoft 365® (Redmond, Washington State).

All tele-interconsultations conducted between August 2022 and December 2023 were included in the study. All patients participating in telemedicine care were selected for this type of care by PHC doctors according to the need for clinical discussion.

The specialist doctors hired by BP also carried out their work remotely from the home office, with a strategic alignment to contribute to reducing the project's carbon emissions, although the impact of the specialized team was not analyzed in this study.

The resolution rate was calculated by dividing the number of tele-interconsultations that resulted in a complete specialized care visit with guidance on follow-up within the primary health care system by the total number of tele-interconsultations conducted by the project during the study period. The evaluation of service satisfaction in the TeleNordeste project was conducted through the application of the Net Promoter Score (NPS), a methodology used to evaluate customer satisfaction in relation to the service provided.[12,13] The responses were categorized into three groups: promoters, neutrals, and detractors. The structured question was, "How likely are you to recommend TeleNoredeste to a friend?" Each participating PHC doctor received the question by email, and each patient received the question via a message on WhatsApp.

Variables

The variables analyzed by the project were the total distance and total time (round trip) saved by telemedicine care, the amount of carbon emissions not released into the environment, the cost of gasoline, care resoluteness through tele-interconsultation, which indicates the completion of care without the need for referral to a specialized in-person consultation, and evaluation of the NPS.

Data analysis

According to documents provided by the State Health Departments of Alagoas, Maranhão, and Piauí, references for specialized care were identified for referrals from Basic Health Units, making it possible to establish estimates of travel required to carry out in-person consultations with specialist doctors. Referred patients are usually transported to a reference point in the capital of each state in cars or minivans, as defined by the municipal departments of each city. It was assumed that all treated patients waited for a specialized face-to-face consultation and would leave the central point of the municipality with a round-trip by car to the reference capital. All patients included in the study were registered with the PHC.

The distance traveled in kilometers and times (in minutes) were calculated in May 2024 using data available on Google® (Menlo Park, California). Briefly, the locations were identified by latitude and longitude, and the distance between two locations

was calculated by establishing an available route involving highways with the shortest distance and travel time. It is important to note that the locations served by the project also had ferries along their route. Of the 360 municipalities participating in the project, sixteen municipalities (4.44%) required a ferry to access specialized references.

Traveling patients to specialized care involves several variables, such as the scheduling date and address of the reference outpatient clinic for each specialty, and companions are often necessary for children, older adults, and patients with special needs. Therefore, it was difficult for a car to transport these four patients to the references. In this way, the estimate of this study considered travel for each tele-interconsultation individually, but considering the optimization of the variables presented, the costs were also estimated if the car was fully occupied. This study calculated the distance traveled in a scenario of four passengers for a UBS that conducted four or more tele-interconsultations. For appointments of < 4, occupancy was adjusted according to the number of teleconsultations.

The CO_2 emissions saved from vehicle travel were calculated using the Environmental Protection Agency (EPA) emissions parameters, which estimate that the average passenger vehicle emits about 400 grams of CO_2 per mile, and the CO_2 emissions from a gallon of gasoline are 8,887 grams of CO_2/gallon.[14] The United States Regular Gasoline Price[15] data was used as of June 17, 2024, with the price of gasoline being US$ 3.435 per gallon, to calculate the estimated gasoline costs saved.

To convert into reality, this study used data from the Ministry of Finance with dollar value for conversion to the real for June 2024, worth US $1, quoted as R$ 5.14.

Statistical analysis was performed using the PSPP-GNU® statistical software, GNU General Public License, version June 3 29, 2007. Continuous variables without a normal distribution were presented as medians and interquartile ranges.

Approval by the research ethics committee

The study protocol was approved by the Ethics and Research Committee of the hospital BP – A Beneficência Portuguesa de São Paulo, and approved under number CAAE 72813923.6.0000.5483, with waiver of informed consent.

RESULTS

From August 2022 to December 2023, 25,194 teleinterconsultations were conducted via telemedicine, requiring in-person referral in 775 tele-interconsultations, representing a resolution of 96.92% of the clinical conditions treated by BP specialists in partnership with PHC doctors. Travel from PHC units to reference services was avoided, saving approximately 10,737,287.12 miles (equivalent to 17,279,988.6 km) for patients and municipal health departments, with an estimated time savings of 264,302 h. Regarding the reduction of CO_2 emissions according to EPA parameters, it was approximately 4,294,915 kg of CO_2 (**Tables 1 and 2**) and equivalent, according to the parameters, 483,280.61 gallons of gasoline, saving US$ 1,660,068.89 (R$ 8,532,754.09) on gasoline. The median distance saved was approximately 442 miles with an interquartile range of 308 miles (equivalent to 712 km and an interquartile range of 496). Regarding carbon emissions, the median amount of CO_2 avoided was approximately 177 kg of CO_2, with an interquartile range of 123.28. If it were possible to optimize trips to reach a maximum occupancy of passengers per vehicle, the estimated distance would be 3,843,362.57 miles (equivalent to 6,185,292.5 km), representing approximately 172,988.07 gallons of gasoline. This would save US$ 594,214.03 (R$ 3,054,260.11). The reduction in CO_2 emissions according to EPA parameters was approximately 1,537,345 kg of CO_2. The median distance saved was approximately 123 miles, with an interquartile range of 91.65 (equivalent to 198 km, with an interquartile range of 147.5). Regarding carbon emissions, the median CO_2 avoided was approximately 49.21 kg of CO_2, with an interquartile range of 36.66 kg (**Table 1**). Carbon emission reductions by specialty are shown in **Figure 1**.

For the state of Alagoas, the median distance saved was approximately 139.2 miles with an interquartile range of 144.6 miles (equivalent to 224 km with an interquartile range of 232.7 km). Regarding carbon emissions, the median CO_2 avoided was approximately 55.67 kg of CO_2, with an interquartile range of 57.83.

For the state of Maranhão, the median distance saved was approximately 484.67 miles with an interquartile range of 221.2 (equivalent to 780 km with an interquartile range of 356 km). Regarding carbon emissions, the median amount of CO_2 avoided was approximately 193.86 kg of CO_2, with an interquartile range of 88.48.

Table 1. Variables according to the state

State	Number of teleconsultations*	In-person referral*	Economy			Resolution of teleconsultation**	Referral fee**
			Distance (miles)*	Time (hours)*	Carbon emission (grams)*	Primary health care	Specialist consultation
Alagoas	5,842	166	1,006,539.06	26,025.32	402,615,624	97.16%	2.84%
Maranhão	10,851	359	5,615,626.62	146,094.57	2,246,250,648	96.69%	3.31%
Piauí	8,501	250	4,115,121.44	92,182.20	1,646,048,576	97.06%	2.94%
Total	25,194	775	10,737,287.12	264,302.09	4,294,914,848	96.92%	3.08%

* Absolute values and; ** Percentage (%).

Table 2. Variables according to specialties

Specialty	Number of teleconsultations*	In-person referral*	Economy			Resolution of teleconsultation**	Referral fee**
			Distance (miles)*	Time (hours)*	Carbon emission (grams)*	Primary health care	Specialist consultation**
Cardiology (AL)	661	11	103,760.54	2,708.33	41,504,215.38	98.34%	1.66%
Cardiology (MA)	1,031	20	539,105.62	13,985.53	215,642,249.30	98.06%	1.94%
Cardiology (PI)	807	5	378,957.89	8,562.87	151,583,154.40	99.38%	0.62%
Cardiology total	**2,499**	**36**	**1,021,824.05**	**2,556.73**	**408,729,619.08**	**98.56%**	**1.44%**
Pediatric cardiology (AL)	5	0	929.32	23.3	371,729.10	100%	0%
Pediatric cardiology (MA)	15	0	9,846.25	249.47	3,938,499.17	100%	0%
Pediatric cardiology (PI)	18	0	7,663.0	175.3	3,065,199.24	100%	0%
Pediatric cardiology total	**38**	**0**	**18,438.57**	**448.07**	**7,375,427.51**	**100%**	**0%**
Palliative care (AL)	11	0	1,594.44	45.06	637,775.40	100%	0%
Palliative care (MA)	5	0	3,084.49	78.5	1,233,794.64	100%	0%
Palliative care (PI)	23	0	12,666.03	278.77	5,066,412.15	100%	0%
Palliative Care total	**39**	**0**	**17,344.96**	**402.33**	**6,937,982.19**	**100%**	**0%**
Dermatology (AL)	887	61	154,619.40	4,009.77	61,847,759.09	93.12%	6.88%
Dermatology (MA)	1,553	142	811,642.01	21,167.53	324,656,804.30	90.86%	9.14%
Dermatology (PI)	1,030	67	488,505.09	10,972.90	195,400,361.90	93.5%	6.5%
Dermatology total	**3,470**	**270**	**1,454,762.31**	**36,150.20**	**581,904,925.29**	**92.22%**	**7.78%**
Endocrinology (AL)	1,033	7	188,427.21	4,886.33	75,370,884.04	99.32%	0.68%
Endocrinology (MA)	1,652	18	844,135.87	21,847.50	337,654,348.60	98.91%	1.09%
Endocrinology (PI)	1,246	10	586,459.95	13,142.66	234,583,979.60	99.2%	0.8%
Endocrinology total	**3,931**	**35**	**1,619,023.03**	**39,876.49**	**647,609,212.24**	**99.11%**	**0.89%**
Geriatrics(AL)	188	6	34,863.90	882.33	13,945,557.94	96.81%	3.19%
Geriatrics (MA)	510	9	266,473.80	6,815.83	106,589,517.20	98.23%	1.77%
Geriatrics (PI)	242	1	104,247.57	2,345.37	41,699,027.68	99.58%	0.42%
Geriatrics total	**940**	**16**	**405,585.27**	**10,043.53**	**162,234,102.8**	**98.29%**	**1.71%**
Gynecology (AL)	516	7	84,084.32	2,265.11	33,633,729.02	98.64%	1.36%
Gynecology (MA)	1,013	23	522,563.36	13,987.73	209,025,342	97.73%	2.27%
Gynecology (PI)	805	30	421,092.44	9,418.56	168,436,978	96.27%	3.73%
Gynecology total	**2,334**	**60**	**1,027,740.12**	**25,671.40**	**411,096,049.02**	**97.43%**	**2.57%**
Hematology (AL)	48	5	5,465.58	155.2	2,186,232.40	89.58%	10.42%
Hematology (MA)	96	1	45,270.62	1,182.13	18,108,247.83	98.96%	1.04%
Hematology (PI)	64	4	31,157.42	706.86	12,462,966.28	93.75%	6.25%
Hematology total	**208**	**10**	**81,893.62**	**2,044.20**	**32,757,446.51**	**95.19%**	**4.81%**
Infectology (AL)	32	0	5,508.95	143.64	2,203,581.09	100%	0%
Infectology (MA)	126	4	64,372.81	1,667.8	25,749,125.11	96.83%	3.17%
Infectology (PI)	31	4	13,647.30	306.03	5,458,919.91	87.1%	12.9%
Infectology total	**189**	**8**	**83,529.06**	**2,117.47**	**33,411,626.11**	**95.77%**	**4.23%**
Family physician (AL)	17	3	2,086.69	58.63	834,675.50	82.35%	17.65%
Family physician (MA)	41	4	21,244.68	542.6	8,497,872.43	90.24%	9.76%
Family physician (PI)	33	1	14,962.62	350.3	5,985,047.32	96.97%	3.03%
Family physician total	**91**	**8**	**38,293.99**	**951.53**	**15,317,595.25**	**91.21%**	**8.79%**
Neurology(AL)	724	13	127,414.15	3,224.88	50,965,660.54	98.2%	1.8%
Neurology (MA)	1,162	41	577,664.07	15,019.10	231,065,626.70	96.47%	3.53%
Neurology (PI)	1,030	37	488,198.67	10,974.87	195,279,467.90	96.41%	3.59%
Neurology total	**2,916**	**91**	**1,193,276.89**	**29,218.85**	**477,310,755.14**	**96.88%**	**3.12%**
Pediatric neurology (AL)	37	3	10,614.51	252.67	4,245,804.50	91.89%	8.11%
Pediatric neurology (MA)	126	3	63,541.42	1,629.33	25,416,567.25	97.62%	2.38%
Pediatric neurology (PI)	130	8	64,876.62	1,461.93	25,950,648.21	93.85%	6.15%
Pediatric neurology total	**293**	**14**	**139,032.55**	**3,343.93**	**55,613,019.96**	**95.22%**	**4.78%**
Pediatrics (AL)	242	21	40,871.93	1,068.40	16,348,773.16	91.32%	8.68%
Pediatrics (MA)	626	35	311,241.97	8,151.70	124,496,788.80	94.41%	5.59%

Continue...

Table 2. Continuation

Specialty	Number of teleconsultations*	In-person referral*	Economy			Resolution of teleconsultation**	Referral fee**
			Distance (miles)*	Time (hours)*	Carbon emission (grams)*	Primary health care	Specialist consultation**
Pediatrics (PI)	409	35	233,100.44	5,251.43	93,240,177.36	91.44%	8.56%
Pediatrics total	**1,277**	**91**	**585,214.34**	**14,471.53**	**234,085,739.32**	**92.87%**	**7.13%**
Pneumology (AL)	260	9	47,177.36	1,199.43	18,870,943.69	96.54%	3.46%
Pneumology (MA)	531	19	255,336.96	6,633.53	102,134,782.90	96.42%	3.58%
Pneumology (PI)	492	7	239,085.86	5,331.46	95,634,345.42	98.58%	1.42%
Pneumology total	**1,283**	**35**	**541,600.18**	**13,164.42**	**216,640,072.01**	**97.27%**	**2.73%**
Psychiatry (AL)	486	12	81,784.38	2,129.8	32,713,751.69	97.53%	2.47%
Psychiatry (MA)	777	15	428,386.60	11,051.73	171,354,638.90	98.07%	1.93%
Psychiatry (PI)	963	24	475,256.13	10,529.13	190,102,451.70	97.51%	2.49%
Psychiatry total	**2,226**	**51**	**985,427.11**	**23,710.66**	**394,170,742.29**	**97.71%**	**2.29%**
Child psychiatry (AL)	153	3	26,330.73	661.96	10,532,291.42	98.04%	1.96%
Child psychiatry (MA)	515	6	276,558.65	7,198.16	110,623, 459	98.83%	1.17%
Child psychiatry (PI)	330	3	163,588.52	3,634.63	65,435,407.22	99.09%	0.91%
Child psychiatry total	**998**	**12**	**466,477.90**	**11,494.76**	**186,591,157.64**	**98.8%**	**1.2%**
Rheumatology(AL)	542	5	91,005.65	2,310.45	36,402,260.80	99.08%	0.92%
Rheumatology (MA)	1,072	19	575,157.46	14,886.36	230,062,982.20	98.23%	1.77%
Rheumatology (PI)	848	14	391,660.08	8,739.10	156,664,032.10	98.35%	1.65%
Rheumatology total	**2,462**	**38**	**1,057,823.19**	**25,935.91**	**423,129,275.10**	**98.46%**	**1.54%**

AL, Alagoas; MA, Maranhão; PI, Piauí; * Absolute values; ** Percentage (%).

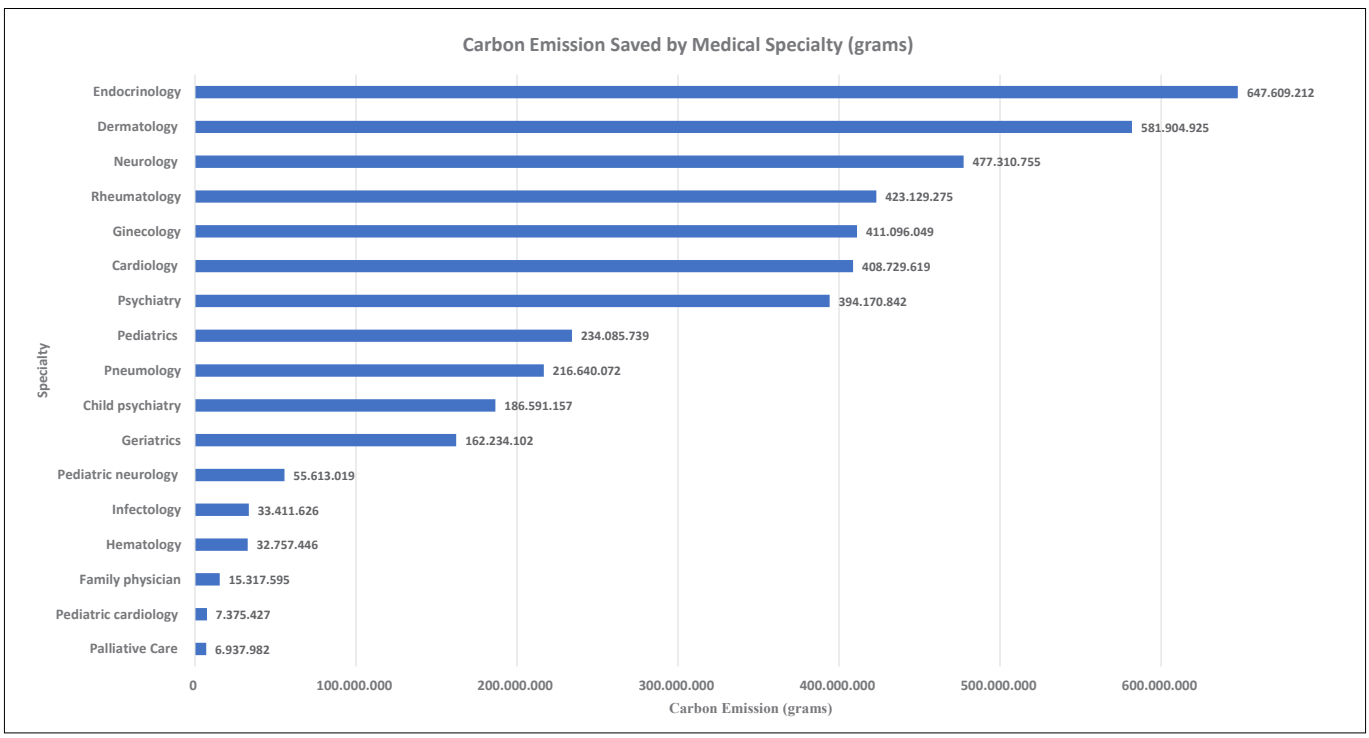

Figure 1. Carbon emission saved by medical specialty (grams).

For the state of Piauí, the median distance saved was approximately 492.13 miles with an interquartile range of 208.78 (equivalent to 792 km with an interquartile range of 336 km). Regarding carbon emissions, the median amount of CO_2 avoided was approximately 196.85 kg of CO_2, with an interquartile range of 83.51 g.

The three specialties with the highest numbers of teleconsultations were Psychiatry, Endocrinology, and Dermatology.

Some specialties, such as pediatric cardiology and palliative care, showed 100% resolution in clinical discussions. Additional information is presented in **Table 2** and **Figure 2**.

Regarding the evaluation of satisfaction with TeleNordeste services, the NPS of PHC medical professionals was 91, and the result related to patients served was 89.3, considering the three states served by the project.

DISCUSSION

The implementation of the TeleNordeste project avoided the movement of patients to specialized references and promoted positive socioeconomic and environmental impacts, as there was a reduction in costs for municipal health departments, saving between US$ 594,214.03 (R$ 3,054,260.11) and US$ 1,660,068.89 (R$ 8,532,754.09) on gasoline, and a reduction in CO_2 emissions for the environment between 1,537,345 and 4,294,915 kg, depending on transportation optimization. Besides the quantitative aspects, the project enabled qualitative gains for care provided through support for PHC, establishing greater resolution with overall results of 96.92% with agile and timely access, directly impacting the care of people using local healthcare networks, and developing a care repertoire of professionals benefiting from the intervention with positive NPS results for participating PHC users and doctors.[10]

It is important to highlight that in-person referrals, established after evaluation by BP specialists, provided timely guidance for each tele-interconsultation and, when relevant, requests for examinations and therapeutic prescriptions were made, enabling the coordination of care until access to in-person consultation. In this context, this study highlights the experience of the project's team of dermatologists, who referred 7.78% of patients evaluated in tele-interconsultation, and many of these clinical conditions required a biopsy to be carried out for an effective diagnostic conclusion; therefore, the indication for the procedure was guided by a specialist.

These results indicate a significant impact on carbon emissions, congruent with current evidence on the topic, which highlights that reducing face-to-face consultations has become a vital tool for sustainable health development.[5,16–18] According to a systematic review carried out by Purohit, Smith, and Hibble[16] in 2021, all studies analyzed unanimously reported that the use of telemedicine promoted a reduction in CO_2 emissions from healthcare, mainly by reducing the costs associated with emissions during travel. Carbon footprint reduction ranged between 0.70 and 372 kg CO_2 per consultation.

Furthermore, BP's proposal to structure a remote work model for medical specialists contributed to the reduction of carbon emissions by the health service and is also a factor associated with less

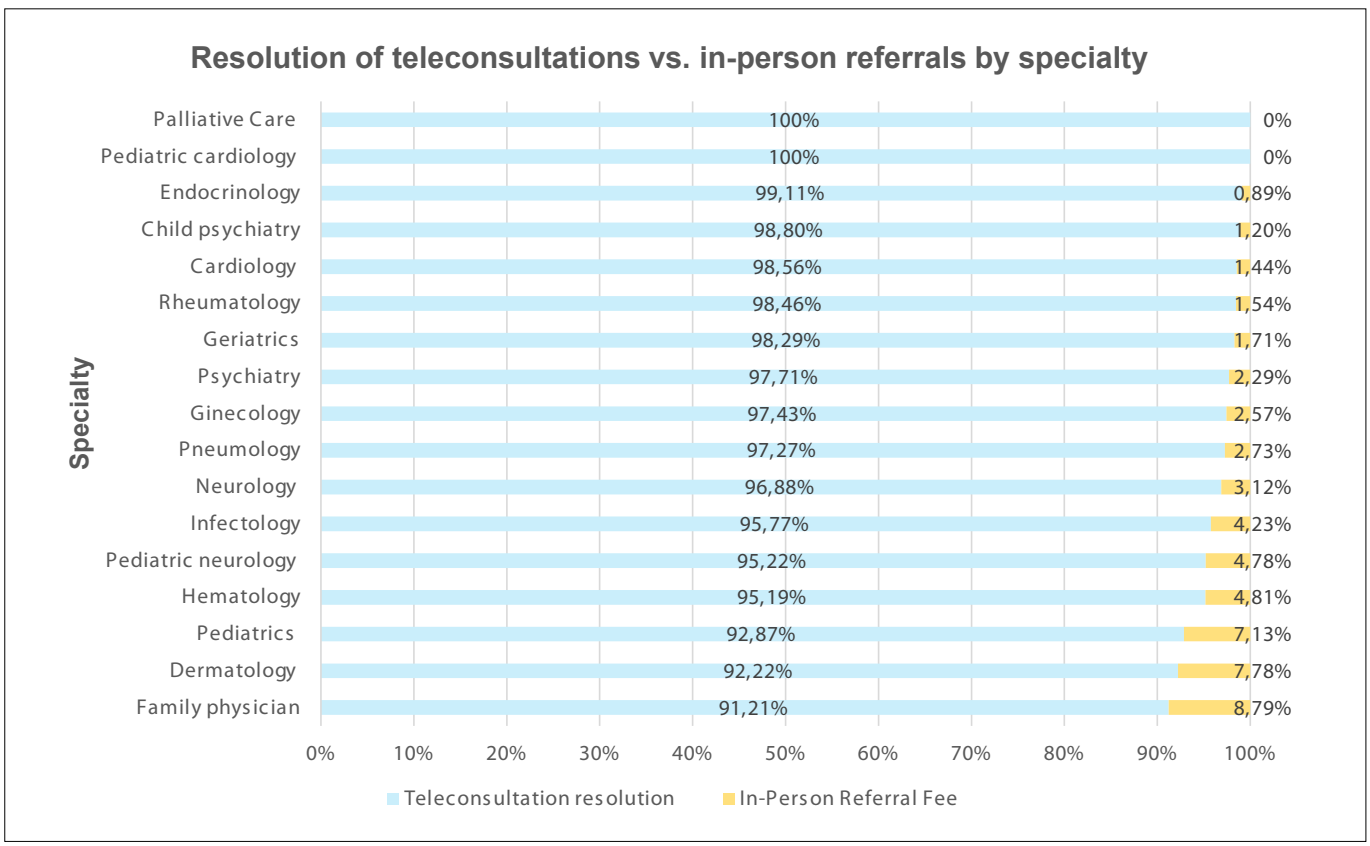

Figure 2. Resolution of teleconsultations versus in-person referrals by specialty.

medical exhaustion, which can consequently improve the quality of patient care.[5]

Considering the environmental impact related to the reduction of 4,294,915 kg of CO_2 emissions promoted by the TeleNordeste project, according to the EPA calculator,[19] these results are equivalent to carbon sequestration by 71,017 tree seedlings grown over 10 years, 5,014 acres of United States forests in one year, or 27,5 acres of United States Forests saved from conversion to farmland in one year. This is equivalent to the greenhouse gas emissions avoided by 1,491 tons of waste instead of landfilling or 186,554 trash bags of waste recycled instead of landfilling.

The advantages of telemedicine care reported by studies include not only carbon emissions but also lower financial costs, greater satisfaction, easier access for residents of rural areas, fewer appointments missed due to abstention,[16] and reduced waiting times in referral queues.[20] It is also important to highlight that, according to national medical demographics, Brazil reached 2.6 doctors per 1,000 inhabitants in 2023, but the distribution of doctors by region is diverse in the country, and the Northeast region has 1.93 doctors per 1,000 inhabitants. In 2022, 62.3% of doctors in Brazil were specialists.[21] The project also presented itself as a possibility of access to specialized consultation.

The difficulty in accessing specialized consultation is a reality and mainly affects countries with distant reference centers for most populations. Constanzo et al.[20] carried out a retrospective cohort study in Chile with 1743 patients seen through teleconsultation in neurology and found that the waiting time for care was < 60% for telemedicine than for in-person consultation. A descriptive study conducted in Recife by Aquino et al.,[22] in 2022, identified an average waiting time in the regulation queue of 270 days, with a maximum of 750 days when patients were able to access teleconsultation in the neurology specialty offered during the COVID-19 pandemic.

The average resolution of teleconsultations was 96.92%, with some specialties presenting 100%, according to literature it is known that PHC is capable of resolving around 85% of clinical conditions,[23] the possibility of discussion through telemedicine of the BP's TeleNordeste Project increased resolution, delivered as result quality of life for those who waiting long periods for physicians specialists, and promoted a reduction in travel and, consequently, carbon emissions.

PHC integration with a telemedicine center is a strategy that has proven to be relevant in reducing the carbon footprint, even in a densely populated country with little use of automobiles, like Switzerland.[17] This study presents the experience of a PROADI project in the SUS, enabling the evaluation of the impact of telemedicine on PHC in a continental country such as Brazil, which, besides the significant distances, the necessary means of transport involved, in the regions served by the project, required roads and/or ferries, making it difficult for many SUS users to travel to their specialized references.

Considering these aspects, an important concept is that prevention is the most effective means of ensuring the sustainability of health care from environmental, social, and economic aspects; health systems must devote attention to health promotion and disease prevention to the detriment of the focus of disease treatment,[2,24] which requires policies that support PHC and public health, robust screening programs, fair and universal access to health resources, including financing models that align incentives bringing value to well-being and health.[2] BP's TeleNordeste project aims to promote timely and agile universal access to SUS users, articulating care pathways and assistance to improve health outcomes, aligned with the sustainability of health systems and environmental responsibility, presenting the first result of the socioeconomic and environmental impact of a telemedicine project implemented in the SUS.

This study had limitations. This study carried out an analysis of estimates of travel distances according to the shortest route, not presenting precise measurements of travel that would be carried out; however, many of the assumptions are conservative and, if wrong, would underestimate, rather than overestimate, reducing CO_2 emissions. It was also not possible to estimate the amount of carbon emissions related to ferries used on routes from some municipalities to a specialized reference site. Furthermore, this study did not have access to the socioeconomic data of the patients treated; therefore, it was not possible to calculate individual patient savings related to travel and reduction in work absences, considering the indirect impacts of the project.

CONCLUSION

To our knowledge, in Brazil, this study is one of the first to present results on the impact of telemedicine on the reduction of carbon emissions, savings for Municipal Health Departments regarding patient travel to reference centers in Health Care Networks and the resolution of care provided in the context of the PROADI-SUS TeleNordeste Project developed by hospital BP – A Beneficência Portuguesa de São Paulo, and promotes reflection on the potential benefits of telemedicine as a valuable opportunity to promote the sustainability of the Health System in a continental country and the need for continued investment in digital health technologies such as strategy to promote health and preserve the environment.

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Histopathological evaluation in post-mortem renal biopsies of patients with COVID-19 and comorbidities: a case-control study

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ABSTRACT

BACKGROUND: Acute kidney injury is one of the main systemic complications of severe coronavirus disease 2019 (COVID-19).

OBJECTIVES: To examine histopathological changes in post-mortem kidney biopsies of patients who died as a result of the disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2).

DESIGN AND SETTING: A case-control study was conducted at a tertiary hospital located in Curitiba, Paraná, Brazil.

METHODS: The study group, called "COVID," consisted of kidney biopsy samples obtained from deceased patients with COVID-19, with a "Control" group included for comparison. Samples were selected based on sex, age, and comorbidities, with an emphasis on diabetes mellitus and systemic arterial hypertension (SAH). Morphological evaluation was performed by pathologists using preestablished criteria with glomerular, tubular, and vascular characteristics among the parameters.

RESULTS: Tubular atrophy and interstitial fibrosis, markers of chronic kidney injury, were observed with equal frequency in both groups, probably because of the initial pairing of the samples. These findings are in line with what would be expected from chronic exposure to proteinuria. In relation to SAH, the main identification was interstitial vascular damage, particularly arteriolosclerosis/arteriosclerosis. Acute tubular injury was the most frequently observed feature in patients in the COVID group, which was probably related to ischemic damage.

CONCLUSION: This study demonstrated that the main change identified in the renal parenchyma of patients with COVID-19 was acute tubular injury, which was expected considering the context of severe systemic ischemia to which these patients are subjected, with the other findings being the consequences of chronic damage.

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus emerged in the last quarter of 2019, rapidly spreading worldwide.[1] Infection has been documented in various clinical presentations, ranging from asymptomatic infections to fatal cases requiring prolonged treatment in intensive care units.[2,3] Among the main systemic complications of severe cases, studies highlight interstitial lung disease, thromboembolic events, encephalopathy, and cardiopathies.[4–7]

Besides the respiratory and cardiovascular systems, patients with coronavirus disease 2019 (COVID-19) may also experience impairment of renal function, with an incidence ranging from 0.5% to 28%.[8] There is a correlation between the onset of acute kidney injury (AKI) and the need for mechanical ventilation support, with some patients requiring renal replacement therapy.[9] Furthermore, laboratory tests showed abnormalities such as albuminuria, hematuria, elevated urea, and high levels of creatinine.[10]

The histological findings of renal biopsies in patients with COVID-19 show that acute tubular injury is the most prevalent outcome, likely related to ischemic damage to the renal parenchyma.[11,12] However, the presence of the virus directly affecting kidney tissue has not yet been proven,[9] and further studies are needed to elucidate the worse prognosis of patients with renal injury associated with SARS-CoV-2 infection and to better understand the pathophysiology of the disease.

This study aimed to describe glomerular, tubular, and vascular histopathological alterations in post-mortem renal biopsies of patients who died because of COVID-19. Additionally, these findings were compared with those of renal tissues from a properly matched control group.

METHODOLOGY

This case-control study comprises the study group, termed the "COVID group" (n = 17), with renal biopsy specimens preserved in paraffin blocks. Samples were obtained from patients who died owing to complications of different natures caused by COVID-19; however, they did not require dialysis when monitoring AKI. Minimally invasive *post-mortem* renal biopsy was performed through percutaneous puncture of the flanks, following appropriate authorization from family members who signed informed consent forms. This study was approved by the Ethics Committee of the Pontifícia Universidade Católica do Paraná (PUC-PR), CAAE: 30188020.7.1001.0020, opinion number 3.944.734.

The following criteria were defined for the inclusion of biopsies in the study: patients admitted to the intensive care unit (ICU) of a tertiary hospital located in Curitiba, Paraná, aged ≥ 18 years, with immunological and molecular tests confirming COVID-19 infection, and who died because of the disease. Patients who tested negative (PCR and serologies) for COVID-19 were excluded from the study despite meeting the criteria.

The "Control group" (n = 16) consisted of samples from patients matched in sex and comorbidities to the "COVID group," in a ratio of 1:1 to 2:1, obtained from a biological sample archive maintained by a reference hospital, located in São Paulo, collected from surgical specimens of patients undergoing kidney transplantation ("zero time" biopsy). These samples date back to procedures performed before the onset of the pandemic.

Table 1 summarizes the data regarding sex, age, and comorbidities of the biopsied patients comprising the final sample, comparing both groups.

All kidney samples were fixed in formalin and embedded in paraffin (FFPE), subjected to routine processing, inclusion, cutting at 4 µm, and staining with hematoxylin and eosin, and then taken for microscopic analysis. For a more detailed assessment, the slides were stained with periodic acid-Schiff (PAS) with diastase, Masson's trichrome, and methenamine silver (PAMS).

Morphological evaluation of the biopsies was conducted by three independent pathologists based on pre-established criteria to ensure objectivity. All samples were reviewed by the same team, which helped minimize intra-observer variability and ensure consistency in assessment. The parameters utilized were selected based on the Banff Classification Reference Guide for the evaluation of kidney graft biopsies.[12] All the criteria stipulated for the evaluation are described in **Table 2**. The Banff Classification was designed for the evaluation of renal graft biopsies to diagnose and grade rejections. We chose to use this classification, even in the context of native samples (not transplants), because the classification parameters evaluated all renal compartments (glomeruli, tubules, interstitium, and vessels). The evaluators were not exposed to clinical data or sample identification before or during the assessment.

The categorized variables were presented as frequency and simple percentages of the obtained data. The "Control" and "COVID-19" groups were compared using Fisher's exact test. Values of $P \leq 0.05$ indicated statistical significance. The data were analyzed using the IBM SPSS Statistics v.28.0 software (Armonk, New York).

Table 1. Comparative table of sex, age, and comorbidities between the Control and COVID groups

Data	Variable	Group control	Group COVID
Sex	Male	50% (n = 8)	53% (n = 9)
	Female	50% (n = 8)	47% (n = 8)
Age (years) mean/median (min–max)		51,4/56,5 (30–72)	74,5/78 (59–86)
Comorbidities	Diabetes mellitus	50% (n = 08)	29,4% (n = 5)
	Systemic arterial hypertension	50% (n = 08)	70,6% (n = 12)

RESULTS

The results of the morphological parameter evaluation found in the samples of the "Control" and "COVID" groups are presented in **Table 3**. Fisher's exact test revealed no statistically significant differences between the two groups, with all P values exceeding 0.05 and 95% confidence interval (95% CI).

For the variables applied to the morphological evaluation of glomeruli, such as microthrombi, duplication of the glomerular basement membrane, expansion of the matrix, and increased mesangial cellularity, neither the control nor the experimental groups showed alterations. Glomerulitis was identified in 64.7% and 56.3% of patients in the study and control groups, respectively, with no statistically significant differences. It was also observed that there was a prevalence of findings related to chronic organ damage in both the COVID group and the control group (without statistically significant differences), indicating a similar epidemiological profile between the groups, likely due to matching by comorbidities and age, causing an overlap of findings such as tubular atrophy, interstitial fibrosis, and arteriolosclerosis.

Notably, in both groups, all cases presented with acute tubular injury to some degree, albeit not commonly associated with tubulitis, which was observed in only two cases across both groups. Regarding the evaluation of blood vessels in the interstitium, only one case in the COVID group showed changes consistent with vasculitis. However, when considering other vascular alterations,

arteriolosclerosis was the most frequently identified, occurring in 81.2% of the cases in the control group and 64.7% of the cases in the COVID group. **Figures 1 and 2** illustrate these morphological findings.

DISCUSSION

COVID-19 disproportionately affects patients with chronic comorbidities, given the accumulated tissue damage in target organs.[2,3] Consequently, the impact of chronic diseases on the renal parenchyma is expected, with these being the main morphological findings found in the research. The evaluated parameters that indicated the chronicity of the injury were tubular atrophy, interstitial fibrosis, and arteriosclerosis.[13]

Furthermore, the results corroborate those described in the literature when acute tubular injury secondary to hypoxia was identified in all biopsies of the "COVID" group.[14,15] Notably, acute tubular

Table 2. List of parameters and criteria used in the morphological evaluation of renal biopsies

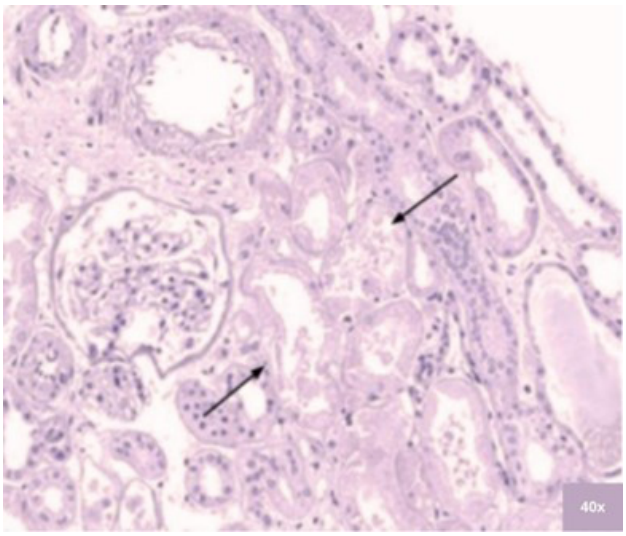
Morphological Parameter	Evaluation criterion
Presence of microthrombi	1 = present or 0 = absent
Duplication of the glomerular basement membrane	1 = present or 0 = absent
Glomerulitis	1 = present or 0 = absent
Acute tubular injury	0 = no changes; 1 = mild changes; 2 = moderate changes; and 3 = severe changes
Tubulitis	0 = no foci; 1 = 1 to 4 foci; 2 = 5 to 10 foci; and 3 ≥ 10 foci or focus of tubular basement membrane destruction
Tubular atrophy	0 = No foci; 1 ≤ 25%; 2 = 26 to 50%; 3 > 50%
Tubulointerstitial inflammation in non-atrophic region	0 ≤ 10%; 1 = 10 to 25%; 2 = 26 to 50%; and 3 > 50%
Interstitial fibrosis	0 ≤ 5%; 1 = 6 to 25%; 2 = 26 to 50%; and 3 > 50%
Vasculitis	1 = present or 0 = absent
Arteriosclerosis in cross-section, using the most affected vessel	0 = no foci; 1 ≤ 25% of vessel thickness; 2 = 26 to 50% of vessel thickness; and 3 > 50% of vessel thickness
Arteriolosclerosis in sample	0 = no foci; 1 = mild to moderate in at least one arteriole; 2 = moderate to severe in one arteriole; and 3 = Moderate to marked in several arterioles

Table 3. Morphological variables evaluated comparing the "Control" and "COVID" groups

Variable	Classification	Groups				P*
		Control		COVID		
		n	%	n	%	
Presence of microthrombi in glomerulus	Absent	16	100%	17	100%	1
Duplication of glomerular basement membrane	Absent	16	100%	17	100%	1
Expansion of mesangial matrix	No foci	16	100%	17	100%	1
Mesangial cellularity	Up to 4 cells	16	100%	17	100%	1
Glomerulitis	Absent	7	43,8%	6	35,3%	0,73
	Present	9	56,3%	11	64,7%	
Signs of acute tubular injury	Mild to moderate alteration	13	81,3%	17	100%	0,1
	Severe alteration	3	18,8%	0	0%	
Tubulitis	No foci	15	93,8%	16	94,1%	1
	1–10	1	6,3%	1	5,9%	
Tubular atrophy	No foci	11	68,8%	9	52,9%	0,48
	≤ 50%	5	31,2%	8	47,1%	
Tubulointerstitial inflammation in non-atrophic region	< 10%	15	93,8%	14	82,4%	0,6
	≥ 10%	1	6,3%	3	17,6%	
Interstitial fibrosis	≤ 5%	12	75%	7	41,2%	0,08
	6%–50%	4	25%	10	58,8%	
Arteriosclerosis in most affected interstitial vessel	No foci	3	18,8%	6	35,3%	0,44
	0%–50%	13	81,2%	11	64,7%	
Arteriolosclerosis in sample	No foci	12	75%	13	76,5%	1
	Some foci	4	25%	4	23,5%	
Vasculitis	Absent	16	100%	16	94,1%	1
	Present	0	0%	1	5,9%	

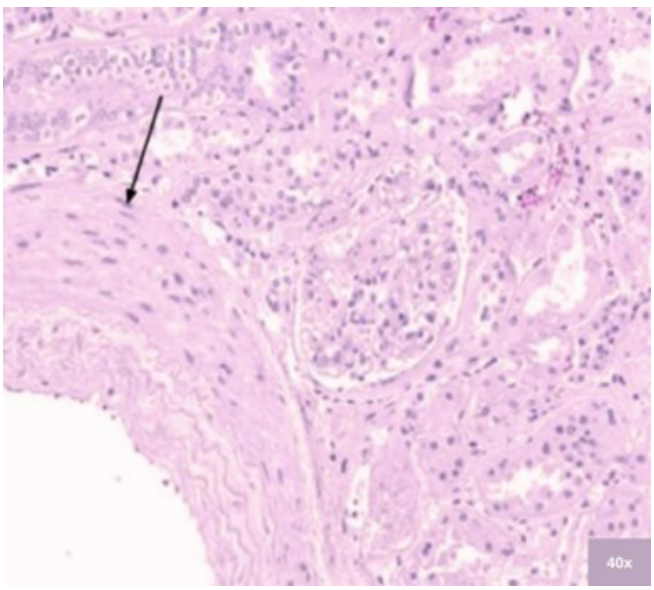
* Fisher's exact test, with significance set at P < 0.05.

injury is not specifically attributed to SARS-CoV-2, but rather to pathological conditions that include tissue oxygen deprivation among their complications. Tubular injury is the most common cause of AKI and is secondary to events that lead to irreversible damage to renal tubular cells and injury to these structures. Among the causes of acute tubular injury, ischemic events are the main triggering factors; however, other causes, including drug-induced nephrotoxicity, may also be associated. The "COVID" group probably presented injuries secondary to hypoxia caused by the infection, since no medications with a high probability of nephrotoxicity were identified in the medical records. Furthermore, signs of acute tubular injury were present in both samples without statistically significant differences, which may be justified based on acute situations involving renal ischemia in the control group (undergoing transplantation), which occurs more easily in patients with the comorbidities.[9,16]



The arrows highlight the tubular epithelium with a desquamative appearance, secondary to irreversible injury of epithelial cells, leading to acute tubular injury, which in this case was related to systemic ischemia, one of the main complications of COVID-19. Hematoxylin and eosin staining at 40× (high-power field, HPF).

Figure 1. Tubular morphological assessment of renal biopsies from the COVID group.



The arrows highlight chronic vascular injury and arteriosclerosis secondary to chronic systemic diseases, especially Systemic Arterial Hypertension, as the main associated comorbidities. Hematoxylin and eosin, of 40× HPF.

Figure 2. Vascular morphological assessment of renal biopsies from the COVID group.

Regarding the findings related to chronic diseases present in both matched groups, arteriosclerosis stands out as an expected event for patients with comorbidities such as systemic arterial hypertension (SAH) and diabetes mellitus (DM), as it is commonly associated with systemic vascular damage, compounded by the average age of the patients in the sample, most of whom were elderly.[17,18]

Regarding DM, the literature highlights that the primary initial damage to the renal parenchyma is the thickening of the basal membranes lining the glomerular capillaries and tubules, secondary to the increase in the concentration of proteins in the glomerular ultrafiltrate.[19,20] Conversely, tubular atrophy and interstitial fibrosis are markers of chronic and prolonged exposure to proteinuria, characteristically observed in patients with diabetes with chronic and advanced renal injury.[21] These latter two morphological aspects were found with equal frequency in both groups of our study as a result of the initial matching of samples.

In the context of SAH, the main histopathological finding is interstitial vascular damage, secondary to increased intravascular pressure and hyperstimulation of the Renin-Angiotensin-Aldosterone System, often observed in these patients. Thus, chronic injury to the structural layers of the vessel walls, arteriolosclerosis/arteriosclerosis, is the main histopathological alteration in these renal samples.[22] Therefore, it was a frequent finding in the research and in both groups, without statistical differences, also resulting from the matching of the sample by comorbidities.[17]

CONCLUSION

The results demonstrate that the primary damage to the renal parenchyma identified in patients with severe COVID-19 is acute tubular injury, which is an expected outcome considering the context of severe systemic ischemia to which these patients are subjected. Other findings include the consequences of chronic damage caused by preexisting comorbidities.

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Mouth Opened with Tongue Extended (MOTE) maneuver: improvement in tomographic T-staging accuracy of oral cavity cancer: a prospective cross-sectional study

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ABSTRACT

BACKGROUND: Accurate T-staging of oral squamous cell carcinoma (SCC) is essential for surgical planning and prognosis. However, conventional computed tomography (CT) may underestimate tumor extent, particularly when performed without dynamic maneuvers.

OBJECTIVES: To evaluate the accuracy of CT in predicting the T-staging of primary SCC of the oral cavity by comparing scans in the neutral position and with the mouth open and tongue extended (MOTE) maneuver.

METHODS: This prospective cross-sectional study analyzed patients with oral SCC who underwent CT in both positions. Two blinded head-and-neck radiologists measured tumor size and depth of invasion (DOI). An anatomopathological study served as the reference. The accuracy of classifying early and advanced T-stage tumors was determined using diagnostic tests.

RESULTS: Twenty-five patients (72% male, mean age 65.6 ± 11.3 years) were included. Tumor detection sensitivity increased from 72% (95% CI: 51.9–86.9) in the neutral position to 100% (95% CI: 83.4–100) with the MOTE maneuver. Correct T-staging prediction improved from 52–56% in the neutral position to 72–76% with MOTE. Accuracy for early-stage (T1/T2) classification rose from 60.0% (95% CI: 39.3–78.1) to 88.0% (95% CI: 68.7–97.4, $h = 0.66$). Lesion size overestimation decreased from 20.9–23.7% to 15.3–16.1% ($p < 0.05$), whereas DOI differences were not significant ($p > 0.05$).

CONCLUSIONS: The MOTE maneuver significantly improved both the sensitivity and accuracy of CT in the preoperative T-staging of oral cavity SCC. Its incorporation into diagnostic protocols may enhance lesion detection and staging reliability in daily clinical practice.

INTRODUCTION

Head and neck cancer was the seventh most common cancer worldwide in 2020,[1] 90% of which were squamous cell carcinomas (SCC). Among these, tumors of the oral cavity are the most frequent subtype and have the highest mortality rate. According to global data, 177,757 deaths from oral cavity cancer occurred in 2020,[2] corresponding to 1.8% of all cancer deaths,[2] with an average 5-year survival rate of approximately 50%.[1]

There has been an increase in the incidence of head and neck cancer in recent years in both developed and underdeveloped countries.[1] Known risk factors include alcohol and tobacco use, as well as betel quid chewing in Southeast Asia.[1] These tumors are more frequent in men and usually affect patients older than 50 years.[3]

The TNM staging system from the American Joint Committee on Cancer (AJCC) is the most widely accepted and used system, and it allows universal standardization.[3] The classification considers the tumor in relation to its locoregional extension (T), lymph node involvement (N), and presence of distant metastasis (M), thereby allowing a lesion to be classified without ambiguity.[4] Since its 8th edition, released in 2017,[4] the parameter of *depth of invasion* (DOI) has been incorporated into the T-stage definition, recognizing its strong prognostic value.[5]

Depth of invasion (DOI) directly influences surgical planning, as the National Comprehensive Cancer Network (NCCN) recommends neck dissection in early-stage cT1–T2 N0 tumors with DOI > 0.3 cm.[6]

Anatomopathological measurements remain the gold standard,[4] but are only available postoperatively. Therefore, a reliable preoperative imaging method is essential for guiding treatment decisions and avoiding both under- and overtreatment.

Computed tomography (CT) is the preoperative imaging study of choice for evaluating the primary lesion and lymph nodes.[3] However, its accuracy may be limited by metallic dental artifacts and mucosal overlap in the neutral position. Several maneuvers have been proposed to improve visualization, such as the "puffed-cheek" and open-mouth techniques.[7–11]

Maneuvers are also used to assess other organs using CT. The phonation maneuver is useful for evaluating laryngeal tumors or lesions affecting the course of the recurrent laryngeal nerve,[12] as it evaluates the mobility of the vocal cords. In assessing the hypopharynx, the Valsalva maneuver distends the pyriform sinuses, which usually have the overlying mucosa in a neutral position.[13,14]

The present study aimed to evaluate the accuracy of CT in the neutral position and with the MOTE maneuver in predicting the presurgical T-staging of oral cavity tumors.

MATERIALS AND METHODS

This was a prospective cross-sectional study in which a comparative analysis of DOI measurements and the size of the lesions obtained on the CT scan was conducted. The presurgical T-staging determined by CT was compared with that obtained from the postsurgical anatomopathological study.

The study followed all ethical recommendations and was registered and approved by the hospital's Research Ethics Committee (CAAE 12810719.8.0000.5463; approval number 3.463.777). Patients were informed about all steps, purposes, potential risks, and benefits of participating in the research and signed a Free and Informed Consent (FIC) form.

Study design

The examinations were performed on a BrightSpeed Elite GE® multidetector CT scanner with 16 channels by two trained radiology technicians. Patients who attended the radiology service after fasting for 4 hours were instructed to remove mobile dental prostheses and were then positioned in dorsal decubitus on the CT scanner. Acquisitions were performed in the axial plane with 1.25 mm slice thickness after intravenous injection of Henetix® hyposmolar non-ionic iodinated contrast medium at a dose of 1.5 ml/kg.

Image acquisition began 60 seconds after the injection of iodinated contrast medium. Initially, images were acquired in a neutral position, in which the patient was instructed to relax the facial muscles, keep the mouth closed, and breathe calmly. The images were then acquired using the MOTE maneuver described by Bron et al.,[9] in which the patient kept the mouth open, extended his tongue out of the oral cavity, and breathed calmly.

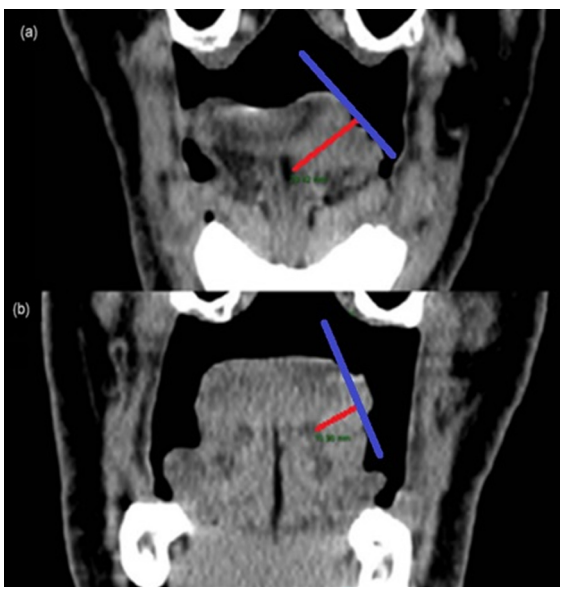
The CT images were transferred to the Carestream® system and analyzed by two radiologists, Head and Neck imaging specialists with more than 20 years of experience - named Evaluator 1 (Ev1) and Evaluator 2 (Ev2) – separately and without interobserver communication. Each evaluator measured lesion size and DOI by analyzing the obtained images. As described by Weimar et al.,[15] DOI was measured perpendicular to an imaginary line drawn along the plane of the normal mucosal surface adjacent to the lesion (**Figure 1**).

The intraclass correlation coefficient (ICC) was calculated[16] to assess the agreement between Ev1 and Ev2 for measuring lesion size and DOI on CT.

Once lesion measurements were obtained, tomographic T-staging was determined independently by each evaluator for each patient. Values for tomographic T-staging were based on the TNM 8th edition of the American Joint Committee on Cancer (AJCC).[4]

After measurements and tomographic T-staging, the patients underwent surgical procedures performed by the institution's head and neck surgery team. The lesion was resected, the tissue was fixed in 10% formaldehyde and paraffin, and the histological sections were stained with hematoxylin and eosin. An anatomopathological analysis was performed 24 hours after fixation. The interval between CT and the surgical procedure did not exceed 44 days.

The size and DOI of the lesion were measured by the same pathologist in all cases. To measure the size of each lesion, the maximum extent observed in macroscopic specimens was considered. For the DOI, the greatest depth of the tumor measured



DOI measurement in ulcerated (a) and vegetative (b) tongue SCC; blue line: plane of the normal mucosal surface adjacent to the lesion; red line: measurement of DOI.

Figure 1. Coronal reformation of the oral cavity.

across all the microscopic sections of the specimen was considered. DOI measurements were performed perpendicularly to an imaginary line drawn between the normal basement membranes adjacent to the lesion, as recommended by the College of American Pathologists (CAP).[17]

Statistical analysis and comparison of lesion size and DOI measured on CT by Ev1 and Ev2 with those obtained in the anatomopathological examination were performed. The mean measurements of each evaluator were determined for each maneuver separately, along with the 95% confidence interval (95% CI) and the percentage of overestimation compared with the anatomopathological values. The Shapiro-Wilk normality test and t-test or Wilcoxon test were used.

Once the measurements of the lesions were obtained, T-staging was determined based on the anatomopathological study of each patient, which served as the reference for the T-staging obtained from tomographic measurements. The 8th edition of the AJCC TNM system was also used.[4]

Tumor T-staging on CT in the neutral position and with the MOTE maneuver was compared with anatomopathology to determine the correct T-staging prediction.

The accuracy of the correct classification of early T-stage (T1 and T2) versus advanced T-stage (T3 and T4) tumors was also determined. Preoperative test accuracy was described in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), expressed as percentages, and 95% confidence intervals (CI) were also calculated. These parameters were determined using diagnostic tests.

RESULTS

Participants

Initially, 40 patients with SCC of the oral cavity diagnosed at the Head and Neck Surgery Service between July 2019 and July 2021 were selected. Patients with a recurrent lesion (1), unresectable tumors (3), lesions with compromised margins on anatomopathology (3), oropharyngeal tumors (4), or other histological types (4) were excluded. Ultimately, 25 patients were included in the study.

Population characteristics

Of these 25 patients, 18 (72%) were men. The mean age was 65.6 years, with a standard deviation of 11.25. The mean interval between CT and surgery was 9.16 days (standard deviation, 9.65).

The most frequent tumor subsite was the oral tongue (14), followed by the floor of the mouth (8) and the hard palate (3).

Sensitivity of tumor detection

The sensitivity to detect the lesion on CT in the neutral position was 72% (18/25, 95% CI: 51.9–86.9) and 100% (25/25, 95% CI: 83.4–100) with the MOTE maneuver. This difference corresponded to a large effect size (h = 1.12). Importantly, the MOTE maneuver completely eliminated metallic beam-hardening artifacts in all cases, thereby improving lesion conspicuity.

Accuracy of tomographic T-staging

The agreement of DOI measurements in the neutral position performed by Ev1 and Ev2 on CT was considered excellent,[16] with an ICC > 0.964.

Using anatomopathological T-staging as a reference, CT in the neutral position correctly predicted the T-staging in 52–56.0% (95% CI: 33.5–77.4) of the cases and the MOTE maneuver in 72–76% (95% CI: 51.5–90) (**Figure 2**).

In the neutral position, tomographic classification of early T-stage tumors (T1 and T2) showed a sensitivity of 44.4%, specificity of 100%, PPV of 100%, NPV of 41.1%, and accuracy of 60% (95% CI: 39.3–78.1) (**Table 1**).

Using the MOTE maneuver, differentiation of early T-stage tumors (T1 and T2) from advanced T-stage tumors (T3 and T4) was accurate for both Ev1 and Ev2, as 15 of the 18 pT1/T2 tumors were correctly T-staged on CT. Sensitivity, specificity, PPV, NPV, and accuracy for early T-stage tumor detection were 83.3% (95% CI:

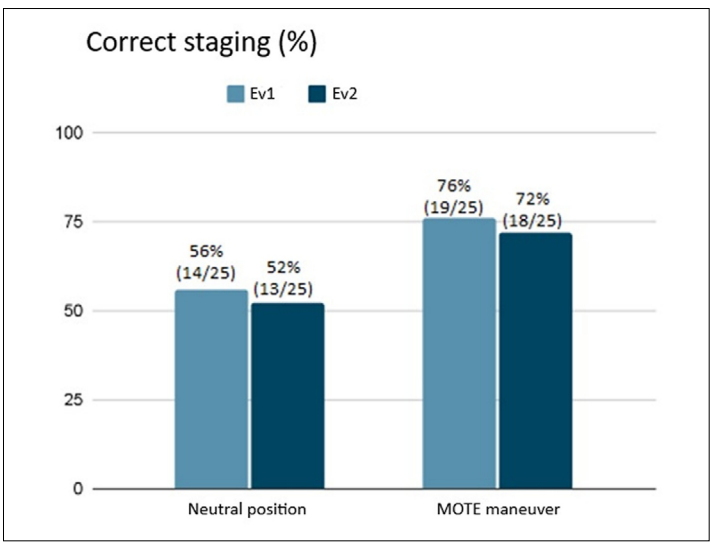


Figure 2. Correct prediction of tomographic T-staging with MOTE maneuver, according to each evaluator in relation to the anatomopathological T-staging of the surgical specimen.

Table 1. Distribution of the number of cases to calculate the accuracy in classifying early T-stage tumors (T1 and T2) using CT in the neutral position

	pT1 e pT2	≠ pT1 e pT2	Total
T1 e T2	8	0	8
≠ T1 e T2	10	7	17
Total	18	7	25

T1 e T2: tomographic staging T1 e T2; ≠ T1 e T2: tomographic staging Tx, T3 e T4; pT1 e pT2: pathological staging T1 e T2; ≠ pT1 e pT2: pathological staging T3 e T4.

58.5–96.4%), 100% (95% CI: 59–100%), 100% (95% CI: 78.2–100%), 70% (95% CI: 45.3–86.7%) and 88.0% (95% CI: 68.7–97.4%), with an effect size of $h = 0.66$. All 7 pT3/T4 tumors (100%) were correctly staged (**Table 2**).

The disagreement between the staging classified by CT and the surgical specimen in formaldehyde led to a comparison of the measurements of the lesions and the determination of the percentage differences. **Table 3** shows the measurements of the lesion size performed by Ev1 and Ev2 and the percentage of overestimation in comparison with the anatomopathological measurements. **Table 4** presents the DOI data.

It was found that the size of the lesions was overestimated on CT compared with anatomopathological measurements ($p < 0.05$). In contrast, although DOI measurements also tended to be overestimated on CT, this difference was not statistically significant ($p > 0.05$; $d = 0.13$, indicating a negligible effect size).

DISCUSSION

Relatively simple maneuvers in imaging examinations have been developed since the beginning of the 20th century to increase the sensitivity of lesion detection, reduce artifacts, and perform adequate pretreatment T-staging.

Jonsson[13] reported in 1934 that the modified Valsalva maneuver provided greater sensitivity for detecting lesions in the hypopharynx on contrast radiography. Later, this technique was named the "trumpet maneuver" by Hillel et al. in 1989,[14] confirming its usefulness for evaluating the piriform sinuses in hypopharyngeal tumors.

In 1981, Gamsu et al.[12] showed that laryngeal structures were better assessed when performing phonation maneuvers during CT scans, favoring the detection of lesions at this site.

For better identification of lesions in the oral cavity, Weissman et al.[7] described the puffed-cheek maneuver on CT scans in 2001, which remains the most accurate technique for evaluating lesions in the buccal mucosa and retromolar trigone. Several studies have shown the benefits of this maneuver, which allows a better assessment of tumor dimensions and their extension.[10,11]

Henrot et al.[8] described in 2003 the open-mouth maneuver on CT scans to reduce dental amalgam artifacts in the oral cavity and oropharynx.

The MOTE maneuver was described in 2019 by Bron et al.,[9] who reported a higher rate of correct staging with this maneuver (83%) compared with conventional CT (68%).

In our study, CT using the MOTE maneuver demonstrated 100% sensitivity in detecting tumor lesions in the oral cavity and increased the accuracy of presurgical T-staging from 60–88% when compared with the neutral position. We observed better delimitation of the tumor, and metallic beam-hardening artifacts of dental origin were excluded in all cases using this maneuver (**Figure 3**).

In our study, the measurements of the tumor lesions on CT were larger than those obtained from formalized specimens. Other authors have also found differences between T-staging on imaging and in surgical specimens, as shown by Kreppel et al. (2016).[18]

Table 2. Distribution of the number of cases to calculate the accuracy in classifying early T-stage tumors (T1 and T2) using CT with MOTE maneuver

	pT1 e pT2	≠ pT1 e pT2	Total
T1 e T2	15	0	15
≠ T1 e T2	3	7	10
Total	18	7	25

T1 e T2: tomographic staging T1 e T2; ≠ T1 e T2: tomographic staging Tx, T3 e T4; pT1 e pT2: pathological staging T1 e T2; ≠ pT1 e pT2: pathological staging T3 e T4.

Table 3. Comparison of the measurements (cm) of the size obtained in the anatomopathological study with the CT measurements (cm) performed by Evaluator 1 (Ev1) and Evaluator 2 (Ev2) in neutral position and with MOTE maneuver

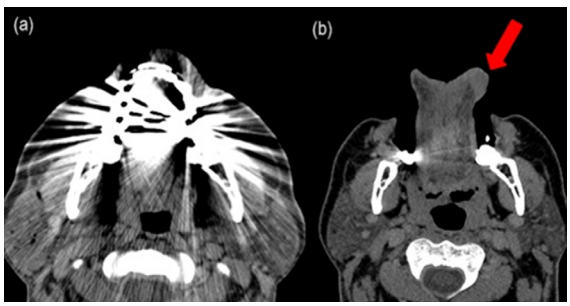
Size	Measurement (cm)	p	Overestimation (%)
Anatomopathological	2.48 ± 0.41	–	–
Neutral Ev1	3 ± 0.58	0.01	20.96
Neutral Ev2	3.07 ± 0.62	0.011	23.79
MOTE Ev1	2.88 ± 0.49	0.001	16.12
MOTE Ev2	2.86 ± 0.5	0.006	15.32

Mean ± 1,96; * SE and t-test/Wilcoxon p value.

Table 4. Comparison of measurements (cm) of depth of invasion (DOI) obtained in the anatomopathological study with CT measurements (cm) performed by Evaluator 1 (Ev1) and Evaluator 2 (Ev2) in neutral position and with MOTE maneuver

DOI	Measurement (cm)	p	Overestimation (%)
Anatomopathological	1.03 ± 0.26	–	–
Neutral Ev1	1.32 ± 0.42	0.288	28.15
Neutral Ev2	1.37 ± 0.6	1	33
MOTE Ev1	1.14 ± 0.33	0.116	10.67
MOTE Ev2	1.09 ± 0.31	0.554	5.82

Mean ± 1,96; * SE and t-test/Wilcoxon p value.



Note the delimitation of the tumor lesion with the MOTE maneuver (red arrow), which is not visualized in the neutral position owing to metallic beam hardening artifacts.

Figure 3. Contrast-enhanced CT in the axial plane in neutral position (a) and with MOTE maneuver (b).

They observed a T-staging agreement of 62%, with the majority of discordant cases (58%) being overstaged.

A justification for the difference in the measurements of the lesions on CT and in the anatomopathological study is probably the shrinkage of the piece when soaked in formaldehyde. The overestimation of lesion size with the MOTE maneuver was 16.1% (Ev1) and 15.3% (Ev2), which was lower than in the neutral position (20.9–23.7%). Our data also demonstrated that measurements obtained using the MOTE maneuver were closer to those obtained pathologically.

Some authors have studied the reduction in the size of fresh surgical specimens compared with their size after fixation in formaldehyde. The findings of Pangare et al.[19] and Umstattd et al.[20] pointed out a reduction in lesion size, ranging from 10.7–23.9%, after 24 hours of fixation in 10% formaldehyde. In our study, lesion size measured on CT showed a reduction ranging from 15.3–16.1% after fixation in formaldehyde, values similar to those reported in these studies, which compared fresh specimens with the same specimens after fixation.

Another important observation is that CT detects lesions in living tissue with preserved architecture, which is altered after surgical resection. This may lead to discrepancies in measurements and, consequently, in T-staging.

Studies have found overstaging of lesions on CT compared with anatomopathological findings in tumors from various anatomical sites, not only the oral cavity. Winiker et al.[21] described the overestimation of the lesion dimensions of esophageal tumors on CT and ultrasonography compared to pathology in 2018, with correct T-staging in only 51% of cases, overstaging in 25.5%, and understaging in 23.5%.

A relevant factor in therapeutic planning is the correct prediction of DOI using presurgical imaging. DOI is an important predictor of occult lymph node metastasis, and neck dissection is recommended for early-stage cT1–T2 N0 tumors when the DOI is greater than 0.3 cm, according to the NCCN protocol.[6] In our research, the overestimation of T-staging occurred due to the discrepancy between CT and anatomopathological measurement of lesion size, as the DOI measurements did not show a significant difference between these methods ($p > 0.05$). The correlation between DOI measurements obtained during imaging and anatomopathological examinations is controversial. Some authors have reported satisfactory correlation between methods, such as Chin et al.,[22] which is consistent with our study. However, a systematic review and meta-analysis by Li et al.[23] demonstrated that magnetic resonance imaging tends to overestimate DOI measurements compared with anatomopathological studies; however, this meta-analysis did not evaluate the use of maneuvers.

The NCCN recommendation to perform neck dissection in early-stage cT1-T2 N0 tumors with a DOI greater than 0.3 cm[6] also motivated us to determine the accuracy of CT in correctly differentiating early T-stage (T1/T2) tumors from advanced T-stages (T3 and T4). In our study, we observed an accuracy of 88.0% for this classification using the MOTE maneuver, whereas in the neutral position, the accuracy was 60%.

The technique for measuring DOI in pathology consists of drawing an imaginary line between the normal basement membranes adjacent to the tumor and measuring the depth of the lesion from this line.[16] A challenge in measuring DOI on CT is that the basement membrane is not visualized, as the thickness of the oral mucosal epithelium is < 0.5 cm.[15] Weimar et al. proposed measuring DOI on CT from the plane of the mucosal surface adjacent to the tumor.[15] This technique was used in our study for DOI measurement.

Our study differs from previous research in the literature. Some prospective studies evaluated the benefits of the puffed-cheek maneuver in imaging examinations of patients with oral cavity tumors and observed improved tumor detection and delimitation; however, they compared imaging examinations with and without the puffed-cheek maneuver, without comparison to anatomopathological measurements. Weissman[7] and Martínez[10] studied 7 and 62 patients, respectively, using CT, while Chang[24] studied this maneuver in 22 patients using PET/CT.

Bron et al.[9] reported greater accuracy in tomographic staging of oral cavity and oropharynx tumors with the MOTE maneuver (83%) compared with conventional CT (68%) in 58 patients. However, that study differs from ours because it was retrospective and included oropharyngeal tumors in addition to oral cavity tumors.

Our research differs from these studies because it is prospective and directly compares lesion size and DOI, as well as the accuracy of tomographic T-staging of oral cavity tumors, with anatomopathological findings. We also evaluated the percentage of overestimation of measurements compared with the anatomopathological study.

The MOTE maneuver is simple, noninvasive, and requires no additional equipment. It reduces metal artifacts, enhances tumor-to-soft-tissue contrast, and improves preoperative staging accuracy. Given its feasibility, we recommend incorporating it into the routine CT protocol for patients with suspected or confirmed oral cavity SCC, while considering the approximately 15.3–16.1% overestimation in lesion size compared with anatomopathological measurements observed with this maneuver.

We suggest that future studies with larger samples may help determine a measurement conversion coefficient that considers statistically consistent differences between the methods, or determine whether the cutoff points for T-staging measures on CT should differ from those obtained from anatomopathological examination for the T classification within TNM staging.

CONCLUSIONS

The MOTE maneuver significantly enhanced CT performance in the preoperative evaluation of oral cavity SCC, providing higher sensitivity, improved T-staging accuracy, and closer agreement with pathological measurements. This maneuver reduced measurement overestimation and eliminated dental metallic artifacts, resulting in clearer visualization of lesion boundaries. Because of its simplicity and reproducibility, the MOTE maneuver should be incorporated into standard CT protocols for oral cavity tumors, as it offers practical clinical benefits for diagnosis, staging, and surgical planning.

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Adverse reactions to etiological treatment in patients with Chagas disease in the Western Potiguar mesoregion of Brazil: a cross-sectional study

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ABSTRACT

BACKGROUND: Chagas disease is a significant public health challenge in Brazil that is characterized by substantial morbidity and mortality rates, coupled with limited etiological treatment options.

OBJECTIVE: To describe and assess the occurrence of adverse reactions resulting from benznidazole treatment in patients from the Western Potiguar mesoregion of Brazil.

DESIGN AND SETTING: This retrospective, longitudinal, descriptive observational study included 106 individuals with Chagas disease who attended the Chagas Disease Outpatient Clinic of the Universidade do Estado do Rio Grande do Norte.

RESULTS: Among patients subjected to etiological treatment with benznidazole, 40.5% (43/106) experienced adverse reactions, manifesting in 13 distinct forms. The most prevalent reactions occurred primarily in the dermatological and hematological systems. Thus, despite the notable frequency of adverse reactions, their severity remained low, as evidenced by the minimal treatment suspension rate. The treatment demonstrated potential benefits to those affected by the disease.

CONCLUSIONS: This study characterized the most frequent adverse reactions to benznidazole, mainly dermatological and hematological reactions, which were mostly mild and rarely led to treatment suspension. Recognizing these events is essential for guiding professionals, enhancing patient confidence, and improving adherence to etiological treatments for Chagas disease.

INTRODUCTION

Chagas disease is caused by the *Trypanosoma cruzi* protozoan. Despite more than a century of research, it remains a significant public health concern in Brazil, particularly in socioeconomically vulnerable populations. In Latin American countries, approximately 15 genera of vectors can transmit the protozoan to humans, with the primary vectors being *Triatoma*, *Panstrongylus*, and *Rhodnius*, which typically inhabit peridomestic regions.[1,2]

In the definition of the chronic phase, patients may present with different clinical forms. The indeterminate form is characterized by at least two reactive serologies using distinct methodologies, absence of characteristic cardiac and digestive symptoms of the disease, as well as normal electrocardiogram, chest radiography, and contrast studies of the esophagus and colon.[3] The cardiac form is characterized by the onset of cardiac symptoms such as palpitations and dyspnea, electrocardiographic alterations such as intraventricular and atrioventricular conduction disturbances, and various ventricular and supraventricular arrhythmias. Patients with cardiac involvement may demonstrate alterations in segmental contractility on echocardiography, including apical or vorticular aneurysms of the left ventricle, or even biventricular involvement. The digestive form of the disease is characterized by the appearance of symptoms such as dysphagia of solids and liquids and/or constipation, resulting from the action of *T. cruzi* on the myenteric plexuses, potentially leading to the development of megacolon and/or megaesophagus.[4]

A systematic literature review and meta-analysis has indicated that between 1980 and 2012, the average prevalence of Chagas disease in Brazil was 4.2%. The prevalence throughout this period was higher in the central-west (4.7%), northern (4.2%), southeast (4.1%), northeast (4%),

and southern regions (2%) than in other regions. Bahia (20.4%), Pernambuco (9.1%), Paraíba (7.8%), and Rio Grande do Norte (5.9%), among other regions, had the highest prevalence.[5]

Between 1978 and 1980, the northeastern region of Brazil presented a significant infection prevalence, accounting for 3.05% of the prevalence of Chagas disease; the overall prevalence in Brazil was 4.4%, with the most significant data recorded in Bahia, Alagoas, Sergipe, Pernambuco, and Piauí.[6] In the 1960s, seroprevalence data in Rio Grande do Norte reached 15.5%.[7] The Western Potiguar mesoregion included municipalities of relevance for seroprevalence in the state, with Severiano Melo, Felipe Guerra, Apodi, Caraúbas, Campo Grande, and Governador Dix-Sept Rosado being the notable areas. Together, they account for an approximate seroprevalence of 6.5% in the state, affecting approximately 14,000 individuals.[8,9]

According to the Brazilian Society of Cardiology Guidelines on Diagnosis and Treatment of Chagas Disease Cardiopathy Patients, etiological treatment is strongly recommended for children with acute and congenital infections, adults and adolescents with acute or recently acquired infections, children and adolescents with chronic infections, and adults aged < 50 years with indeterminate chronic infections.[10]

Currently, benznidazole (5 mg/kg/day) and nifurtimox (10 mg/kg/day) are used for etiological treatment, with a minimum chemotherapy duration of 60 days. Only benznidazole is available for the treatment of Chagas disease in Brazil.[11]

The mechanism of action of benznidazole remains unclear. It likely acts as a prodrug with trypanocidal effects after undergoing action by type I trypanosomal nitroreductases, thereby becoming an active product owing to the action of these oxygen-insensitive enzymes expressed in protozoa. This action culminates in the blockade of new DNA strand synthesis and inhibition of *T. cruzi's* rudimentary antioxidant system, making it susceptible to oxidative damage.[12–14]

Etiological treatment of patients with Chagas disease with benznidazole has an efficacy of 97.9% in congenital infection (treatment performed between 0 and 6 months), 71.5% in the acute phase, 57.6% in the recent chronic phase, and 5.9% in the late chronic phase.[15] Moreover, its adverse reaction rate is 38%, with the most common outcome being cutaneous rash.[16]

OBJECTIVE

This study aimed to evaluate and describe the occurrence of adverse reactions in patients with Chagas disease in an endemic area of northeastern Brazil who received etiological treatment with benznidazole.

METHODS

This was an observational, descriptive, longitudinal, and retrospective study conducted on patients from the Chagas Disease Outpatient Clinic of the Universidade do Estado do Rio Grande do Norte (ADOC-UERN). The patients originated from endemic areas in the Western Potiguar mesoregion and received etiological treatment for Chagas disease.

Patients included in the study had reactive serologies for *T. cruzi* performed using at least two different methods (indirect immunofluorescence, enzyme-linked immunosorbent assay, or indirect hemagglutination) and were prescribed benznidazole at ADOC-UERN. The study included adults in the acute or chronic phase of the disease, either in the indeterminate form or with mild involvement of the cardiac, digestive, or cardiodigestive forms.

The only exclusion criterion was prior etiological treatment before being followed up at ADOC-UERN, considering that the inclusion of these patients in the study would result in bias because of the inability to monitor and measure the effects presented by the patients before they were admitted to the service.

Patients received 5 mg/kg/day of benznidazole, divided into three doses, with the maximum dose being limited to 300 mg/day. For patients weighing > 60 kg, treatment was extended for another day for each kilogram of weight > 60 kg, not exceeding 80 days of treatment. Patients were followed up with clinical and laboratory evaluations, including complete blood count, aspartate aminotransferase and alanine aminotransferase activity, and creatinine concentration, before treatment initiation, every 15 and 30 days, and at the end of etiological treatment.

Adverse reactions were meticulously recorded in individual medical records according to complaints and physical examination findings during routine outpatient follow-ups, followed by immediate medical evaluation and appropriate intervention for each case. Of the 520 patients receiving care at ADOC-UERN, 106 were included after applying the aforementioned inclusion and exclusion criteria.

Data are described using absolute and relative frequencies. Bivariate analysis was conducted using Pearson's chi-squared test and Fisher's exact test, when appropriate. Significance was set $P < 0.05$, with 95% confidence intervals (CI).

Some risks of methodological biases were observed, including the difficulty of standardizing laboratories responsible for collecting and analyzing data from examinations and the challenge of facilitating access to patients to monitor laboratory results with more precision, given the diverse geographical distribution of individuals served at ADOC-UERN. To mitigate these biases, laboratory tests should be conducted in facilities that adhere to the respective municipal health departments, aiming for reliability of the results obtained.

Before inclusion in the care program of ADOC-UERN, all patients signed an informed consent form approved by the Research Ethics Committee of the Universidade do Estado do Rio Grande do Norte (1,160,553 and CAAE: 43783915.3.00005294,

July 21, 2015). This study adhered to the ethical principles outlined in Resolution 466/12 of the National Health Council of Brazil for research involving humans.

RESULTS

Of the total of 106 participants, aged between 18 and 65 years, 54.7% (58/106) were men, and 45.3% (48/106) were women. The most prevalent clinical form was the indeterminate form (69.8%, 74/106), followed by the cardiac (15.1%, 16/106), digestive (10.4%, 11/106), and cardiodigestive forms (4.7%, 5/106).

Among the patients who received etiological treatment with benznidazole, 40.5% (43/106) experienced adverse reactions, which were observed in 12 different manifestations and distributed in 55 events (more than one reaction could be observed in the same patient). The primary reactions observed were dermatitis (27.3%; 15/55) and pruritus (16.4%; 9/55) (**Table 1**).

The most prevalent manifestations in men were dermatitis (26.3% of 5/19) and leukopenia (21% of 4/19). In women, dermatitis was observed in 27.8% (10/36) and pruritus in 22.2% (8/36). Occasionally, the manifestations pertained to multiple systems (**Table 1**).

In some participants, sweating was recorded in one study and syncope and dizziness in three studies. However, these were not considered possible adverse effects because of the inability to establish a clear causal relationship between the events.

Hematological analysis revealed leukopenia in six patients (four men and two women) and thrombocytopenia in three patients (two men and one woman), with the most significant case reaching a platelet count of 46,000/mm^3. Regarding leukopenia, a decrease between 100 and 3,600 leukocytes was observed in 16 patients, with 14 patients experiencing a relative decrease of > 10% between the leukocyte value before treatment and the value in the second half of the treatment period.

Four patients treated with benznidazole discontinued treatment voluntarily because of adverse reactions (three women and one man). The average number of tablets consumed by the patients until the onset of adverse reactions was 61, which is equivalent to approximately 20 days of treatment at a dose of three tablets per day. In women, the average was 51 tablets or approximately 17 days of treatment. In men, the average was 72 tablets or approximately 24 days from the treatment initiation.

Bivariate analysis revealed a statistically significant association between female sex and the occurrence of adverse reactions (P = 0.009). Adverse dermatological reactions were more frequently observed among female patients (P = 0.023), whereas adverse hematological reactions were more strongly associated with male sex (P = 0.042) (**Table 2**).

Figure 1 presents some examples of the dermatological reactions observed in the patients included in this study.

DISCUSSION

Despite the proven efficacy of medications against Chagas disease, reports on the side effects of their use are few. Benznidazole has the best safety and tolerance record, making it the first choice of treatment.[17,18] The most frequent side effect of benznidazole treatment is dermatitis, which is attributed to hypersensitivity.[19] In our practice, the majority of treated patients exhibited dermatological conditions as a side effect, with dermatitis and pruritus being prominent. Treatment discontinuation was not required because adverse effects could be managed using corticosteroids and antihistamines, in addition to reducing the dosage twice daily and extending the treatment duration to accommodate the calculated dose for each patient.

Leukopenia and thrombocytopenia were the most common hematological reactions. Regarding platelet suppression, the literature reports episodes of thrombocytopenic purpura triggering

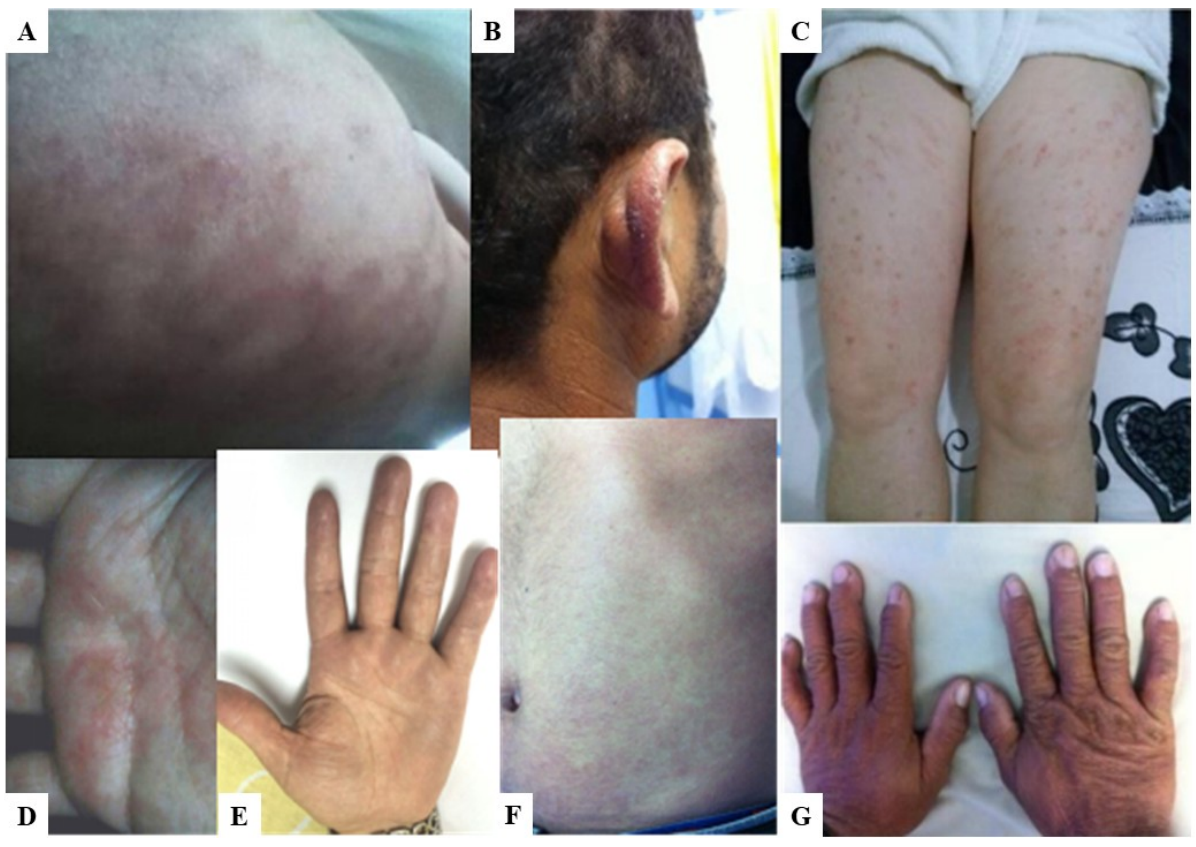
Table 1. Frequency of adverse reactions in patients with Chagas disease treated with benznidazole at the Chagas Disease Outpatient Clinic of the Universidade do Estado do Rio Grande do Norte (ADOC-UERN)

Systems n (%)	Adverse reaction	Sex		Total
		Male	Female	
		n (%)	n (%)	n (%)
Dermatological 30 (54.5)	Pruritus	1 (5.3)	8 (22.2)	9 (16.4)
	Dermatitis	5 (26.3)	10 (27.8)	15 (27.3)
	Xerosis with peeling	2 (10.5)	4 (11.1)	6 (10.9)
Hematological 9 (16.4)	Leukopenia	4 (21)	2 (5.5)	6 (10.9)
	Thrombocytopenia	2 (10.5)	1 (2.8)	3 (5,4)
Gastrointestinal 8 (14.5)	Xerostomia	1 (5.3)	1 (2.8)	2 (3,6)
	Epigastralgia	1 (5.3)	3 (8.3)	4 (7,3)
	Nausea	1 (5.3)	1 (2.8)	2 (3,6)
Neurological 6 (10.9)	Paresthesia	1 (5.3)	4 (11.1)	5 (9,1)
	Insomnia	–	1 (2.8)	1 (1.8)
Musculoskeletal 2 (3.6)	Arthralgia	1 (5.3)	–	1 (1.8)
	Cramps	–	1 (2.8)	1 (1.8)
Total		19 (100)	36 (100)	55 (100)

Table 2. Adverse reaction in patients with Chagas disease receiving etiological treatment with benznidazole at the Chagas Disease Outpatient Clinic of the Universidade do Estado do Rio Grande do Norte (ADOC-UERN). Bivariate analysis of the variables sex, any adverse reaction, and dermatological adverse reaction

Variables		Sex		X^2	P value
		Male n (%)	Female n (%)		
Adverse reaction	Yes	17 (39.5)	26 (60.5)	6.73	0.009[a]
	No	41 (65.1)	22 (34.9)		
Dermatological	Yes	6 (24)	19 (76)	5.203	0.023[a]
	No	10 (58.8)	6 (41.2)		
Gastrointestinal	Yes	3 (42.9)	4 (57.1)	0.081	1[b]
	No	13 (13.3)	22 (21.7)		
Hematological	Yes	6 (75)	2 (25)	5.171	0.042[b]
	No	11 (31.4)	24 (68.6)		
Musculoskeletal	Yes	1 (50)	1 (50)	0.106	1[b]
	No	15 (38.5)	24 (61.5)		
Neurological	Yes	1 (25)	3 (75)	0.321	1[b]
	No	15 (39.5)	23 (60.5)		

[a]Pearson's Chi-squared test.
[b]Fisher's exact test.



A: erythematous plaques on the body; B: erythematous and scaly plaques on the auricle; C: petechiae in the lower limbs; D: eczematous plaques in the palmar region; E: violet spots in the palmar region; F: maculopapular rash; G: eczematous plaques in the photoexposed areas.

Figure 1. Skin lesions with typical presentations of reactions to benznidazole.

flushing and the appearance of petechiae in the palmar and plantar regions within minutes of drug ingestion, potentially leading to digestive, urinary, oral, and nasal mucosal hemorrhages.[20]

Reported as the second most frequent manifestation of side effects,[17,21,22] gastrointestinal adverse reactions were observed in 14.3% of our patients. Adverse neurological effects were reported

after 30 days of treatment, with paresthesia being prominent and more common in women than in men. This finding is similar to those of Pinazo[23] and Tornheim,[18] where 27.6% and 29.8% of their patients, respectively, experienced adverse neurological reactions.

Among the treated patients, 40.5% experienced adverse reactions, a proportion within the range already described in the literature[17,21,22] Women showed a higher incidence of side effects than men, supporting the results of previous studies[17,24,25] The most common categories of adverse reactions in women compared with men were within the dermatological and neurological systems[18,21] The higher prevalence of side effects in women may be attributed to their greater adherence to treatment and metabolic alterations owing to hormonal levels and corporal composition, as women have less muscle and lower basal metabolism than men.[26]

A factor that enabled effective follow-up and consequently a low discontinuation rate of etiological treatment was the team's dedication to providing the best possible care, offering guidance, providing informative materials, and offering the flexibility to adjust symptomatic therapy for patients experiencing adverse reactions.

CONCLUSIONS

This study describes the most frequent adverse reactions associated with the use of benznidazole in patients with Chagas disease. This study highlights the importance of identifying these events to increase the awareness of risks, thereby facilitating professional guidance for patients, instilling greater confidence in treatment, and improving adherence.

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Prevalence of alcohol use disorders in individuals with borderline personality disorder: a meta-analysis and meta-regression study

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Epidemiology.
Borderline personality disorder.

AUTHOR'S KEYWORDS:
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Borderline disorder.
Borderline.
Borderline and alcohol.

ABSTRACT

BACKGROUND: This review examined the prevalence rate of alcohol use disorders (AUDs)–including heavy episodic drinking, heavy drinking, alcohol abuse, and alcohol dependence–among individuals with borderline personality disorder (BPD).

OBJECTIVES: The primary objective of this meta-analysis and meta-regression study was to investigate the prevalence AUDs associated with BPD.

DESIGN AND SETTING: We searched PubMed, Google Scholar, Virtual Health Library (VHL/BVS), SciELO, LILACS, EMBASE, and PsycINFO for studies, reports, or abstracts published without language restrictions.

METHODS: We searched for reports published from database inception through March 2024. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology guidelines (MOOSE). Based on the extracted data, we performed meta-analyses and meta-regressions.

RESULTS: The final sample included 15 articles with 15,603 individuals aged 18 years or older with BPD. The prevalence of AUDs with BPD was 55.28%, while the prevalence of alcohol dependence (AD) was 44.59%, and alcohol abuse (AA) was 18.84%.

CONCLUSION: Our findings indicate a high prevalence of AUDs among individuals with BPD, underscoring the need for targeted prevention and treatment strategies. Integrated dual-diagnosis approaches addressing both disorders simultaneously are crucial for improving outcomes. This high prevalence has important implications for public health.

INTRODUCTION

Alcohol consumption is a major public health concern associated with numerous health problems and a high percentage of mortality[1] Several factors can influence alcohol consumption, and although the prevalence of alcohol use disorder (AUD) in individuals with borderline personality disorder (BPD) has not been well established, emerging evidence suggests increased susceptibility in this population.[2]

AUD is defined by compulsive alcohol use, impaired control over consumption, and negative emotional states during withdrawal, and it often becomes chronic and recurrent.[3] According to the DSM-5, "alcohol use disorder" replaces the DSM-4 categories of alcohol abuse and dependence, and is now classified as mild, moderate, or severe.[4,5] AUD frequently occurs with psychiatric disorders, including personality disorders, further worsening patient outcomes.

BPD is classified in the DSM-5 as a Cluster-B personality disorder and is characterized by pervasive affective instability, impulsivity, interpersonal difficulties, and disturbances in self-image.[6,7] Individuals with BPD often exhibit heightened emotional reactivity and sensitivity to social and interpersonal stressors, contributing to significant psychological distress and functional impairment.

This meta-analysis examined the prevalence of AUD among individuals with BPD with the goal of informing interventions aimed at reducing alcohol-related harm. It synthesizes findings from population-based surveys reporting lifetime comorbidity rates of BPD and AUD.

METHODOLOGY

Review guidelines and registration

This study followed the PRISMA statement for transparent reporting of systematic reviews and meta-analyses[8] and the MOOSE guidelines for meta-analysis of observational studies in epidemiology.[9]

Both checklists are provided in the supplementary materials (**Figure 1 and 2**), detailing where each item is addressed. This study was registered with the Center for Open Science/Open Science Framework (https://osf.io/6c5np?mode=&revisionId=&view_only=).

Information sources

Following Cochrane methodology, we searched seven databases–PubMed, EMBASE, Google Scholar, Biblioteca Virtual em Saúde (BVS), SciELO, LILACS, and PsycINFO)–between November 2023 and March 2024 for studies published up to

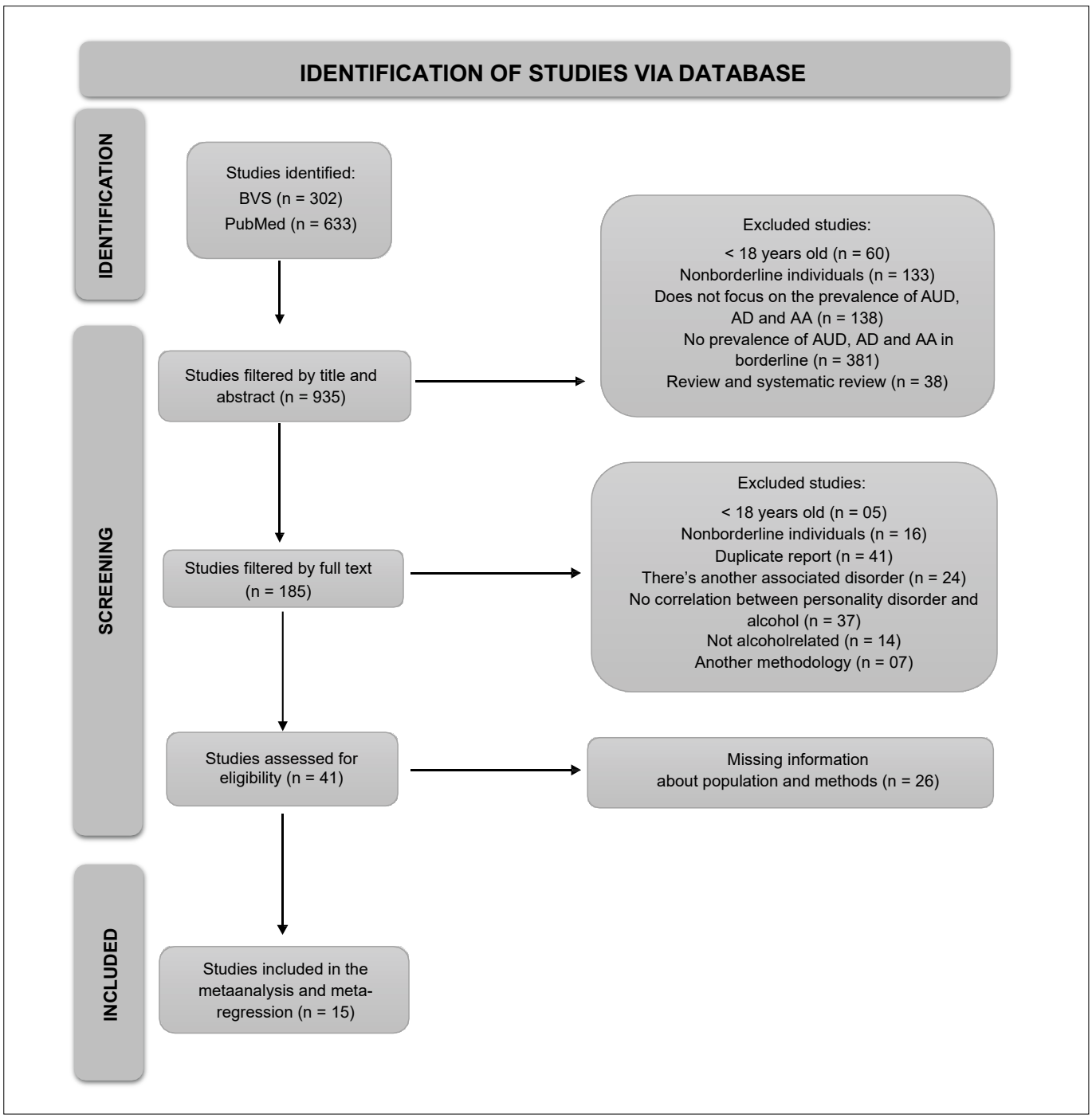

Figure 1. Study's selection flow chart.

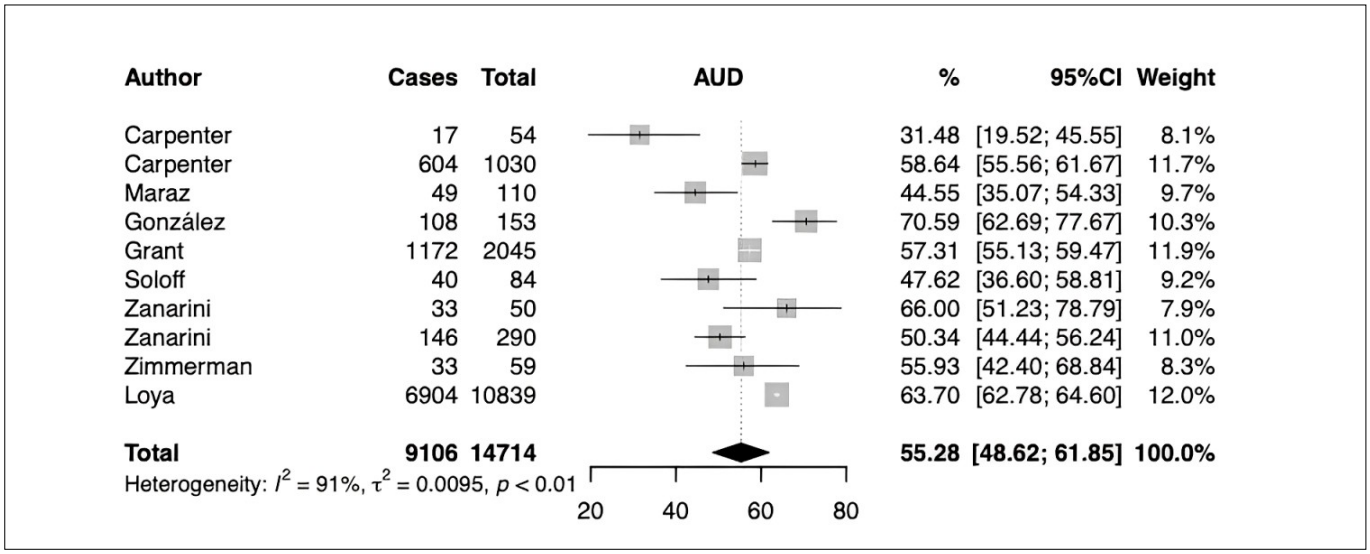

Figure 2. Subgroup analysis of alcohol use disorders.

January 15, 2024. No language restrictions were applied. The final search was conducted on March 10, 2024.

Medical Subject Headings (MeSH) use included: (alcohol use OR alcoholism OR binge drinking OR alcohol use disorder OR hazardous drinking OR alcohol abuse OR alcohol dependence)) AND "(((“prevalence”[Mesh]) OR “epidemiology”[Mesh]) AND “borderline disorder”[Mesh]".

Health Sciences Descriptors (DeCS) terms were also used: "(epidemiologia) OR (prevalência) AND (alcoolismo) OR (beber em binge) OR (abuso de álcool) OR (alcoolismo) AND (transtorno de personalidade borderline)". In PICO terms, the Population was adults aged ≥ 18 years; the Intervention/Determinant was borderline disorder; the Comparison was without borderline disorder; and the Outcome included AUD, alcohol abuse and alcohol dependence. Books and dissertations were excluded.

Selection criteria

Studies were included if they met the following criteria: (i) cross-sectional and longitudinal observational design; (ii) assessment of Alcohol Dependence (AD) Alcohol Abuse (AA), and AUD using validated questionnaire, such as SCID, ICD, MINI, PAI-BOR, PDQ4+, SADS, DIPD-IV, or clinical assessment scales; (iii) participants aged ≥ 18 years; and (iv) no language restrictions.

Articles were selected based on the title and abstract, and then reviewed through full-text analysis. All abstracts were independently assessed by two authors, with disagreements resolved by consensus.

Data extraction

Two reviewers independently extracted data, with a third reviewer consulted if needed. Extracted variables included authors, year of publication, total number of participants with a diagnosis of AD, AA, or AUD, total number of participants with BPD, sex, age, study design, country, diagnostic instruments, and diagnostic criteria.

Quality assessment

Methodological quality was assessed using the Joanna Briggs Institute checklist for analytical cross-sectional studies,[10] and was applied to all studies registered in the current systematic review. The checklist evaluates sample structure, process, size, description of the context, coverage of data analysis, valid and reliable evaluation methods, appropriate statistical analysis, and adequate response rate. Fifteen studies scored ≥ 6 (maximum = 8 points) and were therefore retained (supplementary material, **Table 1**).

Data analysis

We first determined the prevalence of AD, AA, and AUD among individuals with BPD. Heterogeneity test (Q-test) was used to determine whether the differences between the prevalence estimates in the studies were greater than those predicted by chance. Significant heterogeneity prompted the use of random-effects models. Univariate analyses were performed to assess the relationships between each variable. These included methodological factors, age, sex, and geographical location of the study participants. The combined prevalence of AUD was estimated using a meta-regression approach. Variability in the estimate of AUD prevalence was assessed using a random-effects regression model. A significance level of 5% was used for all the analyses.

The prevalence and 95% confidence intervals (CIs) were found for the numbers of AD, AA, and AUD related to BPD. The contribution of each study to each meta-analysis was assessed using sensitivity analysis. R software version 3.5.0 was used to analyze

Table 1. Descriptive summary of the included studies

Author (year)	Study population	Setting	Diagnostic criteria	Prevalence rates (N)
Carpenter et al. (2017)[12]	N: 54 F/M: 4.4 USA MEAN AGE: 26.02	COMMUNITY	DSM-IV	AUD 31.48%
Carpenter et al. (2016)[13]	N: 1030 USA	COMMUNITY	DSM-IV	AUD 58.64%
Tadic et al. (2009)[24]	N: 159 F/M: 2.2 EUROPE MEAN AGE: 33.45	CLINICAL	DSM-IV	AD 49.69% AA 11.95%
Picci et al. (2012)[14]	N: 62 F/M: 0.631 EUROPE	CLINICAL	DSM-IV	AD 83.87%
Maraz et al. (2016)[14]	N: 110 EUROPE	COMMUNITY	ICD-10/DSM-IV	AUD 44.55%
Dulit et al. (1990)[22]	N: 137 F/M: 4.1 USA MEAN AGE: 29	CLINICAL	DSM-III	AD 15.33% AA 33.58%
Stepp et al. (2005)[42]	N: 356 F/M: 1.3 USA MEAN AGE: 18	CLINICAL	DSM-IV	AUD 36%
González et al. (2019)[15]	N: 153 EUROPE MEAN AGE: 37.54	COMMUNITY	DSM-IV	AUD 70.59%
Grant et al. (2008)[16]	N: 2045 USA	CLINICAL	DSM-IV	AUD 57.31% AD 41.56% AA 15.7%
Soloff et al. (1994)[17]	N: 84 F/M: 2.652 USA MEAN AGE: 26.9	CLINICAL	DSM-III-R	AUD 47.62%
Walter et al. (2009)[25]	N: 175 F/M: 2.9 EUROPE MEAN AGE: 32.1	CLINICAL	DSM-IV	AD 34.86% AA 17.14%
Zanarini et al. (1989)[18]	N: 50 F/M: 1.941 USA MEAN AGE: 29.2	CLINICAL	DSM-III	AUD 66%
Zanarini et al. (2011)[19]	N: 290 F/M: 25.363 USA MEAN AGE: 27	CLINICAL	DSM-III-R	AUD 50.34%
Zimmerman et al. (1999)[20]	N: 59 F/M: 1.565 USA MEAN AGE: 32.6	CLINICAL	DSM-IV	AUD 55.93%
Loya et al. (2024)[21]	N: 10839 F/M: 1.315 USA	COMMUNITY	DSM-V	AUD 63.7%

*F/M, proportion; USA, United States of America.

the data. The significance threshold was calculated for p-values below 0.05 ($P < 0.05$).

Statistical regression models have been used in studies where people are considered as the unit of analysis to assess how one or more covariates relate to a dependent variable.[11] The use of meta-regression instead of the AUD subgroup analysis enabled the inclusion of continuous covariates and only one covariate at a time. Radom effects meta-regression measures the variance between studies in a

modified Knapp–Hartung model using restricted maximum likelihood residuals.[12] Permutation tests were used to correct for multiple testing by calculating the adjusted p-values after analyzing all covariates (sex, age, region, and diagnostic criteria).[12]

RESULTS

Figure 1 shows the study selection process. A total of 935 records were screened by title and abstract. Of these, 750 articles were considered for abstract and full-text reading. All abstracts were reviewed by the first author, and some were selected for further review based on the following criteria: (1) articles with BPD individuals, (2) articles focusing on AUD, AA, and AD prevalence, or (3) original articles evaluating AUD, AA, and AD prevalence in samples diagnosed with BPD. In total, 184 articles underwent full-text review. After exclusions–including age < 18 years (n = 5), no BPD diagnosis (n = 16), presence of other associated disorder (n = 24), duplicates (n = 41), no assessment of the BPD–alcohol relationship (n = 37), not alcohol-related (n = 14), and methodological incompatibility (n = 7). **Table 2** (supplementary material) presents the main findings of the included studies.

Fifteen unique studies met the inclusion criteria. The final sample comprised 15,603 individuals with BPD, age ≥ 18 years. The studies were classified as clinical (n = 10) and community (n = 5). These data are presented in **Table 1**.

The studies were conducted in 6 countries, with the United States contributing to the largest proportion (n = 10). Diagnostic criteria for AUD and BPD varied across studies, mostly commonly DSM-IV (n = 10). Others used DSM-V, DIB, DIPD-IV, DIPD-R, ICD-10, DSM-III, SADS, MCMI-III, PAI-BOR, SCID-I, MINI, AUDIT, or PDQ4+. Six articles were selected based on three criteria (ICD-10, AUDIT, DSM-IV, PAI-BOR, SCID-I, MINI, PDQ4+, DSM-III, DIB, SADS, and DIPD-IV). Three articles were selected based on two different criteria (DSM-IV, MCMI-III, DSM-III, and SCID).

Figure 2 shows that 55.28% (95% confidence interval [95% CI] = 48.62–61.85%) of the BPD were diagnosed with AUD,[13–22] 10 studies included the prevalence of AUD. The lowest AUD prevalence was 31.48% (95% CI = 19.52%–45.55%),[13] while the highest prevalence was 70.59% (95% CI = 62.69%–77.67%).[16] The pooled prevalence of AD[17,23–26] in individuals with BPD (**Figure 3**) was 44.59% (95% CI =22.61%–67.73%), and the subgroup analysis investigated five studies involving 1063 individuals. In **Figure 4** four studies investigated AA[17,23,25,26] prevalence among individuals with BPD (n = 2516) and obtained a pooled prevalence of 18.84% (95% CI =11.08%–28.06%). The regression analysis (**Table 2**) revealed no statistically significant variables.

Geographic location was significantly associated with the prevalence of AUD, AA, and AD. The prevalence of AUD in North America was 80% (eight studies) and 20% in Europe (two studies). The prevalence rates of AA were 50% in Europe (two studies) and 50% in North America (two studies). The prevalence rates of AD were 60% in Europe (three studies) and 40% in North America (two studies).

DISCUSSION

To the best of our knowledge, no previous systematic review or meta-analysis has investigated the co-occurrence of alcohol dependence (AD), alcohol abuse (AA), and alcohol use disorder (AUD) in individuals with borderline personality disorder (BPD). This meta-analysis sought to synthesize the available evidence to address this gap and provide a comprehensive understanding of the prevalence and combined patterns of AD, AA, and AUD in individuals with BPD. We also explored the possible relationships, clinical implications, and targeted interventions.

Our findings indicate that individuals with BPD have a higher risk of AUD relative to the general population. For comparison, data from 2016 estimated AUD prevalence at 8.6% among men (95% CI:8.1%–9.1%) and 1.7% of women.[3,27] In contrast, our pooled estimates revealed substantially higher prevalence rates among individuals with BPD: 55.28% for AUD, 18.84% for AA, and 44.59% for AD. These results demonstrates a significant burden of comorbid alcohol-related disorders in this population.

The rationale for conducting this meta-analysis stems from both the lack of comprehensive investigations on this topic and the profound public health impact of alcohol misuse. Harmful alcohol use accounts for approximately 3 million deaths annually–representing

Table 2. Results of the meta-regression models for alcohol use disorders among individuals with borderline personality disorders

Covariate	Coefficients	Upper bound	Lower bound	Std. error	P value
Year	0.001	0.016	–0.013	0.007	0.847
Female	–0.467	0.147	–0.147	0.314	0.136
Age	–0	0	–0	0	0.341
Type	Clinical (reference)				
Community	–0.012	0.387	–0.362	0.191	0.947
Region	Europe (reference)				
U.S.	0.008	0.346	–0.329	0.172	0.959
Criteria	DSM (reference)				
Mixed	0.1	0.445	-0.245	0.176	0.569

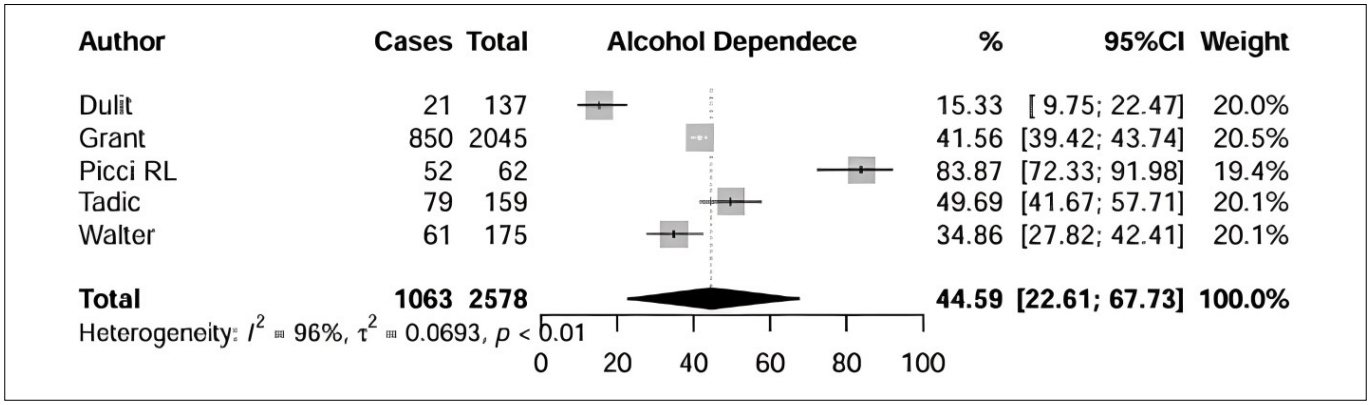

Figure 3. Subgroup analysis of alcohol dependence.

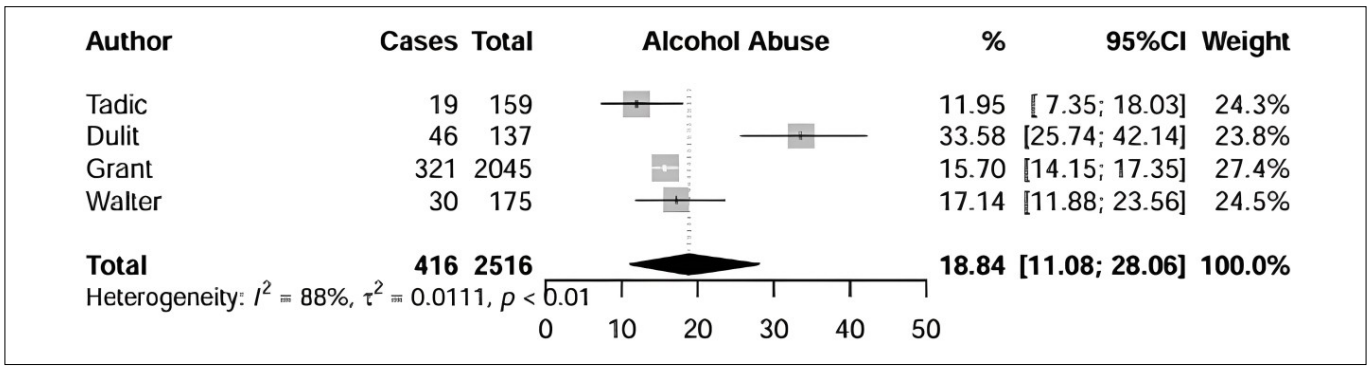

Figure 4. Subgroup analysis of alcohol abuse.

5.3% of all global mortality,[28] and is linked to wide range of psychiatric conditions, including personality disorders. AUD trajectories varies considerably: some individuals experience transient episodes, whereas others exhibit patterns of relapse and remission or a persistent and chronic course.[29] These patterns not only poses health risks but also impose extensive burdens on public health systems, social services, law enforcement, and administrative infrastructures.[30] Furthermore, AUD frequently coexists with other psychiatric disorders, such as bipolar disorder,[31] and more than 30% of individuals with AUD present with at least one additional psychiatric diagnosis.[32]

BPD is frequently underdiagnosed but may be present in up to 6.4% of adults in primary care visits, four times higher than in the general population[7]. It is also associated with numerous medical and psychiatric comorbidities, including obesity, excoriation (skin picking) disorder, and substance use disorders, including alcohol.[33–35] Studies have indicated that individuals with BPD are more susceptible to developing AUD, largely due to emotional dysregulation, impulsivity, and heightened sensitivity to interpersonal stressors.[1,36,37]

The high prevalence of AUD among individuals with BPD likely reflects a complex interplay between emotional, cognitive, and genetic factors. Self-damaging impulsivity–a core feature of BPD–has been identified as a strong genetic risk factor for AUD, even more predictive than categorical BPD diagnosis.[38] Moreover, coping- and conformity-related drinking motives appear to mediate the association between BPD and alcohol-related problems, suggesting that individuals with BPD often use alcohol as a maladaptive strategy for emotion regulation and social belonging.[39] Emotional dysregulation also plays a key role as BPD individuals show greater mismatches between physiological and subjective emotional responses, which is associated with more frequent alcohol use.[40] Interestingly, although both BPD and BPD+AUD groups display high levels of impulsivity and maladaptive schema modes, these domains do not differ significantly between groups, indicating shared vulnerability mechanisms regardless of alcohol use.[37]

In addition, evidence highlights that impulsivity and affective dysregulation contribute not only to AUD comorbidity but also to poorer treatment outcomes. This underscores the need for comprehensive, multimodal interventions that incorporate social network support, psychoeducation, and targeted treatments for both BPD and AUD.[41,42] As the clinical importance of empirical data on the co-occurrence of BPD and AUD remain fragmented, our review identified substantial gaps across regions and a lack of large-scale epidemiological studies.

Our findings also reveal substantial heterogeneity in reported prevalence across studies. This variability highlights the need for further research to identify underlying mechanisms and contextual factors influencing these differences. Addressing AUD in individuals with BPD represents a pressing clinical priority, as targeted interventions may reduce alcohol-related harm and improve overall treatment outcomes in this high-risk population.

Limitations

This meta-analysis has several limitations. Although the study used broad measures, heterogeneity could not be fully explained by the moderators. Four studies did not stratify participants by sex, instead analyzing as a single population,[13,15–17] which limited our ability to assess sex-specific patterns. Additionally, data were insufficient to examine all regions; in the lack of studies in Africa, South America, Asia, and Oceania highlights the need for more geographically diverse research.

Five studies lacked adequate information on age distribution, restricting age-related analyses.[14,15,17,22,24] One study did not differentiate between AUD, AA and AD among individuals with BPD, reporting them collectively; this study was therefore excluded from the meta-analysis.[43]

Small sample sizes in some studies may have limited the statistical power needed to detect significant differences. In addition, social stigma associated with reporting alcohol consumption may have contributed to the underreporting of alcohol consumption, especially in specific ethnic groups. The lack of a standard diagnostic method is a limitation of this study. In addition, Google Scholar limits the results of any search to the 1000-most cited papers, potentially omitting relevant but less frequently cited studies.

CONCLUSION

The high prevalence of AUD among individuals with BPD highlights the critical need for early detection and integrated treatment approaches. Individuals with AUD and BPD face increased risks of developing other physical and emotional comorbidities. Therefore, treatment strategies should target both conditions concurrently to mitigate harm and improve clinical outcomes. Future research should explore the interaction between BPD and AUD using diverse methodological approaches, as well as the correlation between AUD and other psychiatric disorders–such as major depressive disorder and substance use disorder–aiming to improve treatment outcomes, reduce harm, and improve public health outcomes.

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Implementation of a new histological grading system in ovarian mucinous carcinomas and its association with the risk of recurrence: a retrospective cohort study

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ABSTRACT

BACKGROUND: This retrospective cohort study evaluated the prognostic significance of the Growth-Based Grade (GBG) system compared to International Federation of Gynecology and Obstetrics (FIGO) grading in ovarian mucinous carcinoma (OMC). Although FIGO grading is commonly used, its prognostic value remains controversial. The GBG system, which classifies tumors as low-grade (G1) or high-grade (G2) based on the proportion of infiltrative growth, has emerged as a potential prognostic tool.

OBJECTIVES: To assess the prognostic significance of GBG and compare it with FIGO grading in OMC.

DESIGN AND SETTING: This retrospective cohort study included 37 women with OMC treated at a single institution between 2009 and 2022.

METHODS: GBG was determined by a histopathological review of hematoxylin and eosin-stained slides. Clinical and demographic data, including FIGO stage, CA125 levels, surgical procedures, and follow-up information, were collected. Kaplan-Meier analysis and Cox regression were used to assess the associations between GBG grading, FIGO stage, and survival outcomes.

RESULTS: GBG 2 tumors were significantly associated with elevated CA125 levels, advanced FIGO stage (III), and bilaterality. Multivariate analysis showed that GBG 2 conferred a 5.4-fold higher risk of recurrence compared with GBG 1. While FIGO stage III was predictive of overall survival, FIGO grading was not associated with recurrence risk.

CONCLUSION: This study suggests a potential prognostic value of the GBG system in mucinous ovarian carcinoma. GBG 2 tumors showed a higher risk of recurrence than GBG 1 tumors, whereas FIGO grading showed no such association. These findings align with previous reports and should be interpreted in the context of additional studies to clarify the system's clinical relevance.

INTRODUCTION

Primary mucinous carcinoma of the ovary is rare, accounting for only 3% of all ovarian carcinomas.[1,2] Historically, ovarian mucinous carcinoma was diagnosed in 15% of ovarian carcinoma cases; however, many of these were later identified as metastatic tumors, resulting in significant overdiagnosis. The therapeutic approach remains challenging, with ongoing debates on multiple aspects. These include the role of systematic lymphadenectomy, the necessity of adjuvant chemotherapy in cases of tumor rupture, and the optimal choice of chemotherapeutic agents: carboplatin and paclitaxel versus capecitabine and oxaliplatin.[3]

Approximately 80% of cases are diagnosed at stage I according to the International Federation of Gynecology and Obstetrics (FIGO) classification,[1,4] with a five-year survival rate of 83% in women with the disease confined to the ovaries. In contrast, patients with advanced disease (stages III and IV) have a five-year survival rate of only 14%.[5]

Differentiating ovarian mucinous carcinoma from ovarian metastases requires a combination of clinicopathological evaluations, imaging studies, and immunohistochemical analyses. Most ovarian metastases originate from gastrointestinal tract cancers, but can also be secondary to breast, cervical, or endometrial cancers.[4] Serum tumor markers such as carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and the CA125/CEA ratio,[6] along with imaging studies — including total chest and abdominal computed tomography (CT), total abdominal magnetic resonance imaging (MRI), upper gastrointestinal endoscopy, and colonoscopy — can assist in the diagnostic process.[4]

The following findings suggest a primary ovarian tumor: a tumor larger than 10 cm, unilateral involvement, absence of mucin in the peritoneal cavity, and a normal appendix. Histological diagnosis of ovarian mucinous carcinoma requires evidence of complex malignant cell proliferation covering an area greater than 10 mm^2 in histological sections of the tumor.[4] Adequate tumor sampling — collecting one to two tissue samples per centimeter of the tumor's largest diameter — and a thorough review by an experienced pathologist are essential. Immunohistochemical profiling of ovarian mucinous carcinomas primarily relies on markers such as CK7, CK20, and CDX2 to differentiate them from primary gastrointestinal tract carcinomas.[4] However, diagnostic challenges persist due to frequent overlaps in immunohistochemical staining patterns, necessitating correlation with imaging studies.[7] In some cases, ovarian mucinous carcinoma remains a diagnosis of exclusion when extensive investigations fail to identify disease at another site.[8]

Although there is no definitive evidence regarding the prognostic role of histological grading in ovarian mucinous carcinomas, the International Collaboration on Cancer Reporting recommends using the endometrioid carcinoma grading system if grading is performed.[9] This corresponds to the FIGO grading system, which classifies tumors as well-differentiated (G1), moderately differentiated (G2), or poorly differentiated (G3) based on the proportion of solid glandular components and the presence of nuclear atypia.[9] In 2014, the World Health Organization (WHO) officially recognized a classification previously described by Lee and Scully in 2000,[10] which categorizes ovarian mucinous carcinomas into expansile and infiltrative subtypes based on stromal invasion patterns. The expansile subtype exhibits a confluent glandular growth pattern with minimal or no destructive stromal invasion, whereas the infiltrative subtype is characterized by overt destructive stromal invasion by nests of cells, glands, or isolated tumor cells, often associated with a desmoplastic stromal reaction.[10]

In 2020, Busca et al.[11] proposed a novel grading system for ovarian mucinous carcinomas, the Growth-Based Grade (GBG), classifying tumors as low-grade (G1) or high-grade (G2): G1 when the growth pattern is only expansile or infiltrative in ≤ 10% of the tumor and G2 when infiltrative invasion exceeds 10%. In their study, staging, GBG, and Silverberg histological grading[12] were associated with disease-free survival.[11] A subsequent validation study by the same research group confirmed that GBG G2 tumors had a higher recurrence risk than GBG G1 tumors. The Silverberg and FIGO classification systems also showed a correlation with progression-free survival in univariate analysis. However, multivariate analysis indicated that only GBG was statistically significant. In addition, the percentage of infiltrative growth was identified as the sole predictive factor for disease-specific survival.[13]

The prognostic role of histological grading in ovarian mucinous carcinomas appears to be less significant than the invasion type classified by the GBG system,[11] which is endorsed in the latest edition of the WHO Classification of Tumors — Tumors of the Female Genital Tract.[14] However, the same edition acknowledges that no definitive consensus has been reached regarding which grading system should be used, as the FIGO histological grading system may also provide useful prognostic information to guide appropriate management strategies.

OBJECTIVE

This study aimed to assess the prognostic significance of GBG histological grading and compare it with FIGO grading in a cohort of 37 women with primary ovarian mucinous carcinoma.

METHODS

Study design and population

This retrospective study was based on a convenience sample, and was approved by the Research Ethics Committee of Unicamp (approval number 1092/2009 and CAAE: 33451720.7.0000.5404). Women referred for adnexal masses to the Ovarian Oncology outpatient clinic at the Women's Hospital, Prof. Dr. José Aristodemo Pinotti, CAISM-Unicamp, were selected. All participants signed an informed consent form during their first outpatient visit between December 2009 and July 2022 (N = 1,950). Patients histologically diagnosed with primary ovarian mucinous carcinoma were included in this study (n = 45).

Seven women were excluded because of the unavailability of hematoxylin and eosin (H&E)-stained slides for review by a gynecologic pathologist (L.A.L.A.A), and one was excluded because of a diagnosis of teratoma with a 1 mm mucinous adenocarcinoma focus, resulting in a final cohort of 37 women. Of these patients, 36 were diagnosed surgically. One patient was diagnosed via percutaneous core needle biopsy, which was performed due to the suspicion of an adnexal mass based on physical examination, serum tumor marker assessment, and imaging studies.

Data collection and definitions

This study did not alter the standard hospital treatment protocols for women with ovarian mucinous carcinoma. Immunohistochemical staining was performed on tumor samples from 33 women to aid in the differential diagnosis and characterization of the tumor subtypes. All H&E-stained slides were reviewed by a single pathologist with extensive expertise in gynecologic pathology and classified strictly according to the diagnostic criteria proposed by Busca et al.,[11] for study purposes only and without any clinical application. Following treatment, patients were followed up in outpatient clinics, and their status

was updated through electronic medical records until November 2024. A subset of women who were lost to follow-up or discharged from the hospital was contacted by phone, while the survival status of the remaining patients was confirmed through two national databases: the CPF (Brazilian national identification number, canceled upon death) and the National Registry of Deceased Persons.

Statistical analysis

To compare categorical variables between groups (G1 and G2 of the GBG), the chi-square test or Fisher's exact test was used, as appropriate. Numerical variables were compared using the Mann–Whitney U test for two-group comparisons and the Kruskal-Wallis test for three-group comparisons. Disease-free survival and overall survival curves were analyzed using the Kaplan–Meier method, and comparisons were performed using the log-rank test. Factors associated with survival outcomes were assessed using both univariate and multivariate Cox regression analyses, employing a stepwise selection criterion for variable inclusion. The significance level was set at 5% ($P < 0.05$). Statistical analyses were performed using SAS for Windows (Statistical Analysis System), version 9.4 (SAS Institute Inc., 2002–2012, Cary, NC, North Carolina).

RESULTS

Table 1 presents the demographic and clinical characteristics of the two groups of women classified according to the GBG grading of ovarian mucinous carcinomas. GBG 2 tumors were associated with elevated CA125 levels, advanced stage (III), and bilaterality compared with GBG 1 tumors. The sample predominantly included white participants with a smaller proportion of women of other ethnicities. Owing to the limited sample size, racial diversity was restricted.

Regarding surgical treatment, 28 women (75.7%) underwent omentectomy, and 23 (62.2%) underwent appendectomy. Uterine and contralateral ovary preservation was performed in six (16.2%) of the 37 women. Thirty women (81.1%) were diagnosed at stage I, one (2.7%) at stage II, and six (16.2%) at stage III. The tumors were classified as GBG 1 in 27 women (73%) and GBG 2 in 10 women (27%).

Tables 2 and 3 present the results of univariate and multivariate Cox regression analyses of factors related to disease-free survival. Multivariate analysis indicated that GBG grading significantly influenced the recurrence risk, with GBG 2 associated with a 5.4-fold increased risk of recurrence compared to GBG 1.

Three patients experienced recurrence (one in the GBG 1 group and two in the GBG 2 group), with a mean disease-free survival time of 130.3 months in the entire cohort. **Figure 1** presents the Kaplan-Meier disease-free survival analysis for the significant variables identified in **Tables 2 and 3**.

Tables 4 and 5 present the results of the univariate and multivariate Cox regression analyses of factors associated with overall survival. In the multivariate model, FIGO stage III remained a significant predictor of mortality, with a 15.2-fold higher risk of death compared with earlier stages.

Table 1. Demographic, clinical, and pathological characteristics of women according to the growth-based grading (GBG) classification of tumors

	Growth-Based Grading		
	GBG 1	**GBG 2**	**P**
Age n (%), years			
< 50	10 (37)	4 (40)	1
≥ 50	17 (63)	6 (60)	
BMI n (%), kg/m²			
< 30	19 (70)	5 (50)	0
≥ 30	8 (30)	5 (50)	
Race* n (%)			
White	14 (70)	6 (86)	0.633
Non-white	6 (30)	1 (14)	
Menopausal status n (%)			
Premenopausal	11 (40)	2 (20)	0.44
Postmenopausal	16 (60)	8 (80)	
CA125 median, U/mL	60.26	253.95	**0.014**
CEA median, ng/mL	3.35	3.38	0.62
FIGO Stage n (%)			
I and II	26 (96)	5 (50)	**0.003**
III	1 (4)	5 (50)	
Tumor size median, cm†	25	21.5	0.421
Laterality n (%)			
Bilateral	0 (0)	3 (30)	**0.015**
Unilateral	27 (100)	7 (70)	
Lymphadenectomy‡ n (%)			
No	12 (44)	6 (60)	0.476
Yes	15 (56)	4 (40)	
Cyst rupture n (%)			
No	18 (67)	4 (40)	0.258
Yes	9 (33)	6 (60)	
FIGO Grade n (%)			
Well differentiated	18 (67)	3 (30)	0.067
Moderately differentiated	9 (33)	7 (70)	
Chemotherapy n (%)			
No	20 (74)	4 (40)	0.118
Yes	7 (26)	6 (60)	
Recurrence n (%)			
No	26 (96)	8 (80)	0.172
Yes	1 (4)	2 (20)	
Death n (%)			
No	23 (85)	6 (60)	0.174
Yes	4 (15)	4 (40)	
Final Status n (%)			
Death	4 (15)	4 (40)	0.171
Alive	1 (4)	1 (10)	
Alive without disease	22 (81)	5 (50)	

BMI, body mass index; * Data unavailable for 10 women; † n = 36, as one case was diagnosed via percutaneous biopsy; ‡ Pelvic and para-aortic lymphadenectomy; FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Results of univariate Cox regression analysis for disease-free survival (n = 37)

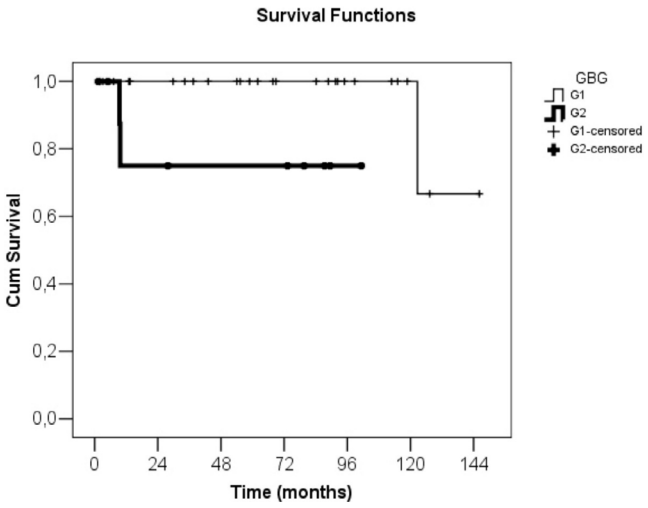
Variable	Categories	P Value	H.R.*	95% CI
Age	Continuous variable (years)	0.979	0.999	0.936–1.066
BMI	Continuous variable	0.606	1.043	0.888–1.225
FIGO Grade	Well-differentiated (ref.)	–	1	–
	Moderately differentiated	0.631	1.82	0.16–20.84
GBG	G1 (ref.)	–	1	–
	G2	0.011	5.4	1.01–53.23
Complete Staging	No (ref.)	–	1	–
	Yes	0.839	0.75	0.05–11.99
Cyst Rupture	No (ref.)	–	1	–
	Yes	0.612	0.52	0.04–6.34
FIGO Stage	I–II (ref.)	–	1	–
	III	0.141	8.08	0.5–130.16

* HR (Hazard Ratio), risk ratio for recurrence (n = 34 censored, n = 3 recurrences); CI, confidence interval; BMI, body mass index. Ref., reference category; FIGO, International Federation of Gynecology and Obstetrics.

Table 3. Results of multivariate Cox regression analysis for disease-free survival (n = 37)

Variable	Categories	P Value	H.R.*	95% CI
GBG	G1 (ref.)	–	1	–
	G2	0.011	5.4	1.01–53.23

* HR (Hazard Ratio), risk ratio for recurrence (n = 34 censored, n = 3 recurrences); CI, confidence interval; Ref, reference category.

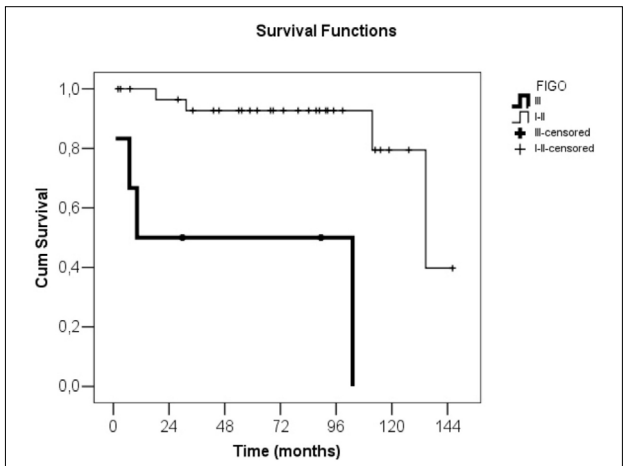


Disease-Free Survival by GBG
Log-Rank Test: $\chi^2 = 6.41$; DF = 1; P = 0.011

Figure 1. Disease-Free Survival analysis for significant variables (in months).

Eight patients died during the study period (four with GBG 1 and four with GBG 2), and the mean overall survival for the entire cohort was 114.9 months. **Figure 2** presents the Kaplan–Meier overall survival curves for the variables identified as significant in **Tables 4 and 5**.

Representative cases from this study are shown in **Figures 3 and 4**, illustrating ovarian mucinous carcinomas classified as GBG 1 (**Figure 3**) and with an infiltrative invasion pattern (**Figure 4**).



Overall survival by FIGO stage
Log-Rank Test: $X^2 = 16.90$; df = 1; P < 0.001

Figure 2. Overall survival analysis for significant variables (in months).

DISCUSSION

Our study demonstrated that the GBG classification was correlated with disease-free survival, with GBG 2 tumors associated with a 5.4-fold higher risk of recurrence compared to GBG 1 tumors. This finding is consistent with the results reported by Momeni-Boroujeni et al.,[13] who also observed a higher recurrence likelihood in GBG 2 tumors than in GBG 1 tumors. Notably, in contrast to GBG grading, the FIGO histological grading was not associated with recurrence risk in either study.

The prognostic role of FIGO histological grading remains controversial. A study involving women with tumors presumably confined to the ovary found that lymph node metastasis, although rare (1.4%), occurred more frequently in women with poorly differentiated tumors (histological grade 3).[15] Because ovarian mucinous carcinoma is rare and typically diagnosed at an early stage, divergent results across studies are expected. The FIGO grading

Table 4. Results of the univariate Cox regression analysis for overall survival (n = 37)

Variable	Categories	P value	H.R.*	95% CI
Age	Continuous Variable (years)	0.067	1.049	0.997–1.103
BMI	Continuous Variable (years)	0.608	1.028	0.925–1.143
FIGO grade	Well differentiated (ref.)	–	1	–
	Moderately differentiated	0.628	0.7	0.17–2.94
GBG	G1 (ref.)	–	1	–
	G2	0.025	7.19	1.29–40.13
Complete staging	No (ref.)	–	1	–
	Yes	0.146	0.3	0.06–1.53
Cyst rupture	No (ref.)	–	1	–
	Yes	0.811	1.19	0.29–4.85
FIGO stage	I–II (ref.)	–	1	–
	III	0.002	15.22	2.74–84.67

* HR (Hazard Ratio), risk ratio for death (n = 29 censored and n = 8 deaths); CI, confidence interval; BMI, body mass index; Ref., reference category; FIGO, International Federation of Gynecology and Obstetrics.

Table 5. Results of the multivariate Cox regression analysis for overall survival (n = 37)

Variable	Categories	P value	HR*	95% CI
FIGO stage	I–II (ref.)	–	1	–
	III	0.002	15.22	2.74–84.67

* HR (Hazard Ratio), risk ratio for death (n = 29 censored and n = 8 deaths); CI, confidence interval; Ref., reference category, FIGO, International Federation of Gynecology and Obstetrics.

system is based on the proportion of solid growth and the presence of nuclear atypia, providing a morphological assessment of tumor differentiation.[9] However, these features may not fully represent tumor biology. In contrast, GBG considers infiltrative invasion, a feature associated with greater aggressiveness, higher recurrence risk, and poorer prognosis. Therefore, GBG may offer a more accurate prognostic assessment by identifying invasive features that are not captured by morphology-based grading alone.[11,13]

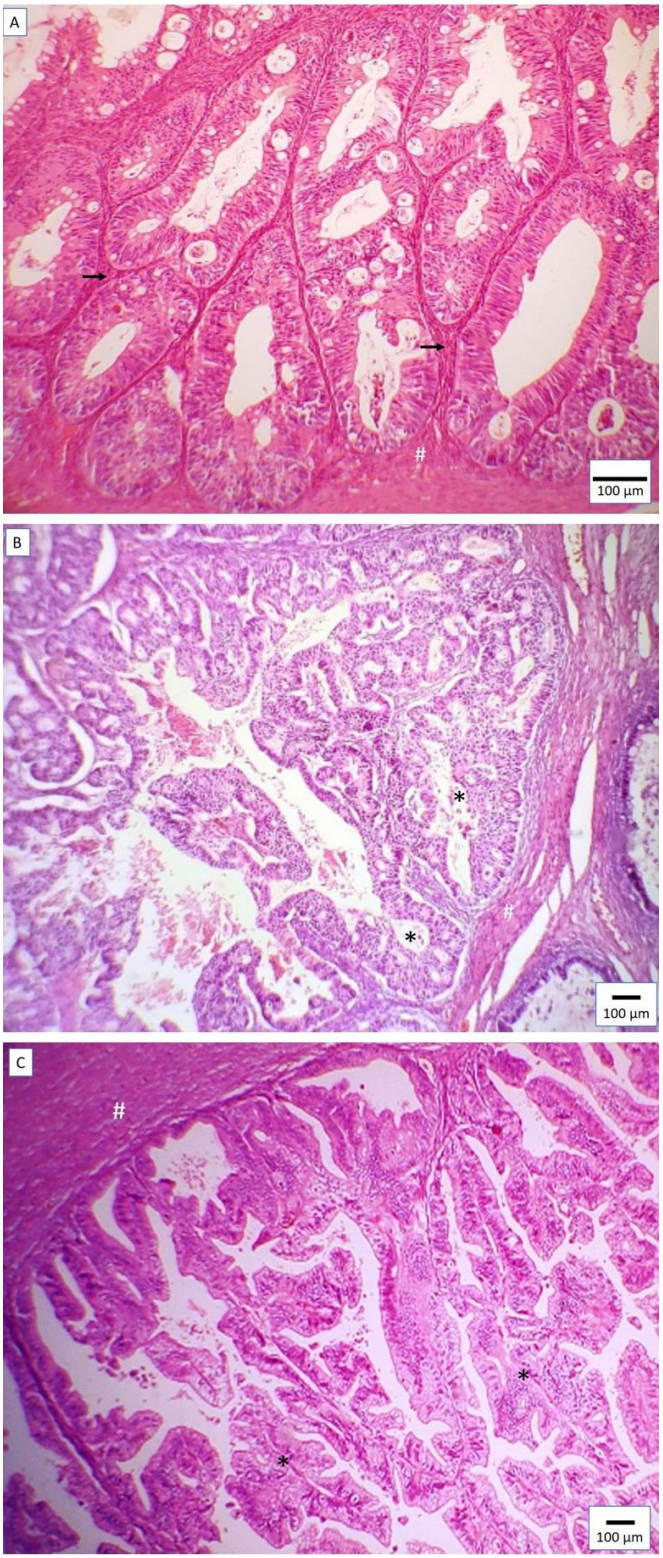
The National Comprehensive Cancer Network® (NCCN) recommends that, in cases of ovarian mucinous carcinoma diagnosed during intraoperative frozen-section analysis, lymphadenectomy may be omitted if no suspicious lymph nodes are present.[3] Additionally, the NCCN guidelines suggest that chemotherapy may or may not be prescribed in cases of tumor rupture in stage I expansile-type mucinous tumors.[3] Supporting these recommendations, large-cohort studies have shown that systematic lymphadenectomy may be omitted in tumors that appear to be at stage I.[16,17] However, these studies did not differentiate between expansile and infiltrative subtypes. In our study, complete staging with pelvic and para-aortic lymphadenectomy and tumor rupture were not associated with disease-free or overall survival.

Women with infiltrative subtype tumors are more often diagnosed at an advanced stage, have a higher incidence of lymph node metastasis, undergo more frequent restaging after initial surgical staging, and experience poorer oncologic outcomes than women with expansile subtype tumors.[4] A recent study involving 409 women with stage I ovarian mucinous carcinoma found that complete staging with lymphadenectomy was associated with improved overall survival in the infiltrative subtype, but not in the expansile subtype.[18] In addition, Algera et al.[8] suggest that omitting peritoneal staging (peritoneal washing, peritoneal biopsies, and omentectomy) is likely safe for expansile tumors at stage I. The finding that GBG 2 tumors are associated with a higher recurrence risk provides a valuable threshold for defining the infiltrative component, enabling the classification of tumors into two groups with distinct prognostic implications. This distinction may support more tailored management strategies.

One important limitation of our study is the small number of recurrence and death events (three and eight, respectively), which restricts the statistical power of our analyses and could lead to overfitting of the Cox regression model. Therefore, survival outcomes should be interpreted with caution. Overall, our findings support incorporating invasion-based criteria, such as those used in the GBG system, into the pathological assessment of ovarian mucinous carcinoma. This new classification could guide surgical management, with systematic lymphadenectomy indicated for GBG 2 tumors and potentially omitted in GBG 1 cases. Adjuvant chemotherapy is currently recommended for patients with infiltrative-type mucinous ovarian carcinomas from stage Ib onwards.[3] Incorporating the GBG classification may further refine this recommendation, with adjuvant chemotherapy potentially considered for GBG 2 tumors at these stages. Although further validation is needed, this approach could contribute to more tailored treatment decisions and also guide the development of post-treatment surveillance protocols, with closer follow-up recommended for patients with a poorer prognosis (GBG 2).

CONCLUSION

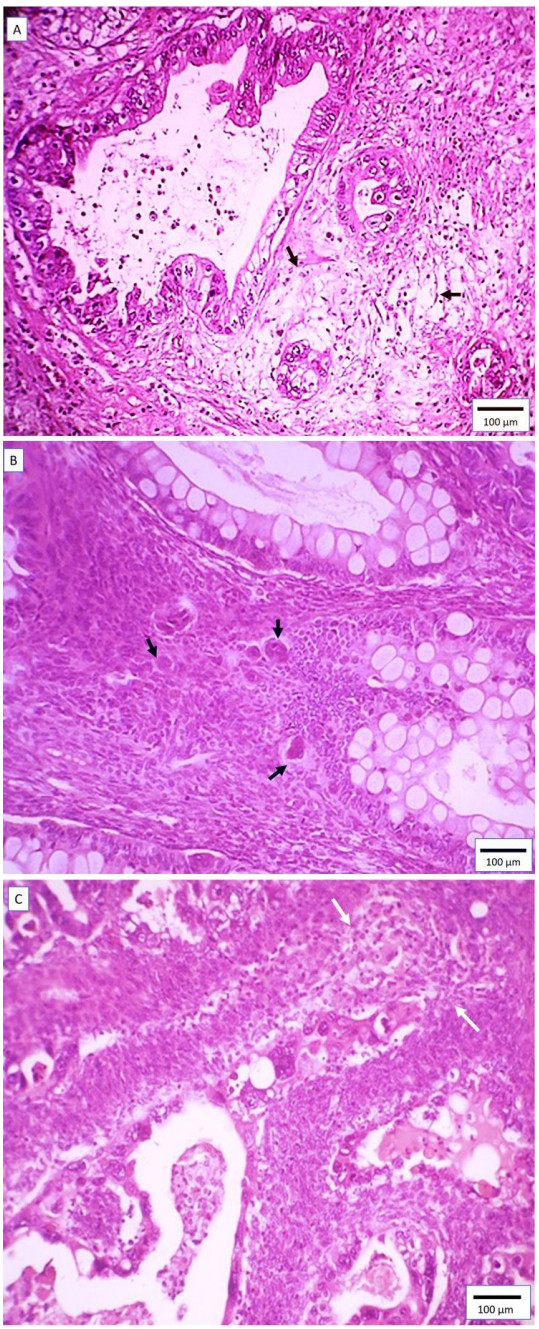
While the present findings align with previously published data, they should be interpreted with caution, given the limited sample



Well-differentiated ovarian mucinous adenocarcinoma (FIGO grade 1) with crowded glands showing very little stroma (arrows) in A and no stroma between them (*) in B and C, with well-defined contours (#) in C. H&E, 40×, 20×, and 20× magnification.

Figure 3. A, B, and C depict an expansile invasion pattern (GBG G1).

size and retrospective nature of the study. Additional validation using larger, independent cohorts is essential before any firm conclusions can be drawn. Nonetheless, the observed trends suggest that the GBG grading system may have potential value in refining risk assessments for mucinous ovarian carcinomas.



Ovarian mucinous adenocarcinoma (FIGO grade 1) with stromal invasion by small glandular clusters (A, arrows), isolated neoplastic cells (B, arrows), and atypical cell blocks with an inflammatory reaction (C, white arrow). H&E, 40×

Figure 4. A, B, and C illustrate an infiltrative invasion pattern (GBG G1 or G2).

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Postoperative delirium in patients with cancer: a narrative review of major risk factors

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Cancer.
Aged.

AUTHOR'S KEYWORDS:
Malignant neoplasm.
Risk factors
Older adults.

ABSTRACT

BACKGROUND: Postoperative delirium (POD) is a severe complication and the most frequent adverse event in older patients, particularly those with cancer. With the increase in the older surgical population and cancer diagnoses, the incidence of POD is expected to increase.

OBJECTIVES: To identify and evaluate major risk factors for POD in patients with cancer.

DESIGN AND SETTING: Narrative review conducted at the A.C.Camargo Cancer Center in São Paulo, Brazil.

METHODS: PubMed, LILACS, and Embase database searches were conducted using relevant keywords from June 2023, to September 2024. We identified 279 studies; after screening and applying the eligibility criteria, 49 studies were included in the analysis.

RESULTS AND DISCUSSION: POD risk factors in patients with cancer are associated with inflammation and the cumulative burden of intensive therapeutic modalities. These factors can be categorized into three domains: directly related to cancer, indirectly related to cancer, and preexisting predisposing factors. Among these factors, age is important. Additional relevant contributors include frailty, cognitive impairment, sarcopenia, pain, anxiety, and depression. A complex interaction exists between these factors that renders POD management in patients with cancer challenging; however, the impact of each factor remains unclear.

CONCLUSION: Multiple overlapping risk factors often contribute to POD development in patients with cancer. Age is a significant risk factor, as reported in the literature. Other relevant factors have been described; however, the relative contribution of each factor to the etiology of POD remains unclear. Further research is required to address this knowledge gap.

INTRODUCTION

Postoperative delirium (POD) is a serious complication and the most frequent adverse event in older patients.[1,2] POD is associated with a prolonged hospital stay, functional and cognitive impairment, increased risk of dementia, mortality, and high medical expenses.[3,4] Furthermore, delirium is often a distressing and traumatic experience for patients and their families as well as healthcare staff.[1,5–7]

POD is defined as a state of acute confusion characterized by fluctuating levels of attention and awareness, disorientation, disturbances in perception and memory, and disorganized thinking. Several risk factors have been identified, among which age is widely recognized as highly prominent.[5,8–11]

Recent population aging, combined with greater access to advanced medical treatments, has led to an increase in the older surgical population.[7] Additionally, the number of cancer diagnoses has been increasing. Globocan 2022 data revealed nearly 20 million new cancer cases, with projections estimating that annual cases will rise to 35 million by 2050, marking a 77% increase.[12] Most patients with cancer require one or more surgeries as part of their oncological treatment. Therefore, we expect a higher number of patients with cancer and older patients with cancer in surgical centers and, consequently, a greater prevalence of POD.

POD has gained increasing attention in recent years and is recognized as a pertinent topic in medical research. Although the importance of POD is acknowledged, comprehensive reviews consolidating the major risk factors in patients with cancer are lacking, leading to gaps in understanding. This narrative review aimed to identify and analyze the major risk factors for POD in patients with cancer.

METHODS

To conduct this narrative review, we performed a comprehensive search of the PubMed, LILACS, and Embase databases from June 2023 to September 2024 at the A.C.Camargo Cancer Center in São Paulo, Brazil. We used the following index terms (E.G. MeSH): "postoperative delirium," "delirium," "surgical oncology," "cancer," and "aged," combining them with Boolean operators "AND" and "OR." Although this study did not follow the rigorous methodology of a systematic review, a structured approach was adopted to ensure comprehensiveness and quality in the selection and analysis of studies.

The eligibility criteria were as follows:

Inclusion criteria:

- Studies published between 2014 and 2024
- Studies involving adults (aged > 18 years)
- Studies published in English, Spanish, and Portuguese
- Systematic literature reviews, randomized clinical trials, prospective and retrospective cohort studies (with or without a control group), case reports, case series, observational research, consensus documents, and guidelines
- Full-text publications only

Exclusion criteria:

- Stand-alone abstracts and letters
- Opinion pieces without original data
- Unpublished studies
- Studies involving the pediatric population
- Duplicated records

The reference lists of the selected articles were screened for additional relevant publications. Study selection was conducted in a sequential process that involved the removal of duplicate records, screening of titles and abstracts, evaluation of full-text articles, and determination of final inclusion. Ethical approval was not required for this study narrative review.

RESULTS

The initial database search yielded 279 articles. After the removal of duplicates, screening of titles and abstracts, and examination of citations, 84 studies were selected for a full-text assessment. Based on the predefined eligibility criteria, 49 studies were included in the qualitative analysis. The selection process is detailed in the flowchart shown in **Figure 1**.

The selected articles, along with their locations of origin, year conducted, and type, are listed in **Table 1**. Of these, 10 were systematic reviews with meta-analyses, three were meta-analyses, one was a systematic review, one was a randomized controlled trial, 13 were prospective cohort studies, 11 were retrospective cohort studies, two were consensus reports, three were guidelines, two were cross-sectional studies, two were case reports, and one was a book chapter.

The final selection comprised a diverse set of study designs that reflected high-level evidence and complementary sources. This diversity provided a more comprehensive view of the research question while maintaining the methodological rigor.

DISCUSSION

Definition and prevalence

POD, as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition, is a neurocognitive syndrome characterized by disturbed attention and reduced orientation to the environment; POD develops over a short period of time, typically within the first 3 days after surgery.[5,13] This acute change from baseline awareness and attention often fluctuates throughout the day, and the additional cognitive disturbance is not attributable to preexisting dementia.[5,6,14]

POD affected 5%–50% of patients, with a wide range of prevalence rates reported in the literature owing to differences in patient characteristics, surgical aggressiveness, and diagnostic methods used.[5,6,15] A substantial body of research exists in the fields of cardiac and orthopedic surgery, owing to the high complexity of these surgical procedures and the clinical conditions of the patient. In the context of cardiac surgery, delirium is recognized as the most

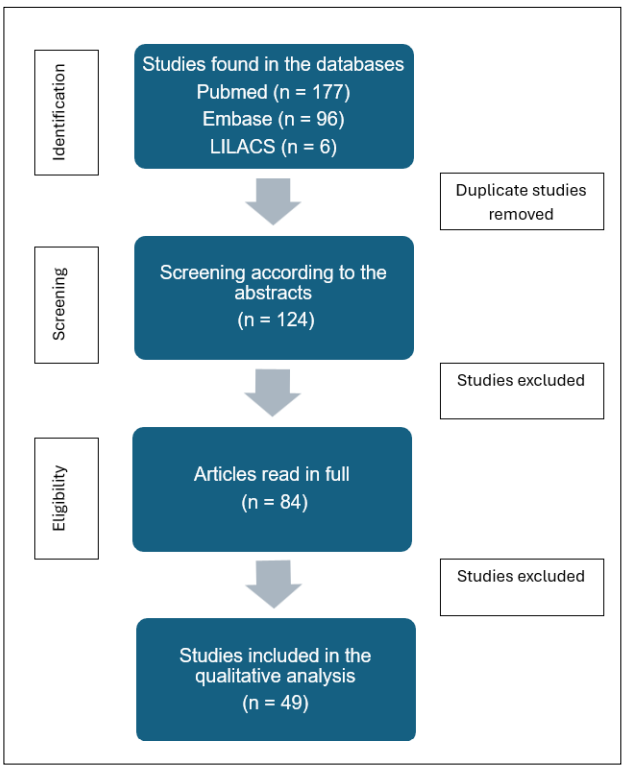


Figure 1. Flowchart of the study selection process.

Table 1. Selected studies summarized by location, year, and study design

Study	Location	Year	Study design
Marcantonio[5]	USA	2017	Case report
Inouye et al.[6]	USA	2015	Case report
Aldecoa et al.[7]	International	2023	Guideline
Inouye et al.[14]	USA	2016	Prospective cohort study
Gong et al.[15]	China	2023	Systematic review and meta-analysis
Patel et al.[16]	UK	2022	Systematic review and meta-analysis
Yang et al.[17]	China	2020	Systematic review and meta-analysis
Griffin et al.[18]	UK	2020	Retrospective cohort study
Papaconstantinou et al.[19]	Greece	2023	Systematic review and meta-analysis
Hartog et al.[20]	Netherlands	2024	Prospective cohort study
Chen et al.[21]	China	2022	Retrospective cohort study
Dong et al.[22]	China	2023	Meta-analysis
Tan et al.[23]	USA	2016	Retrospective cohort study
Honda et al.[24]	Japan	2018	Retrospective study
Janssen et al.[25]	Netherlands	2019	Prospective cohort study
Wang et al.[26]	China	2019	Prospective cohort study
Wang et al.[27]	China	2024	Retrospective cohort study
Varpaei et al.[28]	USA	2024	Systematic review and meta-analysis
Sun et al.[29]	China	2023	Prospective cohort study
Mahanna-Gabrielli et al.[30]	USA	2019	Consensus report
Bush et al.[31]	International	2018	Guideline
Sadeghirad et al.[32]	Canada	2023	Meta-analysis
Lu et al.[33]	China	2023	Retrospective cohort study
Hayashi et al.[34]	Japan	2019	Retrospective cohort study
Heo et al.[35]	South Korea	2020	Prospective cohort study
Shaw et al.[36]	Canada	2022	Systematic review and meta-analysis
Tsai et al.[37]	Taiwan	2022	Prospective cohort study
Fu et al.[38]	China	2021	Meta-analysis
Handforth et al.[39]	UK	2015	Systematic review
Zhou et al.[40]	China	2024	Systematic review and meta-analysis
Tian et al.[41]	China	2023	Retrospective cohort study
Evered et al.[42]	International	2018	Consensus report
Crouch et al.[43]	USA	2023	Prospective cohort study
Harrison et al.[44]	Canada	2021	Book chapter
Regier et al.[45]	USA	2019	Prospective cohort study
Ahles et al.[46]	USA	2022	Cross-sectional study
Mandelblatt et al.[47]	USA	2018	Longitudinal cohort study
Vardy et al.[48]	Australia	2015	Prospective cohort study
Graus et al.[49]	International	2021	Consensus report
Oliveira et al.[50]	Portugal	2020	Retrospective cohort study
Mohile et al.[51]	USA	2018	Guideline
Mosk et al.[52]	Netherlands	2018	Retrospective cohort study
Makiguchi et al.[53]	Japan	2020	Retrospective study
Chen et al.[54]	USA	2024	Systematic review and meta-analysis
Falk et al.[55]	Sweden	2021	Systematic review and meta-analysis
Wada et al.[56]	Japan	2019	Prospective cohort study
Holzer et al.[57]	USA	2024	Randomized controlled trial
Kosar et al.[58]	USA	2014	Prospective cohort study
Snijders et al.[59]	Netherlands	2023	Systematic review and meta-analysis

prevalent neurocognitive complication with reported incidence rates ranging from 6%–46%.[16] Similarly, in orthopedic surgery, the incidence of delirium has been reported to range from 4.5%–41.2%.[17]

Among the surgical procedures for cancer treatment, data are typically analyzed for organ-based procedures. Esophagectomy, a complex and morbid procedure, is associated with postoperative

complication rates ranging from 20%–68%.[18,19] Papaconstantinou et al. demonstrated in a systematic review that the incidence of POD following esophagectomy ranges from 9.2%–50% and is associated with prolonged hospitalization and increased mortality rates.[19] Other complex procedures, such as head and neck surgeries and major abdominal cancer surgeries, have been studied in recent years.[20–27] Together, these studies have consistently shown a high incidence of POD and have highlighted its importance in patients with cancer.

Pathophysiology

POD has a complex etiology and can be considered as functional cerebral decompensation resulting from multiple noxious insults that exceed the capacity of the brain for homeostasis. Decompensation is influenced by several biological factors. Although the etiology of POD cannot be reduced to a single mechanism, neuroinflammation and alterations in neurotransmitter systems are known contributing factors.[5–7]

Neurotransmitter mechanisms involve either cholinergic deficiency or excess dopamine. This imbalance can arise from various factors, including drugs, electrolyte disturbances, metabolic derangements, hypoxia, hypercortisolism and impaired glucose oxidation. Neuroinflammation occurs simultaneously and is secondary to hypothalamic-pituitary-adrenal mediators (corticotropin-releasing hormone, adrenocorticotropic hormone, cortisol, and vasopressin) and inflammatory cytokines that cause inflammation and neuronal injury.[28,29] These mechanisms can affect any patient; however, those with preexisting neurodegeneration, particularly older patients, and those with cognitive impairment and multimorbidity, including patients with cancer, are more severely affected. Vulnerable patients have reduced capacity to cope with adverse conditions.[5,6,30,31]

Risk factors play crucial roles in POD development and are divided into two categories: predisposing factors, which are inherent to the patient, related to their baseline conditions, and increase vulnerability; and precipitating factors, which initiate the onset of delirium and may be reversible. The development of delirium is characterized by a complex interaction between these factors.[5–7,30] In 2014, Inouye et al. elucidated this dynamic through a widely recognized model, demonstrating that these factors can overlap and act concurrently to influence POD.[6]

Risk factors

Several risk factors for POD have been identified in the literature over the past 20 years. Many studies have originated from cardiac surgery groups, and their findings are applicable to this particular population. Recent data have been published on non-cardiac surgeries and specific surgical resections for primary cancers, such as esophageal, gastric, lung, and head and neck cancers.[21,22,24–26,32–35] Based on these findings, we compiled a summary of the most frequently cited risk factors that are directly and/or indirectly associated with POD development in patients with cancer (**Table 2**). Therefore, in this population, beyond the traditional division into predisposing and precipitating factors, risk factors can be categorized into other domains: directly related to cancer, indirectly related to cancer, and preexisting predisposing factors.[31]

These factors are discussed in the following sections, nevertheless, it is worth emphasizing that **Table 2** illustrates that patients with cancer constitute a distinct surgical population with several characteristics that may increase the likelihood of developing POD. In addition to the risk factors that can prevail before cancer

Table 2. Risk factors: directly related to cancer, indirectly related to cancer, and preexisting predisposing factors

Domain	Risk factor
Directly related to cancer	Primary CNS tumors
	Secondary CNS tumors (brain metastases/ meningeal metastases)
	Brain surgery
	Brain radiation therapy
	Chemotherapy-induced neurotoxicity
	Immunotherapy/Hormonal therapy
	Paraneoplastic neurological syndromes
	Diagnostic procedures
	Extensive resections
	Reconstructive surgeries
	Emergency surgeries
	Palliative surgeries
Indirectly related to cancer	Age
	Frailty
	Sarcopenia/Malnutrition
	Depression/Anxiety
	Pain
	Anemia
	Dehydration and electrolyte abnormalities
	Polypharmacy (including opioids and sedatives)
	Multimorbidity
	Longer hospital stay
	Sleep disturbance
	Use of restraints/Immobility
	Catheterization
	ICU admission
	Alcohol or drug abuse
	Infections
	Metabolic encephalopathy due to hepatic, renal, or pulmonary failure
Pre-exiting predisposing factors	Low educational level
	Male sex
	Visual/Hearing impairment
	History of delirium
	Preexisting cognitive impairment or dementia

CNS, Central Nervous System; ICU, Intensive Care Unit.

diagnosis, these patients are exposed to the cumulative effects of cancer and inflammation, as well as the numerous complications and consequences of rigorous treatment modalities, including chemotherapy, radiotherapy, immunotherapy, and multiple surgeries, ranging from aggressive tumor resections to reconstructive, palliative, and emergency procedures. Beyond this context directly related to cancer, cancer predominantly affects the older population, and advanced age, a well-established and consistent risk factor, further contributes to the high incidence of POD in this population.[26,29–31]

Aging is considered responsible for multiple brain transformations, and various theories suggest a gradual accumulation of damage to neurons, dendrites, receptors, and microglia; alterations in brain functional properties and neurotransmission; reduction in blood–brain barrier function; and anatomical disconnection between brain regions. All of these processes associated with cerebrovascular disease, along with the presence of comorbidities common with aging, may explain the vulnerability of the brain and its decreased ability to respond to stressors.[6] Thus, advanced aging is accompanied by cognitive decline, even in the absence of neurodegenerative disease.

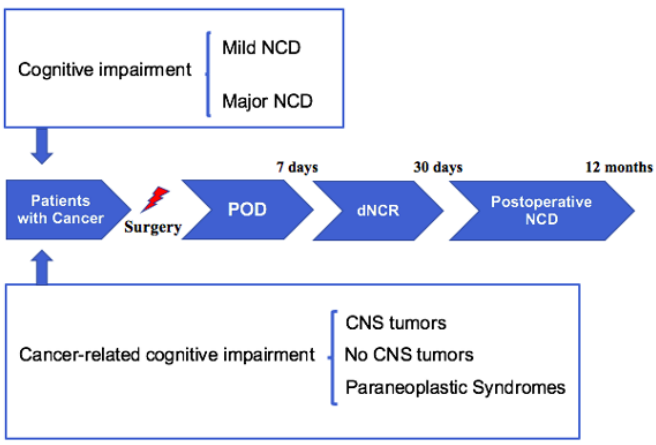
Both aging and cancer are associated with an increased prevalence of frailty. Frailty, characterized by multisystem decline, is a clinical state related to decreased reserves that results in vulnerability to stressors. Frailty develops progressively because of the accumulation of measurable clinical parameters, including comorbidities, functional impairments, and aging itself. Frailty increases the risk of adverse events such as falls, bedsores, recurrent hospital admissions, loss of autonomy, and premature death. Moreover, frailty is associated with poor postoperative outcome. Frailty is a better predictor of perioperative morbidity and mortality than is age, and is an independent risk factor for POD development.[34–36]

Cancer and frailty are interrelated. They have a multifaceted pathophysiology, sharing common factors including metabolic and immune system dysfunction, functional and cognitive decline, multiple medication requirements, weight reduction, depression, certain comorbidities, and advanced age as a significant risk factor. More than half of older patients with cancer have prefrailty or frailty.[37] These conditions, influenced by similar factors, increase the risk of POD development after subject to stressors such as cancer surgery and chemotherapy.[36,38,39] A meta-analysis conducted on patients undergoing colorectal cancer surgeries reported nearly a 2-fold higher risk of encountering any complications, and a 3-fold higher risk of major complications, including POD.[40] Furthermore, a retrospective cohort study conducted on patients with lung cancer revealed a significantly higher prevalence of POD in frail versus robust patients, with the risk being nearly 3-fold higher in the frail group.[41] Consistent with these findings, Tsai et al. reported that frailty was an independent risk factor for POD in older patients with cancer undergoing elective abdominal surgery, with a 2.8-fold increase in the risk of POD occurrence.[37]

Another key issue is precognitive impairment, a well-documented risk factor for POD in patients with cancer. Precognitive impairment is categorized into mild and major neurocognitive disorders (NCD), which are perioperative disorders. The expert panel of the Nomenclature Consensus Working Group in 2018 defined and delineated the perioperative period to establish standardized terminology for all cognitive disorders within this period.[42] In the preoperative period, NCD are categorized into mild and major disorders. Patients with mild NCD experience cognitive decline with minimal functional impairment, whereas those with major NCD experience significant cognitive impairment that significantly affects their daily activities. Both patients were underdiagnosed in the preoperative period. In the postoperative period, delineation includes POD occurring within hours to one week post-procedure or until discharge, whichever occurs first, and long-lasting cognitive decline diagnosed up to 30 days (delayed neurocognitive recovery) and up to 12 months after the procedure (postoperative NCD) (**Figure 2**).

Beyond this established terminology, precognitive impairment in patients with cancer can be divided into those with and without central nervous system (CNS) tumors, collectively referred to as cancer-related cognitive impairment (**Figure 2**). Previously known as "chemobrain," cancer-related cognitive impairment encompasses subjective and objective changes in cognitive function that can occur before, during, and after cancer treatment.[43]

In patients without CNS tumors, precognitive impairment appears multifactorial, and the underlying mechanisms remain unclear. The major hypotheses are related to the neuroimmune



NCD, Neurocognitive Disorder; POD, postoperative delirium; dNCR, Delayed Neurocognitive Recovery; CNS, Central Nervous System

Figure 2. Cognitive impairment in patients with cancer and the terminology of neurocognitive disorders.

and neuroinflammatory changes caused by tumors and cancer treatment, primarily chemotherapy. In patients with CNS tumors, which could be either primary brain tumors or secondary metastases, precognitive impairment is directly related to brain tumors and their treatment, including radiation and/or brain surgery.[43,44]

Cancer-related cognitive impairment affects up to 75% of patients with cancer and can persist long after treatment completion.[43] The main symptoms reported include visual and memory impairment, learning and attention deficits, executive functioning decline, and difficulty in processing new information and multitasking. These symptoms can negatively impact quality of life, level of independence, decision-making abilities, treatment compliance, and consequently work resumption and daily activities.[44,45]

Most studies on cancer-related cognitive impairment have primarily focused on patients with breast cancer. Ahles et al.[46] demonstrated that breast cancer survivors exhibited lower cognitive performance and higher levels of frailty than did controls. Similarly, in a multisite prospective "thinking and living with cancer study" Mandelblatt et al.[47] demonstrated that older cancer survivors experienced decreased cognitive function scores. These findings have been confirmed in patients with colorectal cancer. Vardy et al.[48] reported that the rates of cognitive impairment in patients with localized colorectal cancer ranged from 36%–52% between baseline and 24 months, compared to 6%–19% in healthy patients without cancer.

Considering the role of paraneoplastic neurological syndromes in patients with cancer is crucial, as they may contribute to cancer-related cognitive impairment. Paraneoplastic neurological syndromes are a group of disorders that are not directly caused by brain tumors or the side effects of cancer treatment. These are immune-mediated disorders of the peripheral or central nervous system that are frequently associated with autoantibodies against neural antigens expressed by tumors, resulting in severe neurological deficits. Paraneoplastic neurological syndrome has varying clinical presentations associated with a characteristic spectrum of antibodies and often manifests as severe and well-defined neurological symptoms, the most common of which are subacute cerebellar degeneration, sensory neuropathy, and limbic encephalitis. Although the prevalence of this condition is reported to be rare in some studies, with percentages ranging from less than 0.01%–1% in patients with cancer, it is becoming increasingly common owing to advances in medical treatment and significantly improved survival rates.[49,50]

These findings emphasize the importance of evaluating cognitive function and the potential risks of developing cancer-related cognitive impairment and POD before initiating therapy, as recommended by the American Society of Clinical Oncology guidelines.[51]

Cancer, age, frailty, and cognitive performance are dynamically interrelated; they share many biological pathways that are usually present concomitantly and act synergistically, making perioperative patient management challenging.

Other significant risk factors for POD have been identified in the literature, including sarcopenia, depression, anxiety, and pain.

Sarcopenia, characterized by a decrease in skeletal muscle mass, muscle power, or physical activity, is prevalent in patients with cancer and is considered a significant risk factor for POD in patients with colorectal cancer undergoing surgery. The association between sarcopenia and POD is strong in patients with malnourishment and physical dependency.[52] The interplay between several factors, such as frailty, malnourishment, inadequate food intake, advanced age, and changes caused by disease, surgery, and treatment, leads to a vicious cycle of muscle loss and weakness. Additionally, sarcopenia was a significant independent risk factor for hypoactive and mixed-type POD in oral cancer surgery.[53] These findings emphasize the relevance of sarcopenia, nutrition, and rehabilitation and highlight the need for further studies involving various oncological surgery types and patients.

Depressive and anxiety symptoms are more prevalent in patients with cancer than in the general population, with one in four patients with cancer experiencing depression.[54] In addition to affecting quality of life and treatment adherence, depression and anxiety symptoms are associated with POD and poor surgical outcomes.[55,56] Although the exact underlying mechanisms remain unclear, inflammatory cytokines may be involved. A systematic review and meta-analysis conducted in 2020 revealed the impact of depression on POD following cardiac surgery. Moreover, a prospective observational cohort study demonstrated that anxiety in patients with cancer was a predictive factor for POD.[55,57] Recognizing the implication of the relationship between mental health and cancer is crucial because improving perioperative mental health may have a substantial impact on surgical outcomes in such patients.

Preoperative pain is independently associated with the development of POD.[58] Pain is a common experience among patients with cancer, and most older adults require pain management at some point during their care.[59] Furthermore, pain is strongly associated with depressive symptoms. Similar to previous findings, a study on general elective surgeries indicated that patients with depressive symptoms are more likely to report severe pain and develop delirium.[58] Patients with cancer experience a significant increase in pain and depressive symptoms, making this a serious clinical issue.

In addition to the risk factors described, several others have been listed in the literature, including anemia; dehydration; electrolyte abnormalities; polypharmacy (including opioids and sedatives); multimorbidity; longer hospital stay; ICU admission; sleep disturbance; use of restrains or immobility; catheterization; alcohol and drug abuse; infections; metabolic encephalopathy due to hepatic, renal, or pulmonary failure; low educational level; male sex; visual or hearing impairment; and history of delirium.[5–7,30,32]

Therefore, perioperative management of patients with cancer is challenging because of the complex interactions between multiple factors that are often present and act synergistically. Delirium treatment is complex. Non-pharmacological interventions, including reorientation, early nutrition and mobilization, and the use of personal sensory aids such as glasses and hearing aids, are the primary approaches for managing delirium. Additionally, early catheter removal and identification of potential triggers, such as pain, hypoxia, infection, or bladder distention, with the assistance of a multidisciplinary team, are crucial. Given the poor response observed, pharmacological treatment is typically reserved for agitated patients. It is estimated that 30%–40% of delirium cases are preventable, highlighting the importance of proactive prevention measures.[7,15,28] Moreover, patients often require adjuvant treatment after surgery, which should not be delayed. Therefore, it is essential for patients to resume their activities and treatment as early as possible.

CONCLUSION

POD is a severe complication that is particularly prevalent among patients with cancer and can result in significant morbidity. In light of the prevalence of POD along with morbimortality, high costs, and difficulties involved in the treatment of this complication, preventing up to 30%–40% of its incidence should be a crucial consideration. Furthermore, most patients with cancer require adjuvant treatment following surgery; therefore, it is imperative that these patients return to their normal activities and treatment with minimal delay. Consequently, prioritizing actions to enhance modifiable factors, improve preoperative conditions, and cultivate high cognitive reserve and physical status can ultimately increase resilience against potential stressors, thereby reducing the incidence of POD.

Although the literature on POD is expanding, a major gap remains in understanding the specific impact of individual risk factors on the development of POD. Patients with cancer frequently present with multiple concurrent risk factors, such as advanced age, frailty, and preexisting cognitive impairment. However, the relative contribution of each factor to the etiology of POD remains unclear, and its delineation is complex and requires further clarification. Therefore, additional research is required to address this knowledge gap.

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review and editing (equal); Quezada MMC: writing – review and editing (equal); Mitsunaga JK Junior: conceptualization (equal); Portugal AMMC: methodology (equal), writing – original draft (equal); Joaquim EHG: critical review; Nakamura G: conceptualization, critical review, supervision. All authors have reviewed and approved the final version of the manuscript submitted for publication.

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

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.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

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.

Editorial policy

Papers with a commercial objective will not be accepted: please review the Journal's conflicts of interest policy below.

São Paulo Medical Journal accepts manuscripts previously deposited in a trusted preprint server.

São Paulo Medical Journal supports Open Science practices. It invites reviewers to join Open Peer Review practices through acceptance that their identities can be revealed to the authors of articles. However, this is purely an invitation: reviewers may also continue to provide their input anonymously.

São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

São Paulo Medical Journal applies a publication fee in the form of an article processing charge (APC) for all studies conducted outside of Brazil. This rate will be charged to the corresponding author when the study has been accepted on the grounds of its scientific merit. This fee is US$ 500.00 and is independent of the length of the text. The corresponding author should wait to receive the journal's invoice before making the payment. The article will only be published after presentation of the proof of payment. Submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

Articles accepted for publication become the Journal's property for copyright purposes, in accordance with Creative Commons attribution type BY.

Transparency and integrity: guidelines for writing

The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

All studies published in *São Paulo Medical Journal* must be described in accordance with the specific guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

Conflicts of interest

Authors are required to describe any conflicts of interest that may exist regarding the research or the publication of the article. Failure to disclose any conflicts of interest is a form of misconduct.

Conflicts of interest may be financial or non-financial. The Journal recommends that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest. The existence and declaration of conflicts of interest is not an impediment to publication at all.

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.

This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing or reviewing the study, and whose contributions to the publication do not constitute authorship.

Authorship

The Journal supports the position taken by the ICMJE (http://www.icmje.org) regarding authorship. All authors should read ICMJE's recommendations to obtain clarifications regarding the criteria for authorship and to verify whether all of them have made enough contributions to be considered authors.[10]

All authors of articles published in *São Paulo Medical Journal* need to have contributed actively to the discussion of the study results and should review and approve the final version that is to be released. If one author has not contributed enough or has not approved the final version of the manuscript, he/she must be transferred to the Acknowledgement section.

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

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São Paulo Medical Journal supports Open Science practices. Authors must therefore complete an open science compliance form, which is available from: https://wp.scielo.org/wp-content/uploads/Open-Science-Compliance-Form_en.docx.

Redundant or duplicate publication

São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors regarding format. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

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.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which

is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

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.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

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.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

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.

Sample size

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:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

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.

Interventions

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.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

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.

Short communications

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).

Case reports, case series, narrative reviews and letters to the editor

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.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for

example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
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- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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Você está procurando o local ideal para realizar seu próximo evento especial?

Não procure mais! Aqui na APM, temos espaços incríveis disponíveis para locação que se adequam perfeitamente a todas as suas necessidades.

Seja uma conferência de negócios de sucesso, lançamento de produtos,um jantar inesquecível ou qualquer outro evento que você esteja planejando, **temos o local perfeito esperando por você**.

DESCUBRA O LOCAL PERFEITO PARA SEU **PRÓXIMO EVENTO!**

Por que escolher os espaços da APM?

- **Localizações Exclusivas:** Nossos espaços estão situados em locais privilegiados, garantindo facilidade de acesso para seus convidados.
- **Versatilidade:** Oferecemos uma variedade de espaços que podem ser personalizados para atender às suas necessidades.
- **Serviços de Alta Qualidade:** Nossa equipe experiente está pronta para ajudá-lo em cada etapa do planejamento e execução do seu evento.

Gostaríamos de compartilhar com você nosso guia exclusivo **"Book de Eventos"** que destaca todos os detalhes de nossos espaços, serviços e pacotes disponíveis.

Clique para baixar o ebook

É a sua oportunidade de explorar nossas opções e começar a planejar o evento dos seus sonhos.

Não perca a chance de descobrir como podemos tornar seu evento memorável.

Escaneie o Qr Code e saiba mais!

Contato

Dúvidas e sugestões
11 3188-4248 11 97367-6934
eventos@apm.org.br

apm.org.br

Eleve seu evento ao nível máximo!

Entre em contato conosco para agendar uma visita ao nosso espaço ou para obter mais informações sobre como podemos atender às suas necessidades específicas.

Médicos associados à APM, na Qualicorp, **a sua saúde encontra o melhor plano.**

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Planos de saúde coletivos por adesão, conforme as regras da ANS. Informações resumidas.

A comercialização dos planos respeita a área de abrangência dos produtos e das respectivas operadoras. A disponibilidade dos produtos pode variar de acordo com a região e a entidade de classe com a qual os proponentes mantêm o vínculo.

Os planos podem ser coparticipados. Para conhecer a tabela completa de procedimentos e valores de coparticipação, consulte a operadora.

Todas as informações referentes aos planos, incluindo condições, preços, rede de prestadores e sua abrangência geográfica, são de responsabilidade exclusiva das respectivas operadoras de saúde e poderão estar sujeitas a alterações por parte delas, mesmo após a contratação do plano, respeitadas as disposições contratuais e legais (Lei no 9.656/98). Novembro/2025.

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APM ASSOCIAÇÃO PAULISTA DE MEDICINA 95 Anos

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