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A systematic review of the effect of nutritional status on autism spectrum disorder

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that includes deficits in social interaction, communication and behavior, whose exact cause remains unknown. Its symptoms, such as food selectivity, food refusal and resistance to new habits affect children´s ability to consume food. The aim of this study is to answer the following questions: Do children with ASD have a different nutritional and behavioral profile from neurotypical children? Are dietician interventions capable of bringing benefits in terms of improvements in behavior, communication and socialization status? The methodology used was a systematic review. The authors produced two guiding questions; defined keywords; researched for papers in databases; applied inclusion and exclusion criteria; and analyzed the data obtained from papers that answered the guiding questions. The results revealed 27 publications in the Pubmed, Lilacs, and Capes databases that included keywords cross-referenced between ASD and gluten free, eating behavior, casein-free, nutritional status, food selectivity, vitamin deficiency, nutritional strategy. An analysis of 16 papers in Pubmed, 6 papers in Lilacs and 5 papers in Capes showed that 33.3% of the works had been published in Brazil. Randomized clinical trials (RCT) and cross-sectional studies were the most used methodologies. The analysis concluded that non-nutritional interventions have been effective in modifying unsatisfactory behaviors. Also, a combination of dietary and social/behavioral interventions is effective in circumventing food selectivity, thereby improving food acceptance.

Keywords: Nutrition, Autism, Public Health.

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Introduction

ASD is defined as a neurodevelopmental disorder whose peculiarities include deficits in social interaction and communication as well as restricted or repetitive behavior or interests. Other important characteristics of ASD are limited repetitive patterns, stereotyped movements, activities and interests. Although the exact cause of ASD is unknown, genetic, environmental and immunological factors are thought to play a role in its pathogenesis.[1]

With nutritional transition in Brazil over the years, several advances have been made in controlling energy-protein malnutrition, but the consequences of micronutrient deficiency have become the most important public health concern, especially among children. Studies have shown that children's usual diet is insufficient to meet 100% of their micronutrient needs,

especially for the minerals iron, zinc and calcium. Children with neurodevelopmental disorders are at risk of developing nutritional deficiencies.[2,3]

In line with the International Classification of Diseases (ICD) - 11th revision (ICD 11), the Diagnostic Statistical Manual of Mental Disorders - DSM-5 made the codes previously assigned within Global Developmental Disorders unique and currently integrates autism spectrum disorder as code 6A02. The revision also removed the subcategories and levels of classification, typifying the condition only in relation to functional language impairment and intellectual disability.[4]

ASD causes a disability in the development of individuals' neurological systems and affects their ability to communicate, interpersonal relationships and behavior. It is accompanied by a diversity of functional alterations in which it is possible to notice a series of specific characteristics among children on this spectrum, varying in degree, from mild to debilitating. Among these characteristics, we can highlight the restricted and repetitive standardization of activities and interests, which prevents ASD sufferers from participating in new activities that are not routine, and affects their food consumption in a similar way.[5,6]

The most relevant characteristics observed in children with ASD are mainly associated with poor development of language and social interaction, as well as a succession of gastrointestinal disorders, such as low production of digestive enzymes and inflammations of the intestinal wall, which intensify the symptoms of those with the disorder.[7]

Based on these symptoms, we can classify three categories of behavior that affect the autistic child's eating profile: food selectivity, food refusal (due to a resistance to trying new foods), and indiscipline during meals, a cause that is very characteristic of childhood and the disorder itself. These conditions cause autistic children to have a tiring diet with limited variety, probably leading to nutritional deficiencies.[8]

Methodology

This study was carried out using the systematic literature review methodology, which consisted of the following steps: production of a guiding question; analysis by searching for articles in literature databases with the definition of keywords, databases and application of the criteria defined for the selection of articles; and, as a last step, evaluation and analysis of the data obtained from the selected papers.

The guiding questions were divided in two stages: First, do children with ASD have a different nutritional and behavioral status than neurotypical children? Second, are dieticians' interventions capable of bringing benefits in terms of improved behavior, communication and socialization status?

The study was conducted between April and May 2020. The inclusion criteria for the studies were: original articles, studies on nutritional status, eating behavior and nutritional strategies in children with ASD, the withdrawal of gluten and/or casein, and those that fit the objective of the review, indexed in the LILACS (Latin American and Caribbean Health Sciences Literature), PUBMED and CAPES databases.

The search for papers used combinations of the following keywords, considered to be descriptors in DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings): autistic disorder; autism spectrum disorder; infants; nutritional; casein; gluten- free; nutritional status;

eating behavior; gluten-free diet; and vitamin deficiency. The terms were cross-referenced as descriptors and as words in titles and abstracts.

The following inclusion criteria were used: studies involving children with ASD, aged between 0 and 12 years; cohort studies; cross-sectional studies; case series; randomized clinical trials (RCT); descriptive observational studies that included case reports, cross-sectional studies and case-control studies. We excluded literature review articles, theses, dissertations, duplicate articles, and articles whose full content was unavailable, as well as studies of children with chronic non-communicable diseases, non-autistic children, and other audiences, the elderly, athletes, animals, studies that refer to other types of diets, children of mothers with eating disorders and guidelines.

Results and discussions

Our results initially revealed 8 scientific papers in the LILACS database, 119 papers in the PUBMED database and 36 papers in the CAPES database for exploratory reading of abstracts. Twenty-seven papers were selected based on the inclusion and exclusion criteria, which were then read in full. After analysis, articles presenting aspects that answered the guiding question of this review were included in the object of study (Figure 1).

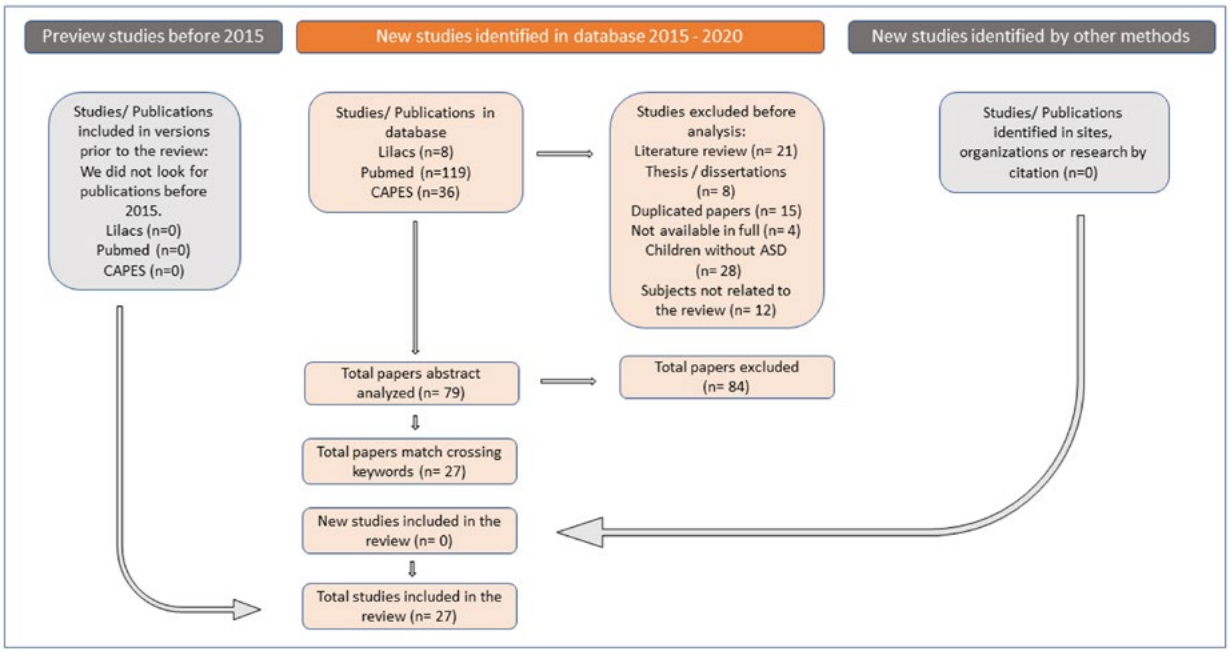

Figure 1. Systematic review flowchart

Source: The authors (2020).

The stages of this process are described in Table 1. Crossing keywords and database we found: ASD / gluten free appeared in 8 of the publications found in Pubmed, 3 in Lilacs and 1 in CAPES. ASD / eating behavior appeared in 2 of the papers selected in Pubmed but in none of the other databases. ASD / casein free appeared in only 3 papers, all of which in Pubmed. ASD / nutritional status appeared in 3 publications in Pubmed, 1 in Lilacs and 2 in CAPES. ASD/ food selectivity appeared in 2 papers in Lilacs. ASD / vitamin deficiency appeared in 1 paper in Pubmed and CAPES. ASD / nutritional strategy appeared in only 1 paper in the CAPES database (Table 1).

Table 1. Distribution of bibliographic publications obtained from the Pubmed, Lilacs and CAPES databases, according to the keywords selected, Brazil, 2020

Database	Keywords cross-referenced at the same time (as words in the abstract and descriptors)	Number of publications found	Abstracts analysed	Papers selected for analysis
PUBMED	ASD / gluten free	38	20	7
	ASD / eating behavior	30	8	2
	ASD / casein free	25	4	3
	ASD / nutritional status	24	10	3
	ASD / food selectivity	0	0	0
	ASD / vitamin deficiency	2	2	1
	ASD / nutritional strategy	0	0	0
LILACS	ASD / gluten free	3	3	3
	ASD / eating behavior	0	0	0
	ASD / casein free	0	0	0
	ASD/ nutritional status	1	1	1
	ASD/ food selectivity	2	2	2
	ASD / vitamin deficiency	2	2	0
	ASD / nutritional strategy	0	0	0
CAPES	ASD / gluten free	3	3	1
	ASD / eating behavior	6	5	0
	ASD / casein free	7	7	0
	ASD / nutritional status	7	3	2
	ASD / food selectivity	2	2	0
	ASD / vitamin deficiency	5	4	1
	ASD / nutritional strategy	8	3	1

Source: The authors (2020).

A wide range of studies, comprising 27 publications, was selected. In terms of location, the countries with the highest number of studies were Brazil and the USA (29.6%) with an equal number of papers, as shown in Table 2, thereby demonstrating widespread interest in this subject.

Regarding the design of the methodology, the studies analyzed had a higher prevalence of RCTs and cross-sectional clinical trials (25.9%), followed by quantitative publications (14.8%) (Table 3).

In terms of sample size, the studies showed an adequate number of individuals for the research designs, ranging from 1 to 538 child participants.

Table 2. Number of publications according to the country in which the study was conducted

Country	Number of publications (N)	Percentage (%)
Brazil	8 (eight)	29.6
USA	8 (eight)	29.6
Spain	2 (two)	7.4
Poland; Iran; Indonesia; Belgium; Germany; Italy; Canada, Egypt	1 each country	3.7 each

Source: The authors (2020).

Table 3. Types of studies found, 2020

Methodology	Samples selected (N)	Percentage (%)
RCT	7 (seven)	25.9
Cross-sectional	4 (four)	14.8
Quantitative	2 (two)	7.4
Qualitative	2 (two)	7.4
Group analysis	1 (one)	3.7
Case-control	3 (three)	11.1
Meta-analysis	2 (two)	7.4
Multiple project	1 (one)	3.7
Action project	1 (one)	3.7
Opinion article	1 (one)	3.7
Systematic review	2 (two)	7.4
Methodological study	1 (one)	3.7

Source: The authors (2020).

The research aimed to use cautious reliable methods, which enable improved verification of the variables in the studies, demonstrating a valid repercussion to the impact of gluten-free and dairy-free diets on children and their problems, including micronutrient deficiency.

The verification of nutritional markers was conducted using quantitative and qualitative methods, namely: biochemical tests with serum quantification of vitamins and micronutrients; and anthropometric parameters, such as BMI (body mass index), W/H (weight-for-height index), TSF (triceps skinfold). These were essential to obtain consistent data and assess possible negative nutritional repercussions.

Table 4 presents the articles selected for the review, with their authors, date and country of publication, aims and main conclusions. In order to answer the research question of the article and in line with the publications found, the studies encompass three subtopics, namely: nutritional profile of children with ASD; eating behavior of children with ASD; and nutritional strategies for children with ASD.

Table 4. Distribution of references included in the systematic review, according to year of publication, country, authors, objectives and conclusions of the article, Brazil, 2020

Country, author and year	Objective of the paper	Description of the study	Main conclusions
Brazil Caetano, M. V & Gurgel, D. C. 2018.	To assess the nutritional status and food consumption of children with autism spectrum disorder (ASD).	Quantitative, descriptive, exploratory and cross-sectional.	Most of the children with autism spectrum disorder who were assessed were overweight and obese. The limited and repetitive food menu revealed a high level of inadequate intake of vitamins (A and B6) and the mineral calcium, showing a link with high consumption of foods rich in calories and poor in micronutrients.
Brazil Rocha G. S. S. et al. 2019	To analyze the possible presence of food selectivity behaviors in children with autism spectrum disorder (ASD).	Descriptive, exploratory quantitative field research.	The participants analyzed in the study present eating behaviors that are prone to food selectivity. The study showed the risk of nutritional deficiencies, especially in micronutrients, given that the childhood phase has a direct long-term influence on an individual's life. For this reason, nutritional monitoring and necessary interventions are required to ensure the correct nutrition of children with autism spectrum disorders.
Brazil Almeida, A. K. A. et. al. 2019	To analyze consumption of ultra-processed foods among children with ASD and its association with nutritional status.	Cross-sectional.	In natura or minimally processed foods were the basis of the diet of the children studied. Despite this, higher consumption of ultra-processed foods was associated with excess weight in children with ASD.
USA Sharp, W. G. et al. 2019	To evaluate the feasibility and initial effectiveness of a structured parent training program for children with autism spectrum disorder and food selectivity.	16-week RCT study.	The MEAL Plan appears to be feasible and its preliminary results are encouraging. If further study replicates these results, the MEAL Plan could expand treatment options for children with autism spectrum disorder and moderate food selectivity.
USA Peverrill, S. B. S. et al. 2020	To examine the developmental progression of eating problems over four time points in preschoolers with ASD.	Group path analysis.	Most of the children's eating problems disappeared as they grew older, but some of them developed chronic problems.
Egypt El-Rashidy, O. et al. 2017	To analyze ketogenic diet versus gluten-free casein-free diet in autistic children	Prospective case-control.	Although the results were satisfactory, the number of subjects used was small and lacked multicentricity, since only a single location was used. Further studies were necessary,
Spain Leiva-García, B. et al. 2019	To evaluate the relationship between eating problems and oral health in children with autism spectrum disorder.	Observational case-control.	Food rejection and limited food variety were associated with an increased prevalence of malocclusion and altered Community Periodontal Index scores in children with ASD.
Poland Piwowarczyk, A., Horvath, A., Pisula, E. et al. 2020	To determine whether a gluten-free diet compared to a gluten-containing diet influences the functioning of children with autism spectrum disorders.	RCT, controlled and blinded study.	No differences were found between the groups with regard to autistic symptoms, inappropriate behaviors, or intellectual abilities after the intervention. A GFD compared to a GD did not affect the functioning of children with ASD.
Iran Ghalichi, F.; Ghaemmaghami, J.; Malek, A.; Ostadrahimi, A. 2016	To investigate the effect of a gluten-free diet (GFD) on gastrointestinal symptoms and behavioral indices in children with ASD.	RCT	GFD may be satisfactory for managing gastrointestinal symptoms and behavioral indices in children with ASD.

Table 4. Distribution of references included in the systematic review, according to year of publication, country, authors, objectives and conclusions of the article, Brazil, 2020 (cont.)

Country, author and year	Objective of the paper	Description of the study	Main conclusions
Indonesia Pusponegoro, H. D. et al. 2015	To determine the effect of gluten and casein supplementation on maladaptive behavior, severity of gastrointestinal symptoms and intestinal fatty acid binding protein excretion (I-FABP) in children with ASD.	Double-blind RCT	The administration of gluten-casein in children with ASD for one week was not sufficient to increase maladaptive behavior, the severity of gastrointestinal symptoms or urinary I-FABP. The effect of prolonged administration or other enterocyte mechanisms corroborated damage in ASD, which should be explored.
USA Hyman, S. L. et al. 2015	To obtain information on the safety and efficacy of a gluten-free / casein-free (GFCF) diet.	Double-blind, placebo-controlled challenge study	Dietary challenges had no statistically significant effects on measures of physiological functioning, behavior, problems or symptoms of autism, although these findings should be interpreted with caution due to the small sample size. The study does not provide evidence to support the general use of a GFCF diet.
Brazil Rosa, M. S. & Andrade, A. H. G. 2016	To trace the nutritional profile of children with ASD in Arapongas - PR.	Cross-sectional study	The conclusion is that children with autism spectrum disorder require continuous nutritional monitoring because of excess weight and obesity.
USA Mieurau, S. B. & Neumeyer, A. M. 2019	To examine possible direct and indirect roles for metabolism in the main symptoms of ASD, as well as evidence of metabolic dysfunction and nutritional deficiencies.	Systematic review with meta-analysis	More research is needed to test metabolic and nutritional interventions for efficacy in treatment of the main symptoms of ASD.
USA Hilman H. 2019	To evaluate the effects of video modeling on the food selectivity of three children with an autism spectrum disorder in a home environment.	Multiple baseline experimental project	The researcher suggests that the video modeling intervention was responsible for an increase in food acceptance.
USA Peterson, A. K.; Piazza, C. C.; Volkert, V. 2016	To apply treatment for food selectivity in children with autism spectrum disorders.	Complex RCT	A potential generalization effect of the treatment during ABA M preceded by SOS ABA was found.
Belgium Ostashchenko, E.; Deliens, G.; Durrleman, S.; Kissine, M. 2020	To explore whether children with autism show selectivity in social learning.	Complex RCT	Children with autism showed reduced attention to speakers' faces compared to the control group.
Brazil Cordeiro, D. A. M. & Silva, M. R. 2016	To describe strategies for implementing nutritional behaviors in autism spectrum disorder.	Action research	The resulting data lead us to believe that it is important to develop a nutritional guideline for the treatment of people with autistic disorder.
Brazil Kummer, A. et al. 2015	To evaluate the frequency of excess weight and obesity in children with ASD and ADHD.	Quantitative study	Children with ADHD and ASD are more likely to be obese or overweight than children without ADHD disorder.
USA Sathe, N.; Andrews, J. C.; Mcpheeters, M. L.; Warren, Z. E. 2017	To evaluate the efficacy and safety of dietary interventions or nutritional supplements in ASD.	Meta-analysis	Little evidence exists to support the use of nutritional supplements or dietary therapies for children with ASD.

Table 4. Distribution of references included in the systematic review, according to year of publication, country, authors, objectives and conclusions of the article, Brazil, 2020 (cont.)

Country, author and year	Objective of the paper	Description of the study	Main conclusions
Germany Lange, K. W.; Hauser, J.; Reissmann, A. 2015	To discuss the role of GFCF diets in the treatment of autism.	Opinion article	The evidence to support the therapeutic value of this diet is limited and weak. A GFCF diet should only be administered if an allergy or intolerance to gluten or nutritional casein has been diagnosed.
USA Polfuss, M. et al. 2016	To explore parents' perspectives on how their child's ASD attributes impact nutrition, physical activity, screen time behaviors and obesity risk.	Qualitative study	The strategies extracted from the parents' narratives promoted both healthy and unhealthy weight-related behaviors. The main conclusion of this study is that some parents did not follow the HCP guidance when they realized that the HCP did not understand their specific situation.
Spain Marí-Bauset, S. et al. 2015	To compare anthropometric values, nutrients, healthy consumption, healthy eating index and variety of foods with ASD.	Case-control study	A RCT is needed to explore the long-term effects of this diet on anthropometric and nutritional status as well as on behaviors in children with ASD.
Brazil Monteiro, M. A. et al. 2019	To identify and analyze the scientific evidence of nutritional interventions for children and adolescents with ASD.	Systematic review	Although some authors have shown progress in the symptoms associated with autism in individuals with this disorder who have undergone nutritional interventions, scientific evidence to support their use in children and adolescents with ASD is limited.
Italy Peretti, S. et al. 2019	To update current knowledge on maternal nutrition as a determinant of the risk of ASD in offspring.	Systematic review	Several studies have attempted to show a possible relationship between nutritional status and autism. In this review, the authors emphasized the limits and benefits found in the main current empirical studies that have examined the role of maternal diet during pregnancy and diet of ASD children as modifiable risk factors underlying the development or worsening of autism symptoms.
Brazil Lázaro, C.P. & Pondé, M. P. 2019	To construct the items and establish the content and construct validity of the Autism Eating Behavior Scale.	Methodological study	The scale aims to identify the dimensions of eating behavior that are altered, providing a more specific direction for therapy, and can also be used to measure the progress of treatment.
Canada Trudeau, M. S.; Madden, R. F.; Parnell, J. A.; Gibbard, W. B.; Shearer, J. 2019	To describe the use of supplement-based CAM therapies in children with ASD aged between 4 and 17.	Cross-sectional study	The use of complementary therapies in children with ASD is endemic and highlights the need for further research into public health education surrounding safety and efficacy.
Brazil Magnanin, T. 2019	To discuss the importance of a multi-professional approach to food selectivity in children with ASD.	Qualitative study	The activities proposed in the study are recommended for use in the family environment, at school and by the health team, thus becoming part of these children's routine.

Source: The authors (2020).

Nutritional status of children with autism spectrum disorder

The preparation of a group's nutritional profile can be used to improve how the group is treated. A quantitative, descriptive, exploratory and cross-sectional study conducted with 26 chil-

dren in the city of Limoeiro do Norte, Ceará, Brazil, showed that children with ASD have high levels of excess weight and obesity as well as inadequate vitamin and mineral intake.[9]

In another study with identical methodology, sharing the same objective of assessing excess weight in children with ASD and, in this case, attention deficit and hyperactivity disorder, Kummer and colleagues (2015)[10] concluded that a sample of 69 patients with ASD is at greater risk of being overweight and obese compared to children without developmental problems from the same community.

In a study conducted in Arapongas, Goiás, Brazil, Rosa and Andrade (2018)[11] also found that children with autism spectrum disorder require continuous nutritional monitoring because they are overweight and obese.

Thus, these papers suggest that once the children have a nutritional disorder, obesity is one of the patterns that needs to be monitored to prevent excess weight. A healthy nutritional profile must be established for children with ASD.

Eating behavior of children with autism spectrum disorder

The reality that children with autism deserve special attention when it comes to food does not seem far-fetched, considering the developmental disorders and selectivity that may be present.[24] Almeida and colleagues, 2019[12] carried out a cross-sectional study in São Luís, Maranhão, Brazil, on a sample of 29 children, with the objective of analyzing the consumption of ultra-processed foods. They found that fresh or minimally processed foods were the basis of the diet of the children studied and that high consumption of ultra-processed foods was associated with excess weight in children with ASD.

In a multicenter study conducted in Canada with long-term group analysis, Peverill and colleagues, 2018,[13] showed that children lost bad habits over time and naturally improved their nutritional status. In a complex study using RCT methodology, Ostashchenko and colleagues 14 (2020) showed that selective food behavior seems to be a social trait and that the promotion of family health is relevant to ASD children compared to the control group.

In a qualitative study conducted with the parents of autistic children, Polfuss and colleagues, 2016[15], aimed to determine how their children viewed the eating behavior of this type of client. In an innovative approach, the authors inferred that strategies extracted from the parents' narratives promoted both healthy and strange behaviors that could conveniently be related to weight. Also, according to the authors, some parents did not follow the recommendations and guidelines, since this could infer a bad prognosis for the eating behavior of children with ASD, leading to excess weight and obesity, as mentioned in studies on nutritional status.

Through a complex RCT study, Peterson and colleagues, 2016[16], demonstrated, through Applied Behavior Analysis (ABA), the existence of selective behavior in ASD. Thus, the results corroborated our initial hypothesis, that children with ASD have a different nutritional and behavioral status from neurotypical children and this status is a possible contributor to excess weight/obesity or nutrition disorders.

Nutritional strategies for children with autism spectrum disorder

Several interventions are mainly based on a gluten-free and casein-free perspective. In a randomized clinical trial with 80 children conducted in Iran, Ghalichi and colleagues (2016)[17]

concluded that gluten-free diets (GFD) may be helpful in the management of gastrointestinal symptoms and behavioral indices in children with ASD.

In this perspective, the findings of Pusponegoro and colleagues, 2015[18] in another randomized clinical trial with 74 children conducted in Indonesia, contrast with the study by Ghalichi and colleagues, 2016[17]. Using a double-blind approach, gluten and casein were inserted into the diet, with the result that the administration of gluten-casein in children with ASD for one week was not sufficient to increase maladaptive behavior, severity of gastrointestinal symptoms or urinary I-FABP. The possibility of prolonged administration or other enterocyte mechanisms leading to ASD damage should be explored.[18]

Following this same line of clarifying the impact of gluten-free and casein-free diets, a study using RCT methodology conducted with 66 children with ASD for 30 weeks showed that the interventions did not present statistically significant effects on measures of physiological functioning, behavior, problems or symptoms related to autism. Although these findings should be interpreted with caution due to the small sample size, the study does not provide evidence to support the generalized use of the gluten-free and casein-free (GFCS) diets.[18]

Given the fact that ASD presents non-specific behavior and is sometimes refractory to nutritional interventions, studies with different methodologies should be conducted. At this juncture, Hilman,[19] implemented a home video modeling intervention during dinner for three participants that used a multiple baseline experimental design. The results suggested that video modeling was effective in increasing food acceptance, but food acceptance was higher for all three participants when reinforcement with the ABA scale was added.[19]

Through an action research project, Cordeiro and Silva[20] showed that the inclusion of a guide to nutritional guidelines for the treatment of people with ASD is worthwhile, in addition to reinforcing the perspective of the unknown etiology of ASD. The interventions proposed by the authors showed the heterogeneous nature of interventions involving autism.[20]

Despite showing different studies with evidence base, studies using meta-analysis should be considered, In 2017, a meta-analysis within a systematic review found scant evidence to support the use of nutritional supplements or dietary therapies for children with ASD. Priority should therefore be given to studies at the top of the evidence pyramid. In such cases, it is worth mentioning that numerous different interventions will show differences between the groups in terms of autistic symptoms, inappropriate behaviors or intellectual abilities after the gluten diet intervention. A GFD compared to a gluten diet (GD) did not affect the functioning of children with ASD.[21]

In a systematic review with meta-analysis, Mieurau and Neumeyer[22] attempted to examine possible direct and indirect roles for metabolism in core ASD symptoms, as well as evidence of metabolic dysfunction and nutritional deficiencies. Their conclusions infer that more research is needed to test metabolic and nutritional interventions for efficacy in treating the main symptoms of ASD.[22]

In another systematic review with 18 studies, 16 of which were RCT, Monteiro and colleagues, 2020[23] categorically infer that, although numerous studies on interventions can be found, more comprehensive scientific evidence to support drastic changes in the diet of ASD patients is still lacking. Despite this, the authors concluded that there is no point in changing GFD and GFCS diets since their impacts are uncertain.[26,28-30] At this juncture, within the conclusions

imposed for this study, there is still uncertainty among the publications about interventions. The findings of the study corroborates the conclusions of other authors.[25,33-34]

Conclusions

The analysis of the studies in question demonstrated that adherence to gluten-free or casein-free diets by children with ASD confers wider benefits in the prevention of diseases such as cardiovascular diseases, neoplasms and maladaptive processes. Although some studies make a case for the removal of gluten and casein from diets, others do not encourage such a discussion.

What can be observed is that non-nutritional interventions, as discussed in the review, have been effective in reducing unsatisfactory behaviors.[25,33-34] Once this becomes a practice, dietary intervention in conjunction with social/behavioral interventions is one way to improve food acceptance by circumventing food selectivity.

This systematic review identified the nutritional repercussions of a GFCS diet on children on the autistic spectrum. We also included micronutrients, such as vitamins (A and B6) and the mineral calcium, whose levels have been shown to be insufficient or suboptimal in patients in the studies included in this review.

In this respect, one can infer those new studies with a high level of scientific evidence, i.e. RCTs and meta-analyses, are needed, with larger samples of participants, in order to discuss interventions and better characterize dietary selectivity profiles and behavior.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Piperacillin/Tazobactam: an update for clinical use

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Abstract

Introduction: Piperacillin-tazobactam, a broad-spectrum penicillin, is an important option in the treatment of infections, especially in critically ill patients who exhibit high rates of resistance to various antimicrobial agents. Understand this medication and updates on its clinical use is of paramount significance to guide precise therapeutic choices aimed at the optimization of patient care. Objective: To describe the main pharmacological and therapeutic as-pects of piperacillin-tazobactam, highlighting its clinical application and updates related to its use. Methodology: A narrative review of the literature was conducted in order to provide an update on the most relevant aspects related to piperacillin-tazobactam, including (1) a brief history; (2) chemical structure; (3) mechanism of action; (4) resistance mechanisms; (5) spectrum; (6) major clinical uses; and (7) adverse effects. Results: The safe use of piperacillin-tazobactam requires rapid testing for antimicrobial resistance patterns, thus discouraging its empirical use in cases of ESBL-producing microorganisms. In patients undergoing renal replacement therapy, antibiotic goals must be established promptly. For critically ill patients, monitoring pharmacodynamic and pharmacokinetic variability is essential. Conclusion: Piperacillin-tazobactam remains a vital drug in the management of critically ill patients, while requiring constant updates. In addition, further studies are required, especially concerning its continuous use and the selection of alterna-tives to carbapenem-resistant medications.

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Introduction

Penicillins are part of a group of antibiotics called beta-lactams, chemically characterized by having a beta-lactam ring fused to a thiazolidine ring. This bicyclic structure corresponds to 6-aminopenicillanic acid (6-APA), the structural backbone of all penicillins. Various penicillins, both natural ones obtained from fermentation of *Penicillium chrysogenum* (penicillins G and V) and semisynthetic ones, differ from each other by the type of side chain attached to the amino group of the 6-APA structural backbone (Figure 1). The penicillin group is usually divided into five classes: natural penicillins (G and V); penicillinase-resistant penicillins

(methicillin, nafcillin, and isoxazolyl); aminopenicillins (amoxicillin and ampicillin); carboxypenicillins (carbenicillin and ticarcillin); and ureidopenicillins (azlocillin, mezlocillin, and piperacillin).[1]

The penicillins group occurred was discovered in 1928 by Alexander Fleming, after he observed that the contamination of a culture of *Staphylococcus aureus* with the fungus *Penicillium notatum* (currently *Penicillium chrysogenum*) resulted in the lysis of bacterial cells. The substance responsible for the antibacterial activity of the fungus was named penicillin and went on to revolutionize the prognosis of bacterial diseases.[2] A significant breakthrough in the development of new antibiotics came with the isolation of the structural backbone of penicillins, 6-aminopenicillanic acid (6-APA), from which various other penicillins were developed through chemical alterations in the side chain attached to the amino group of this central structure. Even today, the penicillin group is responsible for changing the prognosis of many diseases, and is the subject of numerous studies, for example, on use in critically ill patients as an alternative to carbapenems, which seem to be responsible for an increase in the selection of resistant bacteria.[3]

The primary mechanism of action of penicillins is the inhibition of bacterial cell wall synthesis. This group binds to peptidoglycan-binding proteins, more commonly known as penicillin-binding proteins (PBPs), which are responsible for essential enzymatic activities in the biosynthesis of new peptidoglycan molecules, a crucial component in the formation of the bacterial cell wall. Binding to these proteins results in a defect in cell wall construction, which leads to cell lysis.[1,2]

The expanded spectrum of piperacillin against Gram-negative bacteria, wish distinguishes it from other penicillins, is a result of its high affinity with the PBPs of these microorganisms, including strains of *Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Bacteroides* spp, and *Enterococcus faecalis*.[4,5] On the other hand, tazobactam is a beta-lactamase inhibitor, sulfone of penicillanic acid that irreversibly binds to beta-lactamase enzymes, thereby forming a stable acyl-enzyme complex that allows piperacillin to be effective against bacteria producing beta-lactamas-es.[4,5] The combination of piperacillin and tazobactam makes piperacillin with the broadest spectrum penicillin of all .[5]

In Brazil, Piperacillin-tazobactam is currently used in hospital infections caused by various microorganisms, generally involving critically ill patients.[2] Due to the high resistance rates related to the drugs of choice in the treatment of these patients, especially among microorganisms that produce extended-spectrum beta-lactamase (ESBL), piperacillin-tazobactam has been considered as a possible alternative in treatment. Furthermore, these patients have pathophysiological changes thataffect the outcome of treatments and require the best therapeutic choices, including customized doses due to the severity of the condition.[6,7] As a result, constant reviews are necessary to update therapeutic choices.

Recognizing the importance of updates on this subject, this article aims to review our knowledge of the antibiotic piperacillin-tazobactam, by describing the main commonly accepted, such as mechanism of action, resistance mechanisms, among others, combined with up-to-date information regarding clinical use to assist healthcare professionals in their decision-making.

Methodology

This scientific article on methodological characteristics contains a narrative literature review was conducted, which is characterized as "*not using explicit and systematic criteria for literature search and critical analysis*" (p. 2) and not employing "*sophisticated and exhaustive search strategies*" (p. 2).[8] This review aims to update the most important pharmacological and thera-

peutic aspects related to piperacillin-tazobactam. Unlike a systematic review, therefore, which aims to answer a specific question related to a particular subject matter issue, the literature research used does not require a detailed description of the "*methodology for searching for references, nor [of] the criteria used in the evaluation and selection of the works consulted*" (p. 50)[9], to achieve its purpose of outlining a "*state of the art of a particular subject, from a theoretical or contextual perspective*" (p. 1).[10]

In this context, we proceeded with the identification and meticulous analysis of bibliographic sources, including articles, books, and publications from reputable scientific institutions. This process was conducted based on the researchers' prior knowledge, including a rigorous approach to the comprehensive reading of such sources, followed by a critical evaluation aimed at extracting the most pertinent and relevant information. The sources consulted, written in both English and Portuguese, served as the foundation for organizing the following topics that constitute this study: (1) brief history; (2) chemical structure; (3) mechanism of action; (4) resistance mechanisms; (5) spectrum; (6) major clinical uses; and (7) adverse effects.

Brief history

Penicillin was discovered by Alexander Fleming in 1928, through the observation of the *Penicillium notatum* fungus (now called *Penicillium chrysogenum)* fungus, which contaminated a culture of *Staphylococcus aureus* at St. Mary's Hospital in London.[1,2] Fleming realized that the fungus produced an antimicrobial substance, which came to be named penicillin.[2] In 1940, Florey, Chain, and colleagues isolated penicillin, thus enabling the commercialization of penicillin G, which revolutionized the prognosis of infectious disease cases.[1,2] The emergence of organisms that produce beta-lactamases stimulated the development of components resistant to the hydrolysis of these mi-croorganisms and the search for agents that were more effective than penicillin G against Gram-negative organisms. In 1959, Batchelor and colleagues successfully simplified the isolation of 6-aminopenicillanic acid (6-APA), which forms the central core of penicillin G. This discovery marked the beginning of the field of semi-synthetic penicillin, with part of the product being obtained through fermentation and part obtained artificially through the introduction of radicals into the core structure. The discovery enabled the production and teting of various semi-synthetic peni-cillins, such as methicillin against beta-lactamase-producing *Staphylococcus aureus*, and ampicillin against selected Gram-negative bacilli, among others. Since then, ongoing research has sought drugs with various pharmacological and antimicrobial properties.[1,2]

Piperacillin, a member of the ureidopenicillin group, resulted from research aimed at identifying beta-lactams that are highly effective against *Pseudomonas* spp., have a broad spectrum of action, and are less toxic than aminoglycoside antibiotics. This antibiotic was introduced in 1976, as a derivative of ampicillin formed by the addition of a hydrophilic heterocyclic group to the gamma-amino group.[2,4] This modification gave piperacillin a broad spectrum of action against Gram-negative bacteria, in part due to its increased affinity with penicillin-binding protein (PBP)-3.[5] However, piperacillin is inactivated by plasmid-derived beta-lactamases produced by some microorganisms, and is therefore often combined with tazobactam, a derivative of sulfone of penicillanic acid, to enhance its effectiveness against such microorga-nisms.[2,4]

Chemical structure

Piperacillin is a synthetic penicillin derived from ampicillin, with the chemical name (2S,5R,6R)-3,3-dimethyl-7-oxo-6-[(2R)-2-[(4-ethyl-2,3-dioxo-1-piperazinyl)formamido]-2-phenylacetamido]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (Figure 1).[11]

Its structure features the beta-lactam ring, which is common to all antimicrobials referred to as beta-lactams, including peni-cillins. A lactam corresponds to a cyclic amide.[12,13] Amides are characterized by the presence of a nitrogen atom directly bonded to a carbonyl group. Therefore, in lactams, the nitrogen and the carbonyl carbon are part of a cyclic structure. The Greek prefix "beta" indicates that the cycle consists of a total of four atoms.[14] In penicillins, the beta-lactam ring is fused to a five-mem-bered thiazolidine ring. This bicyclic structure forms the structural backbone of all penicillins, and this structure is known as 6-aminopenicillanic acid (6-APA), biosynthetically formed by the cyclization of a dipeptide formed by the condensation between L-cysteine and D-valine. Am-picillin, as a side chain, has the (R)-2-amino-2-phenylacetyl group attached to the nitrogen at position 6 (N-6) of the central 6-APA skeleton. This structure is chemically formed by the linkage of this nitrogen to the carboxylic acid group of D-phenyl-glycine. Piperacillin, on the other hand, is synthesized from ampicillin by linking the amino group of the D-phenylglycine portion to a 4-ethylpiperazin-2,3-dione carbonyl group. Thus, piperacillin contains a piperazine ring in its structure, from which is derived (Figure 1).[11]

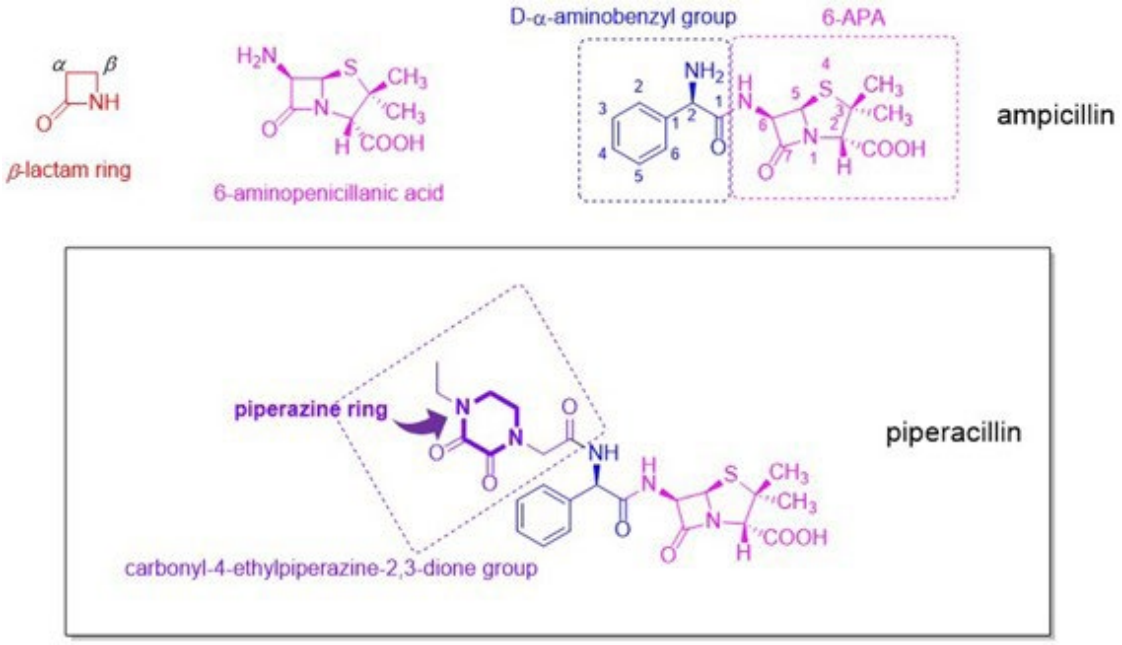

Figure 1. Chemical structures of the beta-lactam ring, 6-aminopenicillanic acid, ampicillin, and piperacillin. Note the piperazine ring as a constituent of the side chain in piperacillin.

Source: Self-generated image based on references.[12,15]

Mechanism of action

The drug's mechanism of action is related to the presence of the beta-lactam ring. The drug binds to penicillin-binding proteins (PBPs), located on the external surface of the cytoplasmic membrane, thereby preventing the formation of peptidoglycans, which are essential components of the bacterial cell wall, anda causes the osmotic lysis of bacterial cells.[2]

Piperacillin belongs to the group of penicillins that act by inhibiting the synthesis of the bacterial cell wall. Bacteria require several enzymes to biosynthesize and link the constitu-

ents of their cell walls, and PBP is responsible for the enzymatic activity of transglycosidases, transpeptidases, carboxypeptidases, and endopeptidases. Bacteria produce four types of PBPs, including high-molecular-weight PBP, low-molecular-weight PBP, which catalyze transpeptidation and carboxypeptidation, respectively, in cell wall assembly, and high-molecular-weight PBP class A, which are bifunctional enzymes with transpeptidase and transglycosylase domains. Penicillins bind to these proteins, by inhibiting enzymatic actions and, consequently, the biosynthesis of new peptidoglycan molecules — the essential component of the bacterial cell wall —and their incorporation into the developing bacterial cell wall. As a result, the cell in development has a defect in the formation of its cell wall, leading to osmotic lysis. Furthermore, the antibiotic action of penicillins also depends on the autolytic action of the bacteria's own enzymes on their cell walls, breaking down the old cell walls and enabling the bactericidal effect of the drug, since the new cell wall will be defective. However, cells that are not actively multiplying or are osmotically protected can survive the presence of penicillin. This suggests that the bactericidal effect of penicillins is directly related to the cell cycle and that the binding of penicillin to PBPs disrupts an essential event, wich possibly occurs during cell division.[1]

Resistance mechanisms

Four main resistance mechanisms exist: the destruction of antibiotics by beta-lactamases; the inability to effectively penetrate Gram-negative bacteria; the efflux through the membrane; and the low affinity of antibiotics to bind to PBPs.[1,16]

The primary resistance mechanism to piperacillin is enzymatic inactivation of the drug caused by the production of beta-lactamases by microorganisms. Beta-lactamases are enzymes that catalyze the hydrolysis of the beta-lactam ring and are divided into four classes (A to D), based on the similarity of amino acid sequences and molecular structure. Classes A and C are the most clinically significant, and class A enzymes are generally effectively inhibited by beta-lactamase inhibitors, unlike class C. However, point mutations can give rise to class A enzymes with an extended spectrum to penicilins, third-generation cephalosporins and aztreonam, referred to as extended-spectrum beta-lactamases (ESBL). The number of microorganisms producing ESBLs has increased in the recent past, and questions have been raised about the efficacity of piperacillin-tazobactam is effective against these bacteria.[4] Class B enzymes are produced by some non-lactose-fermenting Gram-negative microorganisms, with plasmid-mediated enzymes having the broadest spectrum and resistance to all beta-lactam antibiotics except aztreonam.[1] Tazobactam can inhibit class A beta-lactamases but not class B.[4]

Another important resistance mechanism is the drug's inability to penetrate its site of action, with the outer membrane of Gram-negative bacteria functioning as a barrier for this purpose. These microorganisms contain beta-lactamases in the periplasm between the outer cytoplasmic membrane and the outer lipopolysaccharide membrane, a strategy developed to keep PBPs away from beta-lactam antibiotics. However, some porins that allow the passage of mole-cules through this barrier depending on size, structure, and charge. Antibiotics that meet these requirements can pass through and bind to PBPs, but the absence or deletion of an essential porin, often associated with beta-lactamase activity, can lead to possible antibiotic resistance. Efflux is a third mechanism in which the drug that enters the periplasmic space is expelled from the membrane before it can act on PBPs. Usually, this efflux mechanism is accompanied by the destruction of antibiotics by beta-lactamases.[1] The primary mechanism that confers resistance to piperacillin-tazobactam is resistance due to structural differences in PBPs.[4] The action of PBPs in cell wall synthesis and assembly is essential, and the low affinity of PBPs

for beta-lactam antibiotics allows the antibiotic's effectiveness to be circumvented. This form of resistance occurs either through mutations in PBP genes that reduce binding affinity or through the presence of an additional low-affinity PBP.[1]

Spectrum

Piperacillin is a broad-spectrum antibiotic that is effective against strains of *Streptococcus* spp, *Neisseria* spp, *Haemophilus* spp, and other microorganisms of the *Enterobacteriaceae* family, such as *Klebsiella* spp, *Enterobacter* spp, *Serratia* spp, and indole-positive *Proteus*.[1,2] Additionally, it has an effective response against anaerobic cocci and bacilli and can inhibit approximately 60 to 90% of *Pseudomonas aeruginosa* strains at concentrations below 16 micrograms/ml. However, it is hydrolyzed by beta-lactamases of classes A and B, and it is often combined with tazobactam to enhance effectiveness against beta-lactamase-producing organisms.[1] The combination of piperacillin-tazobactam present in vitro antibacterial activity against *Escherichia coli* and *Klebsiella pneumoniae* producing ESBL, although it is less potent against ESBL-non-producing isolates. In clinical practice, bacteria such as *Enterobacter* sp, *Citrobacter* sp, *Burkholderia* sp, *Sal-monella* sp, and *Stenotrophomonas maltophilia* are resistant to piperacillin-tazobactam.

Main clinical uses

In Brazil, due to its efficacy against enterobacteria, anaerobes, and enterococci, piperacillin-tazobactam is prescribed for surgical intra-abdominal infections and hospital-acquired infections caused by *P. aeruginosa, Acinetobacter, Serratia, Klebsiella*, and indole-positive *Proteus*.[2,5] In the treatment of skin and soft tissue infections, pneumonia, intra-abdominal infections, polymicrobial infections, and febrile neutropenia in combination with an aminoglycoside, its efficacy is equal to or greater than antibiotics with a similar spectrum.[1] However, recent studies have concluded that empirical treatment with piperacillin-tazobactam is not recommended, a finding which was also observed in infections caused by *P. aeruginosa*.[3,17,18,19] Regarding empirical use for patients with hospital-acquired sepsis and unknown-source septic shock, a study in Australia recognized a lack of more robust evidence for this recommendation.[17] Furthermore, the same study rejected the recommendation of piperacillin-tazobactam over carbapenems for ESBL producers, which was also certified in other reviews that even mention the reduced effectiveness of piperacillin-tazobactam when associated with carbapenem resistance.[3,17,18,19] Evidence exists for the use of piperacillin-tazobactam in the treatment of urinary tract infections caused by ESBL-producing *Enterobacteriaceae* if susceptibility is confirmed. However, the most appropriate approach to the treatment of ESBL-producing microorganism infections is to conducti tests aimed to identifying resistance patterns and susceptibility in order to guide the best therapy.[6,7]

The use of antibiotics in the empirical treatment of *Pseudomonas* spp infections is risky and uncertain, and the use of piperacillin-tazobactam is not recommended due to the increasing resistance rates, according to a recent study. Therefore, rapid detection of resistance patterns and susceptibility to antimicrobials should be prioritized.[20] Of course, since we are dealing with severe and potentially life-threatening infections, treatment should always be initiated based on the monitoring the presumed sensitivity/resistance profiles of the agent and later adjusted accordinng to culture results.

As previously mentioned, piperacillin is widely used in a hospital environments due to its effectiveness in the treatment of infections that typically affect patients in these settings. However, this usage presents another challenge since critically ill patients require

specific treatment due to physiopathological changes that impact pharmacokinetics and cause variability in treatment effectiveness.[6,21] In such cases, there are good indications for continuous infusions and therapeutic drug monitoring, but further studies are needed to recommend this practice.[6] Establishing the required dose in critically ill patients is a challenge, and it is essential to achieving pharmacokinetic and pharmacodynamic goals. One study showed that defining these goals had more impact on the likelihood of achieving the target than the use or intensity of continuous renal replacement therapy, and it is necessary to define soft or more stringent targets, or even individualized goals depending on the patient, must be defined.[21]

Adverse effects

As in the case of most penicillins, hypersensitivity reactions have been described, ranging from rashes to anaphylaxis, superinfections, neurological toxicity at high doses, and irritative effects on blood vessels leading to phlebitis. During long-term administration at high doses, neutropenia may occur, which is reversible upon drug withdrawal. Less frequen-tly, hypokalemia and changes in bleeding time occur.[1,2,16] Despite drug-related fixed drug eruptions being widely described in association with piperacillin-tazobactam, a recent case of generalized fixed drug eruption was published, which appears to be related to drug reexposure.[7] In addition, specific dos-ing helps reduce adverse effects, while overexposure to piperacillin-tazobactam seems to be associated with increased mortality.[17,21]

It should be emphasized that the action of the drug against anaerobes can, collaterally, determine colonization by multi-resistant microorganisms, particularly in a hospital environments. Intestinal microbiota are predominantly composed of such agents and, therefore, we can result in the emergence of multidrug-resistant infections, including fungal infections such as *Candida* spp, may emerge.[22]

Conclusions

The antibiotic piperacillin-tazobactam is routinely used, primarily in situations that require decisive interventions, and a comprehensive and up-to-date understanding of the drug can assist in the therapeutic choices made on a daily basis. The safe use of this antibiotic for infections now depends on rapid testing of resistance and susceptibility to antimicrobials, and the empirical use of piperacillin-tazobactam or its use for ESBL-producing microorganisms is not recommended. In situations involving patients with renal replacement therapy, it is important to quickly achieve appropriate antibiotic goals, which require meeting pre-determined targets, must be achieved quickly. For critically ill patients, awareness of pharmacodynamic and pharmacokinetic variability is essential. However, several studies reviewed for this article revealed the need for additional research in clinical practice to address doubts and provide certainties, such as the recommendation for continuous therapy. Furthermore, growing concerns about resistance tto antibiotic underscores the need to consider alternatives, for example, to the currently used carbapenem. Although current studies indicate that piperacillin-tazobactam may not be the best alternative for all situations in critical patient care, new studies and new needs may shape innovative developments in this story.

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BJHBS

Open Anterograde Anatomic Radical Prostatectomy, a technique developed at Rio de Janeiro State University

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Abstract

Introduction: Radical prostatectomy is the gold standard treatment for localized prostate cancer, and videolaparoscopic prostatectomy represents a new leap forward. However, the latter approach adds great technical complexity and entails a long and very slow learning curve that can be successfully completed by only a small number of highly skilled surgeons. These factors have significantly hampered a more widespread uptake of this technique. Robotic-assisted laparoscopic surgery democratized laparoscopic radical prostatectomy by allowing many surgeons, even the least experienced ones, to perform this procedure with the same expertise as experienced surgeons. Nevertheless, the high cost of this technology greatly limits its more widespread use, especially in countries in the global south. Methodology: In 2015, a discussion began on the possibility of using some concepts from laparoscopic prostatectomy to improve open prostatectomy. Based on a study of the various techniques performed using the open, laparoscopic and robotic route, we developed an innovative technique to reproduce robotic prostatectomy openly, without recourse to any new special instruments or materials. This technique is called "Open Anterograde Anatomic Radical Retropubic Prostatectomy" (AORP). Results: AORP was superior to Open Radical Prostatectomy in critical parameters: a median estimated blood loss of 300mL versus 500mL (p=0.0003); more rapid urethrovesical anastomosis, at 20min versus 25min (p=0.005); shorter duration of indwelling vesical catheterization, at 7 versus 14 days; increased surgeon perception of nerve-sparing, at 101 (87.8%) versus 71 (67.6%) (p=0.0009); increased early urinary continence, at 70 (60.9%) versus 45 (42.0%); fewer complications (p=0.007) and equivalent oncological control. Discussion: We understand that the gains of robotic surgery depend not only on the introduction of technology but also on improvements in the technique of dissection, preservation and reconstruction that can be reproduced in open surgery, thus enabling similar operations with improved procedures but without access to robotic technology.

Keywords: Prostate neoplasms, Prostatectomy, Laparoscopy, Surgical, Anastomosis, Surgical, Urinary incontinence.

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Introduction

Radical prostatectomy (RP) is the gold standard treatment for localized prostate cancer. A better understanding of prostate anatomy and the contributions of the open prostatectomy surgical technique described by Patrick Walsh in 1982 were fundamental to the improvement of the functional and morbidity results of this surgical procedure.

In the 1990s, videolaparoscopic prostatectomy constituted a new leap forward in the treatment of prostate cancer, enabling smaller incisions and shorter hospitalization times.[1] However, this procedure added great technical difficulty – meaning that only very skilled surgeons with long training in video surgery and subject to a very long learning curve were able to overcome this challenge. These difficulties made the universalization of the technique extremely difficult. Robotic-assisted laparoscopic surgery,[3] in turn, replaced straight instruments with articulated forceps with greater freedom of movement and the possibility of dissection of structures not reached by laparoscopy (Figure 1).

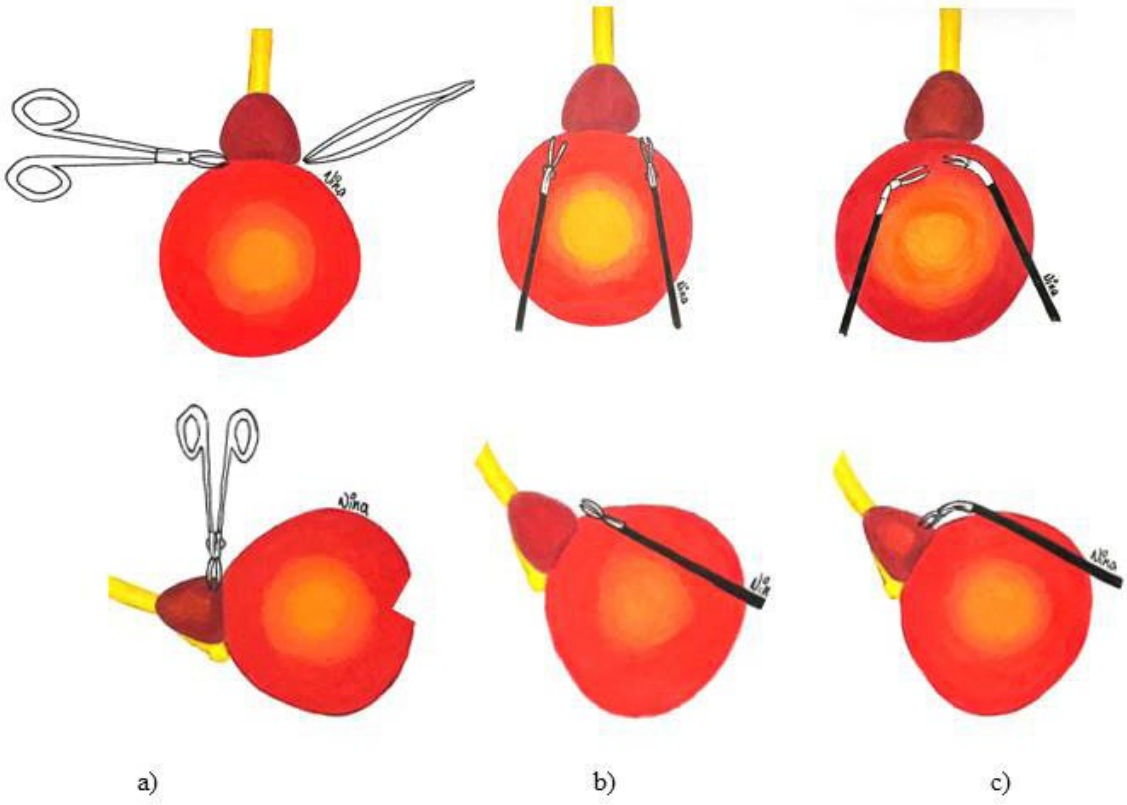

Figure 1. Schematic design demonstrating the working angles of tweezers
Source: The authors (2023).

Furthermore, robotic surgery offered the advantage of the main surgeon being able to control four arms, including the optics and three more clamps, fixing one and working with three others. This ability constituted a very significant advantage, since finding the exact location where the surgeon wants to work in pure laparoscopy is difficult, even with experienced assistants. Another important change in robotic-assisted laparoscopy is that the optics have two cameras that provide the surgeon with a three-dimensional view and a sense of depth, in addition to ensuring that the surgeon's view is exactly at the anatomical point where he wants to work, since he is the cameraman himself. Therefore, robotic-assisted laparoscopic prostatectomy has become the procedure of choice for qualified surgeons and for patients. To date, no differences have been demonstrated in oncological and functional results in the medium- and long-term when compared to other surgical treatment modalities.[4]

Methodology and resources

In 2015, the possibility of using some concepts from laparoscopic prostatectomy to improve open prostatectomy was discussed. Three differences were identified between the techniques that could be adapted: first, the dissection route, which was retrograde in open surgery and antegrade in laparoscopic surgery; second, preservation of the bladder neck and a considerable portion of the abdominal urethra; and third, vesicourethral anastomosis, which is performed with a continuous suture as described by Van Veltholven.[6] Since these differences are partly responsible for making surgery easier laparoscopically, whether or not assisted by a robot, why not try to perform these same techniques of dissection, preservation and anastomosis during open surgery?

A pilot study was carried out and subsequently published using the successful Anatomical Antegrade Open Radical Prostatectomy (AORP) technique.[7] Through a literature review, we identified fundamental studies for the development of the new surgical AORP technique.[2,8-10]

Campbell described the primordial technique of retropubic RP 1959. It was performed with anterograde dissection, however, this surgery used very rudimentary techniques, the principle was early vascular and lymphatic control before the greater manipulation of the gland, in order to avoid the spread of tumor cells, an important consideration in the treatment of all tumors during that time. This wide dissection – reseating the entire nerve vascular bundle without preserving the bladder neck, and therefore requiring bladder neck plastic and a vesicourethral anastomosis – was performed without any sutures.[8]

In 1978, Patrick Walsh described a technique, the most used until today, that was based on the preservation of nerve vascular bundles. This technique includes a more anatomical dissection, close to the prostate capsule, thus managing to preserve more nerves. However, the dissection route was changed from anterograde to retrograde. The dissection of the prostate began by opening the endopelvic fascia, sectioning the pubic prostatic ligaments and the urethra at the beginning of the surgery. This caused a retraction of the urethra with a smaller amount of proximal urethra, because the urethra was fixed at the apex of the prostate and, after sectioning the pubic prostatic ligaments, the surgeon needed to recover the urethral stump retracted into the perineum. For this reason, the urethrovesical anastomosis in the Walsh technique was, in most cases, performed by a simpler suture with separate stitches.[2]

In 2008, Sciarra published a series of 323 RP with surgery by the anterograde route, but without preservation of the bladder neck and with anastomosis by separate Stitches. Until then, no one had reproduced the robotic dissection technique in open surgery.[9]

Another fundamental article in the development of this new technique was the Pasadena consensus, which describes in precise details the technique of robot-assisted laparoscopic RP dissection.[10]

Based on a study of the various techniques performed by the open, laparoscopic and robotic route, the latter of which is described in detail in the recommendations of the Pasadena Consensus Panel, we developed a novel technique to reproduce robotic prostatectomy openly, without the addition of any new instruments or special materials. Its name is "Open Anterograde Anatomic Radical Retropubic Prostatectomy" technique, and its acronym is AORP.[7,10-11] This new technique is based on the 7 main steps described below:

1. Currently we perform this surgery utilizing a Pfannenstiel incision. We no longer perform the incision of endopelvic fascia and section of puboprostatic ligaments with

ligation of the dorsal vascular complex. We have not conducted such procedures for some time, since we prefer the technique of preserving the Retzius space.

2.The dissection of the prostate begins with an anterograde approach, i.e., from bladder neck to the apex, with careful dissection and preservation of the bladder neck, when possible, since it is separated from the prostate.

3. Dissection of the space behind the prostate and bladder neck with identification of ejaculatory ducts and seminal vesicles. Meticulous dissection of these structures with minimal use of cauterization and traction.

4. Meticulous retro prostatic dissection with preservation of the posterior layer of Denonvilliers' fascia, which contains communicating nerve fibers and can be left on the rectum. This dissection must reach the prostatic apex and extend laterally to the pedicle and bundle nerve vascular.

5. Lateral vascular prostate pedicle dissection and ligation of the prostate with an absorbable suture, such as vicryl 2.0 or 3.0. Uni or bilateral nerve-sparing as required through careful lateral dissection of the prostate, without the use of electro cauterization, until the apex is reached. Maximum preservation may be obtained by following the plane between the prostatic capsule and the multilayer tissue of the prostatic fascia when possible.

6. Release of the prostate up to its apex dorsally. Meticulous dissection of the prostatic apex and urethral. Preservation or section of the dorsal venous plexus with traction of the prostate and urethra exposure to be sectioned near the apex, preserving adequate extension of the abdominal urethra to facilitate urethrovesical anastomosis (Figure 2).

7. Urethrovesical anastomosis, without bladder neck reconfiguration or eversion of the bladder mucosa. Anastomosis confectioned with two monofilament, absorbable 3.0 sutures joined at the end to perform a single running suture as described by Van Velthoven *et al*. The first stitch is made through the bladder from the outside to the mucosa and then passed through the urethra from the mucosa to its outer layer (Figure 2).

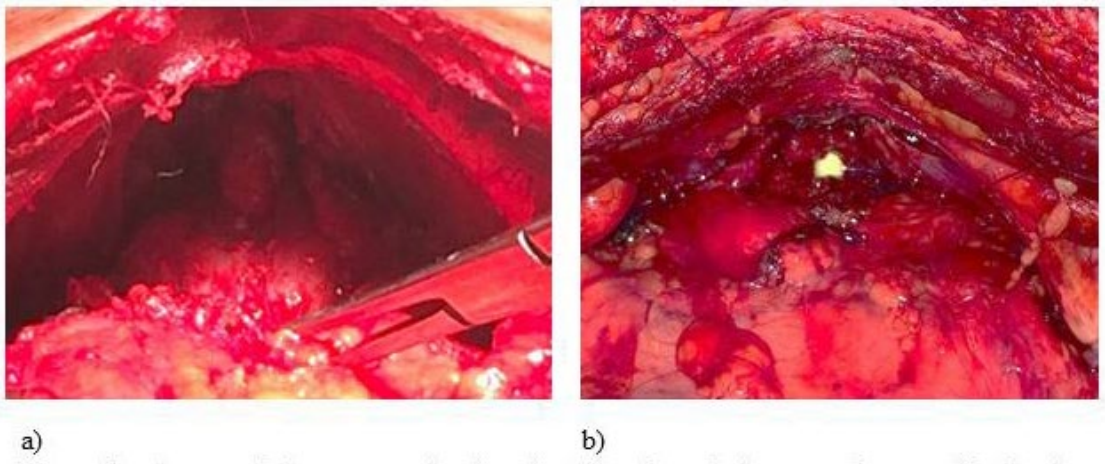

Figure 2. Dissection of the prostatic apex

Legend: Image of the surgery showing the dissection of the prostatic apex (a) by the anterograde technique, preservation of a large portion of the abdominal urethra, 3 cm, which greatly facilitates the anastomosis with continuous suture (b).

Source: The authors (2023).

The main surgical steps of this technique follow the recommendations of the 2012 Pasadena Consensus Panel for Robotic Surgery,[10] modified by the authors to adapt to open retro-pubic surgery: anterograde dissection with preservation of the bladder neck, nerve sparing, preservation of the posterior layer of Denonvilliers' fascia, which remains on the rectum, and preservation of the abdominal urethra. This technique has been described in detail in previous works.[7,10-11] The main changes that occurred over time were the non-opening of the endopelvic fascia, non-section of the pubic prostatic ligaments and, most of the time, the suture or ligation of the penile dorsal vein complex proved to be unnecessary.

Results and discussion

Our first publication was the pilot study cited above, which evaluated ten patients undergoing AORP at the Pedro Ernesto Hospital of UERJ. What surprised us the most in this study was the proportion of continence of 70% in 30 days, where continence is defined as a patient who did not lose control of urination and did not use a protector pad. This proportion of continent patients was a great surprise and motivated us to carry out larger and definitive study.[7]

The second publication focused on presenting the results of the first 50 patients and a video of the entire surgery with details of the technique as described above.[11]

The most recent study included 240 men chosen randomly from March 1, 2016, to February 27, 2019. These were patients with clinically localized prostate cancer, who had been recommended for unilateral or bilateral nerve-sparing open RP. Among these, 220 completed the three-month follow-up; 115 underwent AORP, and 105 were subjected to ORP. Ethical approval was obtained from the local Ethics Committee on November 2015 under number 1.335.683, and registered on the Plataforma Brasil CAAE:41908815.9.0000.5259 and in ClinicalTrials.gov (identifier NCT02687308). We found that: median estimated blood loss was lower in AORP, at 300mL versus 500mL in ORP (p=0.0003); urethrovesical anastomosis was significantly faster, at 20min (15-30) versus 25min (20-30) (p=0.005); and indwelling vesical catheterization was shorter, at 7 days (7-7) versus 14 days (14-15) (p<0.0001). AORP was superior to ORP in critical parameters. In addition to those mentioned above, the surgeon's perception of nerve-sparing occurred in 101 (87.8%) cases versus 71 (67.6%) (p=0.0009). Regarding urinary continence, a larger number of patients achieved early continence through the AORP, at 70 (60.9%) versus 45 (42.0%) for ORP. Our results also showed fewer complications (p=0.007) and similar oncological control.[12]

We are currently conducting a study comparing AORP with RRP in terms of safety, oncological and functional results and costs. This study showed small, statistically insignificant differences in terms of hospital stay and bladder catheterization time. However, it showed a much (3.7 times) higher cost for robotic surgery.[13-14]

In conclusion, we understand that the gains derived from robotic surgery are not only a result of the introduction of technology, as described above, but also of an improvement of dissection, preservation and reconstruction techniques, which can be reproduced in open surgery and allow patients without access to robotic technology to be the subject of a similar operation but with improved procedures. Furthermore, the AORP method was reproducible by low-volume surgeons; therefore, it may assist inexperienced surgeons in developing valuable skills for future training with robotic techniques.

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Validation of the Nottingham Hip Fracture Score as a predictor of 30-day mortality after hip surgery

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Abstract

Purpose: To assess whether the Nottingham Hip Fracture Score (NHFS) can predict mortality in the first 30 days after hip surgery. Material and methods: Upon admission, 216 patients were assessed for age, sex, mobility status (bedridden, assisted or unassisted walking), living accommodations (residential or institutionalized), fracture type (intra- or extracapsular), comorbidities (cardiovascular, stroke, respiratory, renal, diabetes), malignant disease, and cognition (Mini-Mental Status Examination). We applied the NHFS, which evaluates seven factors, with scores that range from 0 to 10, as a predictor of 30-day mortality after hip surgery. Results: Survivor scores showed greater variability (CV=0.28) than those of non-survivors (CV=0.20). The receiver operating characteristic curve identified a score of 5.5 as the optimal cutoff point. At this point, the test's sensitivity and specificity indicate the simultaneous maximum likelihood of 30-day survival or non-survival. Conclusion: The NHFS is a robust predictor of 30-day mortality after hip surgery and an updated equation has been validated for the patients in this sample, which increases its clinical credibility.

Keywords: Hip fractures, Risk scoring tools, Mortality, Older adults.

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Introduction

Among older adults, hip fractures are one of the most common injuries that require emergency surgery and are among the most common causes of death after an accident.[1]

The Brazilian population is clearly aging: the share of the population over 60 years was 4.2% in in 1950, 8.6% in 2000, 12.1% in 2011, and, according to the Brazilian Institute of Geography and Statistics, was expected to reach 14% in 2020.[2] Aging is a dynamic process that involves an increasing loss of functional reserve and biochemical, morphological, and psychological changes, which makes older adults more prone to environmental risks and, consequently, risk of falls. The mortality rate after hip fracture increases by 4% each year, but when combined with comorbidities it can increase by up to 40%.[3]

The mortality rate in older hip fracture patients has been the subject of considerable discussion,[4-6] with several factors affecting prognosis: age, nutritional status, cognitive status,

clinical comorbidities, time between the fracture and surgery, and type of anesthesia. It is unclear whether the most common protocols for identifying patients at higher risk of postoperative complications are suitable for older patients with hip fractures due to their generic and complex measurement systems.[7] The most common preoperative assessment in Brazil is the scale of the American Society of Anesthesiologists, which functions well in the general population, but whose validity is limited in the case of a specific, homogeneous group of patients with hip fracture.[8]

Since 1999, the Queen's Medical Center (Nottingham, UK) has been collecting retrospective data from the charts of its patients with fractures of the proximal femur and is using this information to determine the most important prognostic factors in predicting 30-day mortality risk. This resulted in the Nottingham Hip Fracture Score (NHFS).[7-8]

The NHFS combines previously tested highly significant indices[7-8] that take into account age, sex, hemoglobin and creatinine tests at admission, the presence of cardiovascular, cerebrovascular, respiratory, or renal complications, current or past cancer treatment, living conditions (institutionalization), and a cognitive assessment (Mini-Mental Status Examination) as predictive factors for 30-day postoperative mortality.

The lack of indices to identify high-risk patients among older Brazilians in our health services led us to apply the NHFS initially to a population of hip fracture patients over 65 years of age, correlating the results with their clinical data. However, the aim of the present study was to apply the NHFS prospectively to a cohort of hip fracture patients over 60 years of age to assess whether the NHFS can be used to predict 30-day postoperative mortality.

Material and methods

A total of 216 patients with proximal femur fractures who were treated in the emergency department between March 30, 2016 and March 20, 2018 were analyzed in a non-randomized prospective cohort. The inclusion criteria were hip fractures requiring surgery, age over 60 years, and written informed consent. The exclusion criteria were subtrochanteric hip fractures, pathological fractures, metabolic alterations, congenital deformities, and fracture sequelae. All procedures were conducted per the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Research Ethics Committee (number 68456417.3.0000.5243).

At admission, patients responded to a questionnaire that assessed age, sex, mobility status (bedridden or assisted or unassisted walking), living accommodations (residential or institutionalized), fracture type (intra- or extracapsular), comorbidities (cardiovascular, cerebrovascular, respiratory, renal, diabetes), and previous malignant disease, after which they completed a cognitive assessment test (Mini-Mental Status Examination).[8-10]

Laboratory blood tests were taken on the admission date, as part of a preoperative routine that included: complete blood count, coagulogram, glucose, urea, creatinine, sodium, potassium, principal components analysis, urine culture, total protein dosage, albumin, globulin, 25-hydroxy-vitamin D, serum calcium, parathyroid hormone, total cholesterol and transferrin.

After data collection and laboratory tests, the NHFS was applied, which assesses 7 factors, with scores ranging from 0 to 10. Patients scoring ⩾ 6 are considered to be high-risk (Table 1).

Table 1. Nottingham Hip Fracture Score

Variables	Values	Points
Age	65-85 years	3
	> 85 years	4
Sex	Male	0
	Female	1
Admission hemoglobin level	< 10 g/dl^{-1}	1
MMSE score	< 6 of 10	1
Institutionalized	Yes	1
Number of comorbidities	> 2	1
Malignancy	Yes	1

Legend: MMSE: Mini-Mental Status Examination.
Source: The authors (2023).

To characterize the patient profile, fracture type, and treatment, a descriptive statistical analysis of the behavior of all variables was performed. Data from quantitative variables were summarized using statistical calculations (mean, median, minimum, maximum, standard deviation, coefficient of variation (CV)), simple frequency distributions, and cross tables. A quantitative variable's distribution was considered low if CV<0.20; moderate if 0.20≤CV<0.40 and high if CV≥0.40.

The distribution of patient class frequencies was obtained by determining the number of classes with Sturges' formula, given by $n_c = 1 + 3.32 \log n$, and the range of classes, given by $h = \frac{R}{n_c}$, where R is the total range of the data.

The incidence of mortality was estimated using inferential analysis of the distributions of qualitative variables. The significance of the association between two variables, or the difference between the distributions of proportions, was investigated using the chi-square test. In circumstances where the chi-square results were inconclusive and when possible, Fisher's exact test was used. When a significant association was identified between a factor and 30-day mortality, the estimator used to express the risk was the odds ratio, which evaluated the relationship between the probability that an individual in a group would die in the first 30 days after surgery compared to the probability that an individual in a complementary group would also do so. The significance of the odds ratio was assessed through a confidence interval at the 95% confidence level, which cannot reach 1, since this result would indicate that individuals from both groups have an equal probability of dying in the first 30 days after surgery.

In an inferential analysis of quantitative variables, the independent groups (death and survival) were compared using the Mann-Whitney test due to the small size of the non-surviving group.

When a significant association was found between a quantitative variable and a factor, an optimal cut-off point for it was found using the receiver operating characteristic (ROC) curve methodology. The performance measure for the proposed diagnostic test and cut-off point was the area under the ROC curve (AUC), and the significance of the AUC was evaluated by a test

that assesses the null hypothesis H0: AUC=0.5. In addition to this significance test, an asymptotic confidence interval was obtained for the AUC at the 95% confidence level.

In addition to the ROC curve analysis, a logistic regression analysis was performed to validate the NHFS as a predictor of 30-day mortality after surgery. This procedure generated a mathematical model that can predict, based on patient scores, the probability of 30-day mortality.

All analyses were performed considering a maximum significance level of 5% (0.05), i.e., the null hypothesis was rejected whenever the p-value associated with the test was <0.05.

Results

This study is based on a sample of 216 patients with fractures of the proximal femur, treated at a reference orthopedic hospital. Among these patients, 15 died within 30 days after surgery. Table 2 shows the distribution of patient characteristics, both overall and in groups, according to the 30-day survival rate. The characteristics and treatments of the fractures, both overall and in the groups divided by the 30-day survival rate, demonstrate that 94 patients (43.5%) had unstable fractures and 137 (63.4%) had stable fractures. Additionally, 54 patients (25.0%) were treated with dynamic hip screws, 87 (40.3%) with locking rods, 58 (26.9%) by hemiarthroplasty, 12 (5.6%) by total hip arthroplasty, and five (2.3%) with cannulated screws. In total, 113 patients (52.2%) were able to walk without assistance. The majority of patients did not require blood transfusion or blood products (60.6%) and did not experience postoperative complications (78.7%).

Table 2. Distributions according to sex, living accommodations, and age, both overall and in groups according to 30-day survival

Variable		Global n=216		Death in first 30 days				Subgroup comparison p-value
				No n=201		Yes n=15		
Sex	Female	173	80.1%	161	80.1%	12	80.0%	1.000*
	Male	43	19.9%	40	19.9%	3	20.0%	
Living accommodations	Rest home	9	4.2%	9	4.5%	0	0.0%	1.000*
	Residence	207	95.8%	192	95.5%	15	100.0%	
Age	61 to 66	5	2.3%	5	2.5%	0	0.0%	0.001**
	66 to 71	14	6.5%	14	7.0%	0	0.0%	
	71 to 76	18	8.3%	18	9.0%	0	0.0%	
	76 to 81	33	15.3%	33	16.4%	0	0.0%	
	81 to 86	59	27.3%	56	27.9%	3	20.0%	
	86 to 91	50	23.1%	44	21.9%	6	40.0%	
	91 to 96	24	11.1%	19	9.5%	5	33.3%	
	96 to 101	2	0.9%	2	1.0%	0	0.0%	

Legend: * Fisher's exact test ** Mann-Whitney test.
Source: The authors (2023).

The variability in the score was greater in the survivor group than in the non-survivor group, with coefficients of variation of 0.28 and 0.20, respectively. The distribution of scores in the two groups is presented in Figure 1, in which the NHFS distributions were compared using a non-parametric approach, the Mann-Whitney test, due to the small size of the non-survivor group. This test resulted in a p value <0.001, which indicates a significant difference between the score distributions, with higher scores in the non-survivor group. To find an NHFS cutoff point that would serve as an indicator of 30-day postoperative mortality, an analysis of the ROC curve was performed. A score of 5.5 was identified as the ideal cutoff point, at which point sensitivity and specificity reached maximum simultaneous likelihood. This means that, for patients with scores ⩾5.5 (or ⩾6, considering that the NHFS is always a whole number), the death test is capable of predicting mortality within 30 days after surgery.

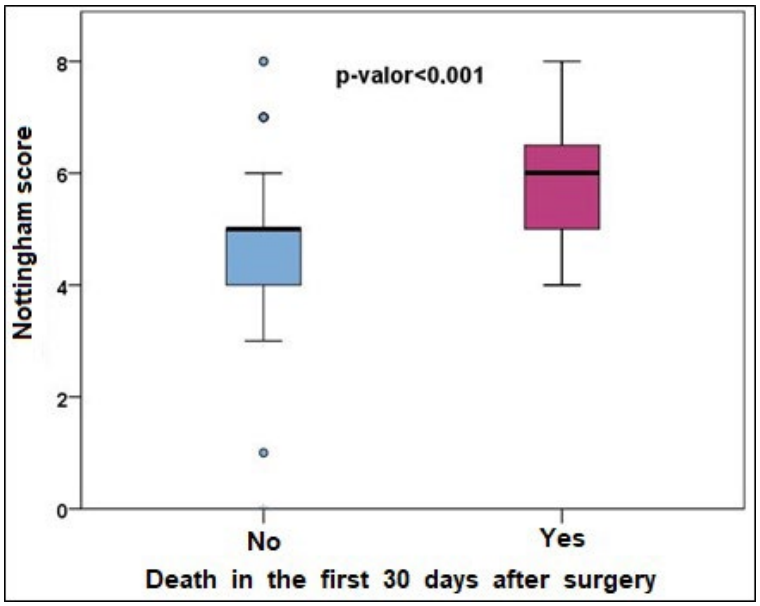

Figure 1. Nottingham Hip Fracture Score distributions according 30-day mortality
Source: The authors (2023).

Table 3 presents the measures of false positives (1-specificity), sensitivity and specificity for different cutoff points, indicating tests with more or less rigorous criteria. Less restrictive cutoff points present greater sensitivity and specificity 1 (points in the upper right corner of the curve), but these cutoff points may result in lower specificity. The ideal cutoff point found was 5.5, which presented an adequate balance between sensitivity and specificity.

For the test based on the cutoff point of 5.5, sensitivity was 0.60, specificity 1 was 0.244, and specificity was 0.756. This means that the test correctly identified 60.0% of patients who died within 30 days but would also have a false positive probability of 24.4%.

A logistic regression model can be used to estimate 30-day mortality based on the NHFS score. The dependent variable of the model is the occurrence of death within 30 days after surgery, while the NHFS score, which showed a significant association with death, is considered to be an independent variable.

Table 3. Nottingham Hip Fracture Score cut-off points for tests with more and less strict criteria

	Cut-off point	1-Specificity	Sensitivity	Specificity
Less strict criteria	-1.00	1.000	1.000	0.000
	0.50	0.990	1.000	0.010
	2.00	0.985	1.000	0.015
	3.50	0.816	1.000	0.184
	4.50	0.547	0.867	0.453
Optimal point	5.50	0.244	0.600	0.756
Stricter criteria	6.50	0.065	0.200	0.935
	7.50	0.010	0.067	0.990
	9.00	00.000	0.000	1.000

Source: The authors (2023).

Figure 2 represents the probability of death after a femoral fracture. Based on this figure, it is possible to predict patient mortality on admission by using the NHFS score. For scores >6, the probability of death is higher than the 30-day mortality rate (6.9%), which was corroborated by the ROC curve analysis.

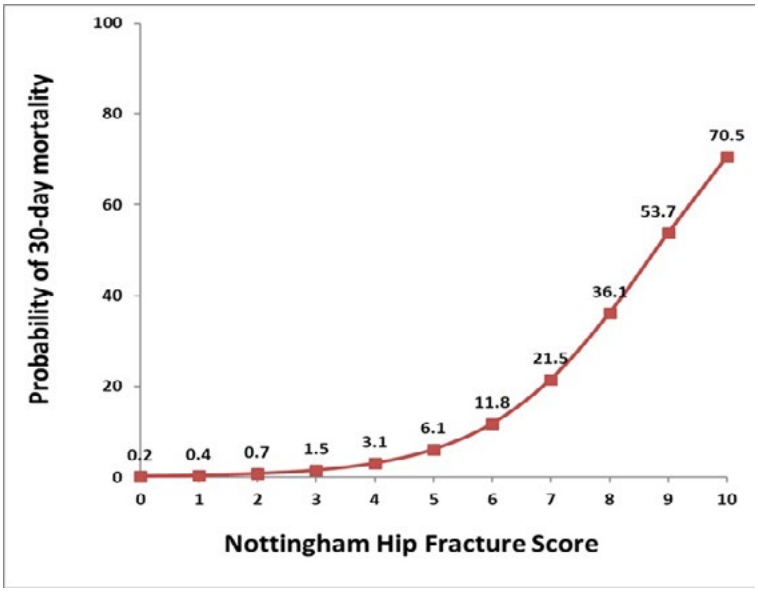

Figure 2. Graphic representation of the probability of death after femur fracture according to Nottingham Hip Fracture Score

Source: The authors (2023).

Discussion

Our study assessed 30-day mortality after hip surgery in 216 hip fracture patients, including patient profiles and treatment, identification of factors associated with 30-day mortality, and validation of the NHFS as a predictor of 30-day mortality. The results indicate that the NHFS is a robust predictor of 30-day mortality.

The NHFS score, developed in 2008 as a predictor of 30-day mortality after hip fracture, shows significantly higher 30-day mortality in high-risk patients (NHFS>4).[7] The equation used to validate the score has been recalibrated twice (2012 and 2015)[5-9] to accommodate the gradual reduction in 30-day mortality after hip fracture. Studies have validated the NHFS' ability to predict 30-day mortality after hip surgery in the UK and in international cohorts.[11-16] Doherty and colleagues[1] concluded that the NHFS is a robust tool for assessing 30-day mortality after hip fracture treatment, demonstrating that the NHFS predicts morbidity well and mortality moderately, but is less effective at predicting length of hospital stay or postoperative complications. A little recalibration was needed to reflect local death rates.

With the objective of determining a simple, economical instrument that is easy to calculate, objective, and precise, Marufu and colleagues[5] conducted a qualitative systematic review of 29 studies that evaluated 25 risk stratification tests. They concluded that the NHFS may be the most appropriate instrument currently available for hip fracture patients. However, more studies are needed to confirm it as the tool of choice for predicting 30-day mortality after hip surgery. Rushton and colleagues[7] suggested that patients with NHFS scores ⩾6 should be considered "high risk", but this must be validated by other studies to identify mortality risk in the small percentage of patients with the highest NHFS scores.

The present prospective study demonstrated that the 30-day mortality rate after hip surgery was 6.9% with a confidence interval of (3.6%, 10.4%). In a sample of 4,967 patients from the United Kingdom, Maxwell and colleagues[8] found a 30-day mortality rate after hip surgery of 7.9%. In a sample of 6,202 patients from the United Kingdom, Wiles and colleagues[4] found a mortality rate of 8.3%. In a multicenter sample of 7,290 patients from the United Kingdom, Moppett and colleagues[11] found a mortality rate of 6.6%. In a sample of 1,079 patients, Rushton and colleagues[7] found a mortality rate of 7.3%. The 30-day mortality rates these authors found after hip surgery in retrospective studies in the United Kingdom did not differ significantly from the rate found in the present study, since all these rates are within our estimated confidence interval.

In our study, 30-day mortality after hip surgery was significantly associated with age, total length of hospital stay, time in ICU, length of hospital stay after surgery, and NHFS score. As a validation study of the NHFS as a predictor of 30-day mortality through ROC curve analysis, our study proposes that a NHFS score of 5.5 is the best cut-off point. That is, if the score is 6 or more, death is predicted within 30 days after surgery. This cut-off point is 1 point higher than that of Maxwell and colleagues[8] who created and validated the NHFS for UK patients. In their study, the AUC was 0.719, slightly lower than that of the present study (0.737). They found a sensitivity of 44.2% and a specificity of 80.8%, although ours were 60.0% and 75.6%, respectively. Thus, adapting the cut-off point to 6 yielded greater diagnostic power for our patients than the cut-off point used in the United Kingdom. Our cut-off point had lower specificity for this population but higher sensitivity in predicting those who would actually die. Since the objective of our study was to correctly predict death, a more sensitive test was considered better than a more specific test, including a lower chance of false negatives. The test of Maxwell and colleagues, despite its higher specificity, had a 55.7% probability of false negatives.[8]

The logistic regression analysis also showed that our model predicted mortality better than that of Maxwell and colleagues,[8] with probabilities >50% for scores of 9 and 10. In Maxwell and colleagues,[8] the logistic model was more conservative and indicated a probability of mortality >50% only for NHFS scores of 10. Comparing our results with those of Maxwell and colleagues,[8] including the ROC curve and the logistic regression model, we conclude that the NHFS is validated for predicting 30-day mortality after hip surgeries in this population. It should be noted that to calculate the NHFS, it was necessary to adapt the version of the Mini-Mental Status Examination commonly used in Brazil,[10] reducing it to a scale of 0 to 10.

This study has some limitations. Although the cohort was prospective, which is important for obtaining accurate data and complete information from patients treated at the institution, the patient sample was small compared to those described in the literature. Also, the study included a single population and was conducted at a single hospital, despite the procedures being performed by three senior surgeons. Limited information may affect the results, and additional studies involving more hospitals could strengthen the evidence. Another limitation was the inclusion of treatment for all proximal femur fractures without differentiation between fractures treated by arthroplasty (total or partial) or osteosynthesis (locking nails, dynamic hip screws, and cannulated screws). This heterogeneity of treatment methods could create a bias and thus affect 30-day postoperative mortality and NHFS results. Despite this, our results are in line with those in the literature (30-day mortality rate, 6.9%).[4,7,8,11] New studies assessing a specific treatment group using the same methods may contribute to stronger and more consistent NHFS results.

Conclusion

The NHFS is a robust predictor of mortality in the first 30 days after hip surgery and, after using an updated equation, was validated for the patients in this sample, increasing its clinical credibility.

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BJHBS

The dynamic of intersected social categories in social interactions in a Brazilian psychosocial care center

Roberta Soares[1*]

Abstract

The Brazilian Psychiatric Reform advocates non-asylum treatment for individuals diagnosed with severe or persistent mental disorders, which is conducted mainly by Psychosocial Care Centers. This study aims to understand the role of intersected social categories in social interactions among social actors in those institutions. This qualitative ethnographic research uses the technique of participant observation. For the theoretical framework, intersectionality theory was chosen, in combination with the concept of intersectional stigma to reflect on intersectional discrimination. Erving Goffman´s works are also used to evaluate how social categories are socially situated. In addition to power relations between staff members and patients, the study examined the intersection of social categories, including how the social actors involved tend to notice their oppressions, but not their privileges, that is, the oppressions of others. The researcher argues therefore that, within that institution, the intersected social categories influence the dynamic of social interactions and generate an even more unjust experience for the patients in the institution in question.

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Introduction

Brazil, like many other countries, underwent a psychiatric reform in response to an anti-asylum movement. The Brazilian psychiatric reform advocates non-asylum treatment for individuals diagnosed with severe or persistent mental disorders, which is conducted mainly by Psychosocial Care Centres. This service replaces hospitalization in psychiatric hospitals. Its official objective is to create a therapeutic project for each patient.[1,2]

This article, which is based on a qualitative ethnographic methodology,[3] focuses on the social interactions between social actors (staff and patients) in a Brazilian psychosocial care center, using participant observation.[4] The conceptual framework is based mainly on intersectionality theory[5,6] and the concept of intersectional stigma.[7,8] The aim of this research is to understand the role of intersected social categories in social interactions in that institution.

Literature review

International research concerning mental health and intersectionality indicates the existence of intersectional stigma, that is, when multiple stigmatized identities converge.[7] Thus, inter-

sectional invisibility, tends to intensify unfair treatment.[8] Even if rarely used in health studies, intersectionality theory has sometimes been employed in public health interventions to analyze their effects and to support the design of such interventions. In research, some social categories (such as ethnicity, gender, and social class) are more present while others (such as sexuality and physical disability) are less present.[9]

Recent Brazilian studies on mental health in general and specifically on the Psychosocial Care Centers show little analysis of the patients' experience in general and, specifically, of how differences in social categories influence their experience. For example, race is not often considered in analysis even though racial inequalities persist in society.[10] However, some studies have focused on the analysis of different social categories, such as race and gender. They emphasize how patients' experiences are affected by these social categories and highlight the importance of decolonial thinking to promote social transformation. In this sense, the defense of psychosocial treatments that add to people's suffering through psychosocial practices could be considered an act of violence in terms of social inequalities.[11] Furthermore, analysis of intersected social categories in the health field demonstrates the importance of diagnosis as a social marker of difference. In fact, the social construction of normality concerning mental health and, consequently, the choice of psychosocial treatments is based on the diagnosis of patients. In this sense, the categorization resulting from the diagnosis further complicates their experience, especially when this experience is viewed from a biomedical standpoint without considering the impact of social dimensions.[12]

Psychosocial Care Centers have been mainly studied with respect to the psychosocial treatments made available (medication, group therapy, and other activities),[13,14] but some studies have also focused on the participation of patients in terms of their autonomy[15] and in relation to the anti-asylum discourse produced.[16]

However, even though research on mental health institutions has advanced on several fronts, numerous questions remain unanswered. Many aspects of the practical functioning of these spaces and the possible effects of this new institutional framework still need to be researched in greater detail, especially with regard to the role of intersected social categories in social interactions.

Theoretical framework

Intersectionality theory takes into consideration the intersection of social categories (e.g., race, gender, and social class, etc.), which can lead to intersected oppressions and intersected privileges. In fact, this theory analyzes how intersecting power relations can influence social relations.[5-6] Social categories, which are socially constructed, are understood to be interdependent by intersectionality theory and they shape each other in several possible combinations, as in a crossroad, resulting in intersecting oppressions and privileges.[5] Thus, intersectionality allows the analysis of how social categories position people differently in the world.[5-6] However, it should be noted that individuals respond to oppressions in different ways, including by resistance.[17]

The term "intersectionality" was coined by Kimberlé Crenshaw, a scholar who identified herself as a black feminist. This theory was born from the need to understand the specific oppressions experienced by black women, that is, the specificity of the unequal reality experienced by black women, a reality different from that of black men and of white women. It involves oppression at the intersection of more than one social category (race and gender).[5] Although nowadays intersectionality theory is used to understand people's reality according to differ-

ent combinations of intersections of social categories, the importance of race in this analysis should be noted considering the whitewashing of this theory in some recent research.[18]

The following characteristics of intersectionality theory should be taken in consideration: 1) it aims to examine oppression at the individual (microsocial) and structural (macrosocial) levels; 2) in addition to being a theory, it is also focused on praxis and the advancement of social justice; 3) it understands identities as being multiple, interdependent and mutually constitutive, that is, one type of oppression is neither hierarchical nor simply added to another; 4) it can be defined in different ways and is always evolving; 5) it offers a critical analysis of the connection between multiple social identities and power structures.[5,6,19] Thus, the identity of an individual needs to be considered in an intersectional way on three different levels: the individual (linked to social interactions), the community (linked to institutions) and public policies (linked to social structures).[20]

The role of social categories, according to Erving Goffman's theoretical perspective on social interactions, must also be taken into consideration. According to Goffman, social categories (e.g., gender, social class, etc.) are socially situated[21] and expectations exist, in terms of ceremonial rules (conduct, dress, attitude), as part of deference and demeanor in the interaction rituals.[22] In order to respond to expectations associated with social roles, markers of belonging to specific categories can be employed, that is, the display of social categories (e.g., gender or social class, etc.). In fact, responding to social expectations in interactions is necessary to build trust among individuals, that is, the alignment of the presentation of the self of an individual and the expectations of society. In this sense, the hyper-ritualization of social categories can be used to reinforce an expectation. For example, a psychiatrist should behave and look like a psychiatrist (e.g., clothing, etc.) in order to be recognized in the intended social role by society.[23]

The presentation of the self also relates to the existence of stigma (which can be known or visible or can be unknown or non-visible), which needs to be managed in social interactions. In the case of unknown or non-visible stigma (e.g. sexuality), the information in social interactions must be managed and, in the case of known or visible stigma (e.g. gender), the tension in social interactions must also be managed.[24] Specifically, the concept of intersectional stigma highlights the convergence of multiple stigmatized identities relating to an individual or a group to understand its effects. Considering that the different types of stigma are interdependent, the intersection of stigmas can generate inequalities also in an intersected manner.[7] In fact, when considering multi-stigmatized individuals or groups, intersectional invisibility needs to be examined because cases of multiple stigmas have different effects than those in which only one type of stigma is involved.[8] However, stigmatized individuals and groups can resist and implement strategies to react to the experience of (intersectional) stigma.[7]

Material and methods

This qualitative research used an ethnographic methodology[3] and, more specifically, the technique of participant observation to collect data.[4] A field notebook was used throughout the research to record the data collected.[25] Consistent with the technique chosen, the analysis of the data focused specifically on the definition of the situation by the social actors involved in social interactions within the institution.[26]

Ethnography is a type of qualitative research which involves immersion in a given community to understand its members' social interactions. The goal is to provide descriptions with sufficient

information to enable those outside the community to fully understand the reality being studied.[27] The technique of participant observation consists of following as closely and systematically as possible the daily context of the social situation studied. It involves following the daily activities of the group in question without relying on previously standardized parameters, as is expected in the context of ethnographic research.[3] The observer must pay particular attention to issues considered by the group or institution studied as being conflicts or problems.[28] In fact, it is important to observe the norms of decorum, that is, the way that the social actors behave when they are on "stage", when they are aware that other people are watching them, even if they are not involved in conversation with other people.[26] As for my posture in the research field during the observations of the social interactions, I tried to be discreet regarding verbal and non-verbal language (e.g., to talk using a low tone of voice, to smile and observe without starting a conversation, but when openings arose, to listen more than talk etc.).

The institution researched treats exclusively adults and is located in the city of São Paulo in Brazil. It currently receives about 300 patients, approximately 50 during the daytime, because the frequency of presence of each individual varies according to the indication of treatment for each case. The unit studied is staffed by about 50 professionals of various specialties (e.g., psychiatrist, nurses, occupational therapists, etc.), with around 15 technicians per shift. In addition, patients may be present in the institution at night and on weekends when the staff deems it necessary. There-fore, the greatest number of patients is concentrated during the daytime from Monday to Fri-day and, consequently, also the number of staff members present during this period is larger. Finally, it should be noted that the researcher spent around 6 hours per week for two years in the institution (from 2014 to 2016).

In terms of research ethics, the study was approved by the Ministry of Health of the government of Brazil. To guarantee the anonymity of participants, only the first letter of their first name is presented when sharing excerpts of the field notebook in the section on the results of the research. Furthermore, since it is an ethnographic study, the researcher did not apply a sociodemographic questionnaire to learn about individuals' self-identification, but their different attributes became evident through self-identification and the categorizations established during social interactions in the institution (e.g., the use of certain personal pronouns indicating gender identification).

Moreover, as indicated in the process of collection and analysis of research data based on an interpretative-critical perspective, the position of the researcher was taken into account. It is important to bear in mind that researchers have their own ideologies and make interpretations when carrying out research.[29] Thus, to conduct an exercise in self-reflexivity, researchers must identify the impact of their privileges and oppressions on the construction of their research. This exercise includes an examination of all stages of the research (from research design to dissemination of the results).[17,30] When conducting research, it is essential to think and act ethically about the following subjects: Who can study whom, and how? Who profits from the research? Are the results of the research considered valid?[29] Thus, as an exercise of self-reflexivity, it is relevant to note that I am a Brazilian woman who comes from a low socio-economic and educational background. In addition, I have never worked in or received treatment at a Psychosocial Care Center, but a member of my family received treatment for a period at a Psychosocial Care Center.

Concerning the analysis of the observations, the definition of the situation was taken into consideration, that is, the analysis of the understanding of social interactions by participating

social actors. According to Goffman,[26] social actors have a facade, that is, expressive equipment used intentionally or unintentionally during their performance (e.g., social position, gender, etc.) and this facade aims to define the situation for observers of the performance. In general, social actors who are part of a social situation seek to define that situation in order to know how to act and react. This definition tends to be provided by society and is not created by social actors, although they can negotiate certain aspects. Social actors in each other's presence look for signals that offer information about the other individual and, at the same time, seek to manage the signals they give, consciously or unconsciously, regarding their performance (impression management).[26] Thus, the definition of the situation is an analysis of how participants try to understand what is happening during social interactions and how they adapt their behaviors, based on the signals sent and received by those present.[26]

Results

In terms of the results of this research, it should first be emphasized that the categorization (and consequently self-identification) resulting from the mental health diagnosis was the main category present in all the social interactions observed. This makes sense considering that the analysis was performed in a psychosocial care center. It should also be noted that the patients observed in this institution refer to this categorization (and consequently self-identification) by different terms, such as: "crazy", "mentally ill", "sick", among others. However, they also resignify these terms, that is, they assign new meanings to terms considered as being socially pejorative. For example, they would sometimes refer to songs that talk about mental health (and mental illness), directly or indirectly, and then refer to the terms mentioned, notably "crazy". In these songs, being "crazy" is presented as a positive trait, for example, as being open-minded. In fact, they emphasize how there had to be something "wrong" with those who were not "crazy". Thus, they use art to process their feelings and their categorization and self-identification in relation to the subject.

In the interpretation of the data, apart from the mental health diagnosis, four social categories (gender, age, social class, and sexuality) were considered in an intersectional way. However, some social categories seemed more prominent than others in specific situations. In addition, it needs to be emphasized that race was not a major element during the social interactions observed, probably because both staff members and patients seemed to share a racial background of mixed ethnicity. The researcher also noticed, through inductive analysis, two relevant themes connected to these social categories: the existence of power relations (between staff members and patients) and the fact that social actors seemed to be aware of their oppressions, but not of their privileges, nor of the oppressions of others. Therefore, the presentation of the data is divided in three topics: 1) power relations between staff members and patients; 2) intersection of the social categories of gender, age, sexuality, and social class; 3) unawareness of the oppressions of others.

Power relations between staff members and patients

During the social interactions observed in the institution, staff members did not often seem to take patients seriously. For example: "B asked her psychiatrist: 'Help me, my head is empty. Is there a medicine for an empty head?' He replied: 'No, it's just that you think a lot, your head is resting'. She then left without saying anything." (Field notebook notes) Thus, this example shows how a patient asked for assistance, did not get the expected help, and left in silence. It should be noted that B is a female patient from a low social economic background and that

her doctor is a male psychiatrist from a higher socioeconomic background. Thus, through an intersectional lens, one can perceive the stereotype of the male doctor suggesting that women "think a lot" and how he disregarded her experience, which can often happen to mental health patients as well as to patients from low socioeconomic backgrounds. Moreover, some patients seemed to get excessively attached to staff members in their social relationship: "During the meeting, B told A [a staff member] that she loves her, and A responded by telling her to pay attention to the meeting." (Field notebook notes) Once again, the response from the staff member was probably not what the patient expected, though it was understandable considering the patient-staff relationship.

Patients also seemed to be considered untrustworthy in the opinion of staff members. For example, a patient shares the distrust she encountered when she asked some staff members for adhesive tape to help me (the researcher) hang papers on a mural in the institution: "After a while she came back with the tape but complaining. She said they questioned her several times before giving her the tape." (Field notebook notes) It is noticeable then how a simple item such as a roll of adhesive tape is cause for suspicion.

Finally, the posture of staff members seemed to influence their social interactions with patients because of existing power relations. Apart from the examples already mentioned which clearly show a boundary between patients and staff members in terms of hierarchical power, the attention of the researcher was attracted to the posture of staff members when talking to patients during meetings in the institution: "The body posture (erect), the tone of voice (firm, loud), and the choice of words (vocabulary indicating higher education) seem to influence social interactions. In fact, after receiving suggestions from the staff, patients changed their minds and agreed with them." (Field notebook notes) In this case, it is noticeable how, through "suggestions", the staff members managed to steer the meeting in the direction that they believed it should go, since patients followed their "suggestions".

Intersection of the social categories of gender, age, sexuality, and social class

The social categories observed (gender, age, sexuality, and social class) intersected, but some of them occupy more space than others during certain social interactions. In terms of gender, a noticeable difference in treatment and behavior occurred between male and female patients. In fact, the behavior of male patients tended to be judged as violent. For example: "F described his previous stay in an 'asylum'. He said that when he got angry, he threw a tray of food at the wall and, because of that, he was put in a straitjacket." (Field notebook notes) In contrast, female patients were expected to control themselves and tended not to be considered as violent by staff members. For example: "She [a staff member] said that R 'screams and swears', but is not physically violent, she said she 'softens when people get close'." (Field notebook notes) In this case, it is important to emphasize the use of the verb "soften" to refer to this patient's behavior. This example shows how stereotypes of gender are reproduced (e.g. men are violent, and women are "soft"), but also how gender intersects with the social category of mental health disability since these gender stereotypes influence how staff members treat the patients.

Gender also seemed to play a role in romantic or sexual advances between patients and from patients directed to staff members, that is, some patients seemed to desire to become closer to some staff members that they found attractive. One example of the dynamics between patients is a young woman (the issue of age often seemed to mix with the issue of gender)

who frequently received invitations (or even advances) from male peers (including some who were much older than her). For example: "He asked B if he could kiss her (he looked much older than her), she said no and told him to leave." (Field notebook notes) Continuing the same interaction, he looked at me (the researcher) and said: "she is beautiful and intelligent, but look at her clothes, they are all dirty, she always wears the same clothes." (Field notebook notes) In the case of this excerpt, the reference to her clothes stands out and can be connected to the issue of social class, in addition to social expectations about how women should dress. Moreover, since this interaction happened inside a psychosocial institution (the individuals in question are patients who receive daily treatment in the institution), B has to repeatedly manage this situation. This example shows how the social categories of gender, age, social class, and mental health disability intersect. The patient in question needs to manage all of them at the same time.

In terms of sexuality, the sexuality of some patients and staff members seemed to be questioned because it did not meet the expectation of heteronormativity. Particularly noteworthy is the case of the patient who, when his requests were denied by a psychiatrist, used to make comments that called into question the psychiatrist's sexuality, as if this were an offense. For example, this psychiatrist once said to a co-worker: "I can't take this anymore. When he is dissatisfied with my answer, he makes comments about my sexuality." (Field notebook notes). This case demonstrates how two different social categories intersect in terms of oppressions and privileges. On one hand, the psychiatrist is oppressed in terms of his perceived sexuality, but is privileged in terms of his social role as a psychiatrist and his "normal" status concerning mental health standards in society. On the other hand, the patient is oppressed in terms of the social category of mental health disability, but is privileged in terms of sexuality (heteronormativity), which he seems to use as a bargaining tool during conflicts of a hierarchical nature (doctor – patient).

Finally, in terms of social class, the Psychosocial Care Center is a public and free organization. Therefore, in general, patients seem (e.g., the way they speak, dress, and behave) to come from low or middle social classes. For example, some written testimonies shared by some patients about activities that took place in the institution showed basic errors in writing: "There are a lot of errors in their texts. It is also interesting to notice that they identified themselves even with their ID number, although identification was not mandatory." (Field notebook notes) The following example is also worth mentioning on this subject: "J was quite agitated. He passed around a petition and wanted to sign it, but just made a scribble since he doesn't know how to write. He seemed irritated (slapping the arms or legs of the people around him)." (Field notebook notes) However, some patients seemed to come from better financial conditions, but their families, according to them, did not want to "spend money on them". (Field notebook notes). This case demonstrates how social class intersects with the social category of mental health disability, since as patients they have to accept the decisions made by family members concerning where their treatment would take place and how much money would be spent on it. Moreover, in the case of J, these two social categories intersect specifically with his educational background because he demonstrated his frustration (apparently related to his inability to write) in a way that was not acceptable to society (slapping people's arms and legs).

Unawareness of other people's oppressions

Finally, it is worth noting that patients seemed capable of noticing their own oppressions (they mainly shared with the researcher the issue of mental health), but not their privileges, that is,

the oppressions of other people around them in that scenario. Thus, they did not seem capable of showing sensitivity to experiences that they did not experience themselves. For example: "a patient said that he doesn't like being called 'crazy', that there is no longer any stigma towards black people and homosexuals, so there shouldn't be any towards 'mentally ill people' either". (Field notebook notes) This excerpt shows how they bring up questions related to their shared oppression as mental health patients and to their demands for social justice (elimination of stigmatization), but fail to notice other (intersected) oppressions in society, such as racism, sexism, and homophobia.

Discussion and conclusion

The data show the presence of intersected social categories that affect the social interactions between the social actors (staff members and patients) in the Psychosocial Care Center researched. Considering that the research took place in a psychosocial care center, the categorization of mental health disability spanned all other social categories. In fact, other studies have also emphasized how mental health diagnosis is an important social marker of difference.[12]

In addition to mental health diagnosis, the data showed the importance of gender, age, social class, and sexuality in daily life in this institution. However, race was not a central element of the analysis, since it was not emphasized by the participants. This can be explained by the fact that the social actors in the case seemed to share a racial background of mixed ethnicity, thus leveling the playing field in terms of racial social relations. Other studies have also shown how some social categories can be more present than others[9] and specifically race is a social category that is not always considered when analyzing social interactions in this specific type of institution.[10]

Intersectionality theory was useful in the analysis of the data because this theory takes into consideration the intersection of social categories, that is, the intersection of oppressions and privileges. Thus, it also takes into account how power relations develop in an intersecting way.[5,6] The data also showed how the social position inside the institution affects social interactions, that is, staff members make decisions concerning patients. In fact, the focus of this type of institution on autonomy and participation does not prevent patients from finding themselves in a position of inferiority in relation to staff members, even concerning their psychosocial treatment.[15] In addition, the anti-asylum discourse produced by the Brazilian government has also shown its limitations when confronted with the reality of Psychosocial Care Centers.[16] In fact, the superiority of certain "bodies" is only possible due to the categorization of patients in terms of their mental health status and the judgment made by society concerning their so-called "abnormality" and its consequences.[31]

Mental health diagnoses influence power relations between staff members and patients in the institution, but other social categories also play a part in social interactions. All social actors involved in social interactions must deal with their own intersectional oppressions and privileges. For example, a young female patient has to deal with the advances of (older) male patients or a patient uses his impression about his psychiatrist's sexuality to try and create a social situation of equality during negotiations about his psychiatric treatment. In fact, it is possible to notice an element of resistance[17] and how their identity is multiple and, therefore, the stigma experienced is also intersectional.[7,8] However, in general, their apparent difficulty in noticing other people's oppressions, only noticing their own, seemed to indicate a unawareness of their own privileges. It should also be noted how the intersected social categories are present at different levels of patients' experience in the institution. This research focused

mainly on the social interactions inside the institution, but the patients also interact with individuals outside the institution, especially with their families.[20]

To be more specific with regard to the role of social categories in social interactions,[21-22] the results demonstrate that ceremonial rules (behavior) are not always respected. In fact, in terms of deference and demeanor, how participants make strategic use of their intersected oppressions and privileges is remarkable. An example of such behavior is the patient who felt comfortable using a psychiatrist's supposed sexuality identity "against" him as a form of resistance to the actions of the psychiatrist, that is, when he was dissatisfied with decisions made concerning his treatment and his self. In fact, since expectations exist in terms of social categories (e.g., a psychiatrist needs to behave and look like a psychiatrist according to societal expectations), when they are not met, the individual's social role can be called into question.[23] However, this expectation is considered not only through display in the form of diplomas, clothing, etc., but also in terms of social categories, that is, doctors can have their role questioned if their social categories do not respond to certain expectations (e.g., not being male, not being white, not being cisgender, not being heterosexual, etc.).

More precisely, in terms of stigma and performance during social interactions, the results indicated that participants identified mental health disability, gender, age, social class, and sexuality as social categories, that is, these were known or visible stigmas that influenced how stigmatized individuals were treated and treated one another during social interactions.[24] It is important to highlight that the mental health diagnosis is an integral part of the intersection of the social categories observed, that is, mental health disability is a social category that added to the patient's experiences in terms of oppression.[5,6] Considering that the analysis concerns a mental health institution, this social category is the main element influencing social interactions in the institution.[4] It should also be noted that other stigmas may have been present in the social interactions in question but were not highlighted by the participants (e.g. race).

In addition, to further explore the analysis in terms of how intersected social categories produce the specific social interactions presented in the results, it is important to notice the possible existence of intersected oppressions or intersected privileges in individuals' experiences[5,6] and even a mix of both, which can be used strategically by the individuals to deal with agency and systemic barriers.[32] For instance, the results showed how one specific patient has to deal with being at the same time a young woman of lower social class or how an older male patient can still exert his power in that space due to how patriarchy works. Furthermore, the importance of considering the influence of psychiatric reform in Brazil[16] and the specificities of the treatment model practiced in this type of institution must also be taken into consideration.[15] To expand the analysis of the intersection between the institutional categories and hierarchies (staff and patients) and the other social categories, one can cite the example of how a patient "used" a psychiatrist supposed sexuality against him, which might only be possible because of how this institution, which is not a psychiatric hospital, not only allows but also expects patient participation. This situation can result in more conflicts in social interactions since the established hierarchy in this institution can be considered more fluid.

Lastly, recent research has shown how different social categories can play a role in the daily life of the Psychosocial Care Center for both patients and staff members.[10–12] However, this research contributes to the existing scholarship on mental health by emphasizing existing power relations, not only due to the mental health diagnosis of patients but also as a result of the intersection with other social categories. This study also contributes to the existing

scientific literature on the subject by emphasizing how patients seemed to notice only their own oppressions, but not their privileges, that is, not the oppressions of others with whom they interact daily.

In future research, it would be interesting to compare this data with those of other units of this same type of institution or of different types of institutions. Furthermore, in terms of recommendations, adequate importance should be given to decolonial thinking when considering not only different minority groups in society,[33] but also mental health institutions and practices to counter social and health inequalities in society.[11]

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Presence of Agger Nasi cells and their relationship with frontal recess thickness: a retrospective study in a Brazilian population

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Abstract

Objective: The aim of this study was to carry out an epidemiological survey of the presence of Agger Nasi (AN) cells, using cone beam computed tomography (CBCT) images, in a Brazilian population in the region of Maringá - Paraná. Materials and Methods: The tomographic analyzes verified the thickness of the frontal beak (FB), anteroposterior length of the frontal isthmus, anteroposterior length of the FR and side-to-side, anteroposterior and vertical (cranio-caudal) diameter of the AN cells. Statistical analyzes were performed using the statistical program Jamovi (V2.5.5.0). For correlation analysis between the variables, the Spearman test was used. The study indicates the presence of AN cells in 100% of the individuals analyzed, being present bilaterally. Results: There was no significant correlation between FB and the AN cell. Significant positive correlations were found relating Right Agger Nasi Cell (ANC-R) and Left Agger Nasi Cell (ANC-L) with Front Recess (FR) and Frontal Sinus (FS). Conclusion: Anatomical knowledge on the part of professionals is of fundamental importance for a surgery to access the FS in a precise and uncomplicated way.

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Introduction

The osteomeatal complex is defined as a system whose function is to drain and ventilate the maxillary sinuses, frontal sinuses (FS) and anterior ethmoid cells. All those structures that surround the osteomeatal complex, such as cells, ostia, cracks, recesses or cavities, are susceptible to pathological processes.[1]

The frontal recess (FR) has been a highlight of interest of many professionals who work in the study and treatment of pathologies in the osteomeatal complex. According to the description of Stammberger, Jacob and Friedman,[1-3] the transition from the FS to the FR, in a tomographic image in sagittal reconstruction, has the shape of an "hourglass". The FS pavement undergoes an inferior narrowing towards the FS ostium (between the nasofrontal beak and the anterior skull base), which corresponds to the “hourglass” waist.[2] Just below the SF ostium, the FR appears, which widens inferiorly, taking the form of an inverted funnel.[4] The FR is composed of

ethmoid cells, which surround it.[5] One of the structures present are the Agger Nasi (AN) cells that are formed when the lateral nasal wall of this cell is pneumatized.

The AN cell is located in the upper part of the first ethmoturbinate plate, which may appear as a tuberosity or a crest close to the middle nasal concha, as shown in the study by Stammnerger[1] Its pneumatization can occur at different levels, and it is possible that the cell reaches laterally to the lacrimal fossa, causing a narrowing in the FR, causing a change in its anatomy physiology. This process may occur due to its location, which borders five different bones of the skull: the lacrimal, the maxillary, the ethmoid, the frontal and the nasal.[1] The AN cell is an air chamber commonly found in anatomy studies, but its prevalence varies according to the study performed.

Due to the advent of endoscopic surgeries in the sinuses, computed tomography (CT) plays a fundamental role in the evaluation of contemporary anatomy, diagnosis and operative plan in surgeries in this region.[6] FR and FS surgery are always a challenge. It is postulated that a common cause for re-surgery is the incomplete removal of cells in this area. This often results in a blockage of the drainage pathway, with persistent inflammation and clinical symptoms. In addition, there are important anatomical structures close to the sinuses, such as the orbit, olfactory region and skull, which during surgical procedures, are at risk of being injured. Thus, an accurate and detailed knowledge of the anatomy is essential for any surgical procedure.[7]

One of the ways to obtain access to the FS through the endonasal route is through FR. However, this can become difficult due to the complex and variable anatomy of this region.[7,8] With CT performed preoperatively, this complexity has been reduced and the identification of anatomical variations in the FR has been facilitated. [6-9]

For these reasons, it is evident that the documentation of the FR morphology with its anatomical variations and their relationships with the FS morphology is fundamental for a surgery to access the SF with precision and without complications. Therefore, the objective of this study was to carry out an epidemiological survey regarding the presence of Agger Nasi cells, using cone beam computed tomography (CBCT) images, in a Brazilian population in the region of Maringá - Paraná.

Methodology

This retrospective and observational study was evaluated and approved by the Standing Committee on Ethics in Research Involving Human Beings of the State University of Maringá (UEM) (CAAE: 33176620.0.0000.0104) and was carried out in accordance with the recommendations of the STROBE initiative (Strengthening the Reporting of Observational Studies in Epidemiology).[10]

CBCT images of Brazilian patients of both sexes were used, who were referred to the Laboratory of Images in Clinical Research (LIPC), of the Health Technology Center (CTS) of the Research Support Center Complex (COMCAP), located at the Department of Dentistry at UEM. The CBCT exams were performed between January 2014 and December 2019 by the same specialist in dental radiology and imaging and they are all archived. 650 CBCT images were analyzed and 388 CT scans were selected. Of these, 266 were female and 122 were male. The study included CBCT scans performed for different purposes and dental specialties, of individuals over 18 years old, who completely contained the regions of interest and with the same image acquisition protocol. Images of individuals with congenital or acquired diseases, craniofacial deformities and with a history of trauma or surgery in the investigated region were excluded.

All images were initiated in the i-Cat Next Generation® equipment (Imaging Sciences International, Hatfield, PA, USA), operated at 120 kVp and 3-8 mA, with an isometric voxel of 0.300 mm and FOV (Field of view) de 17 X 23 cm. The images were protected with the scanner's own software (Xoran version 3.1.62; Xoran Technologies, Ann Arbor, MI, USA). Anatomical identification was supported by multiplanar reconstructions (MPRs) in all three planes and rendering of three-dimensional volumes. Images were evaluated in a quiet room with dimmed lighting.

All analyzes and measurements were performed by two independent radiologists (with more than 5 years of CBCT experience), blinded to gender details to minimize interpretation variation. The evaluators went through a calibration and training process. In this training, a theoretical discussion of all the criteria used in the evaluation was carried out. In this project, initial efforts focused on developing standardized configurations for the structures under study. Then, a practical training was also carried out, in which the examiners evaluated the same exams. After that, discrepancies between the results were tolerated, seeking consensus on the rules and criteria for evaluating the images. Finally, the medication itself was administered. To avoid eyestrain, only 10 images/day were evaluated. These same examiners performed the analyzes twice, with an interval of 15 days between estimates, and intra- and inter-examiner agreement was calculated using the Intraclass Correlation Coefficient (ICC).

In the tomographic analyzes, the following structures were verified and measured:

Greater side-to-side, anteroposterior and vertical (cranio-caudal) diameter of AN cells;

Larger diameter of the height, width and length of the FS;

Thickness of the nasofrontal beak;

Greater anteroposterior length of the frontal isthmus;

Greater anteroposterior length of the FR.

To facilitate this project, definitions were developed, based on traditional descriptions in contemporary anatomy literature, as shown in Table 1.

Table 1. Definition standard and criteria used in image visualization

Assessed structure	Definition
AN cells	• The AN is the most constant and anterior cell of the ethmoid bone.[3,4,11] • It is located below the nasofrontal beak and is identified in coronal reconstructions ahead of the anterior border of the vertical insertion of the middle turbinate.[11,12] • It relates frontally and inferiorly to the upper maxillary bone, and can be easily seen in parasagittal sections.[3,13] • It forms the anterior and inferior wall of the FR and its variable rate of pneumatization has an impact on the size of the FS ostium and the shape of the FR.[2,13–15] • When small, it is associated with a prominent nasofrontal beak which, when extending posteriorly, conditions a narrowing of the FS ostium. When larger, it is associated with a small nasofrontal beak and, consequently, with a wider FS ostium, but with the potential for monitoring the FR in its lower portion, by moving it posteriorly and laterally with the lacrimal fossa and the beginning of the FR lacrimal-nasal canal and supero-laterally with the bones of the nose.[3,13]

Table 1. Definition standard and criteria used in image visualization (cont.)

Assessed structure	Definition
FS	• FSs are usually paired, asymmetrical, separated by a central intersinus septum and with different rates of pneumatization.[16] • In adults, the average dimensions are 24.3 mm in height, 29 mm in width and 20.5 mm in depth. Approximately 10 to 12% of normal adults may have rudimentary FS or even a complete lack of pneumatization of the frontal bone on one side. Around 4% of the asymptomatic population may have bilateral FS agenesis.[16] • Gaafar et al., 2001 reported that the mean diameter of the FS ostium was 5.6 mm, ranging from 4 to 7 mm; • The frontal sinus drainage pathway is composed of three different regions and generally presents an “hourglass” configuration. The most superior part of the “hourglass” is represented by the FS itself, while the narrowest part corresponds to the ostium of this sinus. The lowest part of the “hourglass” is formed by the FR, a space dependent on the variable development of the anterior pneumatized cells.[1–3,16]
FR	• The FR is a complex space roughly shaped like an funnel or inverted cone with the apex at the FS ostium.[3,4] • It is bounded medially by the middle turbinate, laterally by the lamina papyracea, anteriorly by the frontal apophysis of the upper jaw and posteriorly by the ethmoidal bulla.[17] • This space can be pneumatized by various anterior ethmoid cells, including the AN cell, frontal cells, supraorbital ethmoidal cells, suprabullar cells, frontal bullous cells, interfrontal sinus septal cells, and recessus terminalis.[3,18] • In adults, the width, depth and limits of the FR are dependent on the anterior ethmoid cells and the embryonic pattern of neighboring bone lamellae.[4,18] • For the study of the anatomy of the RF, only the coronal images, CT standard, do not provide enough information for the reliable identification of the cells of the FR.[18] • The sagittal circumference provides an invaluable contribution to the assessment of RF.[13]
Nasofrontal beak	• The FB is the bone thickening of the midline, extension of the nasal process of the frontal bone. The FB is considered the anterior limit of the FS, the FS ostium and the FR. It is the posterior bone protrusion at the lowest part of the anterior table of the FS seen on parasagittal CT. Sagittal CT accurately identifies the dimensions of the FS and FR ostium and clearly shows the distance between the FB and the point where the posterior FS plate attaches to the anterior skull base.[19]
Frontal isthmus	• The anteroposterior length of the frontal isthmus is defined as the shortest length between the most prominent portion of the nasofrontal beak and the posterior table of the FS.[20] • High-resolution reconstructed parasagittal CT images clearly show the length between the nasofrontal beak and the junction of the posterior FS table with the anterior skull base.[2] • They show the AN cell size and the anteroposterior length of the frontal and RF isthmus, which is not detected on conventional paranasal sinus standard CT.[20]

Source: The authors (2023).

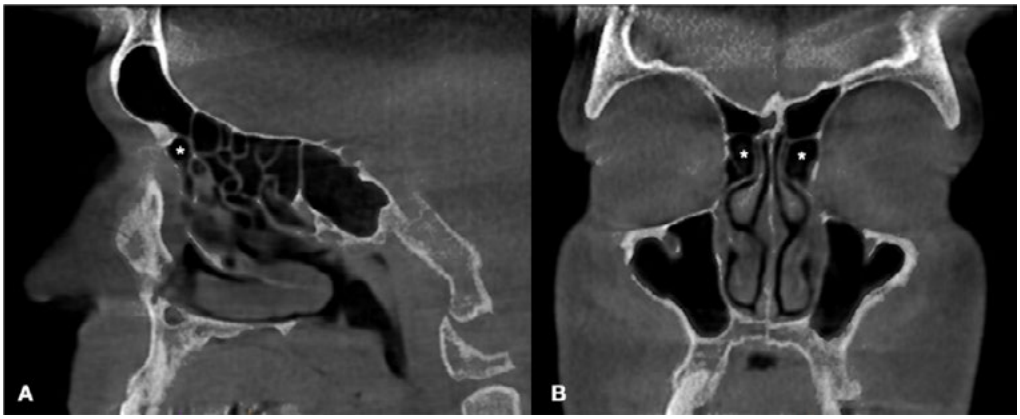

Figure 1. A) Left parasagittal section showing Agger Nasi (indicated by *); B) Coronal section showing bilateral Agger Nasi (indicated by *)

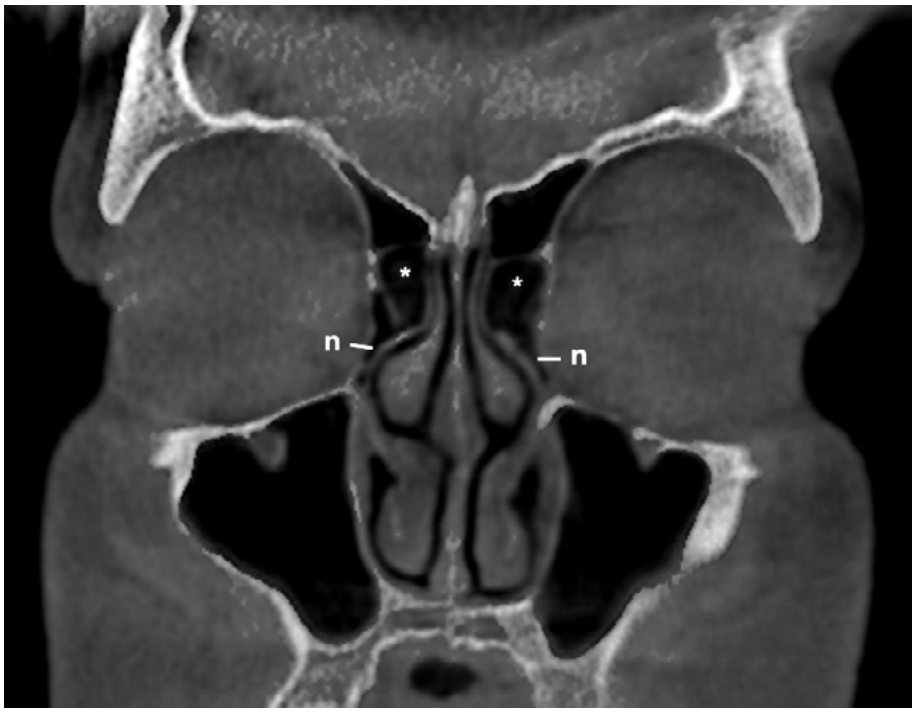

Figure 2. Coronal section shows Agger Nasi (*) above the upper end of the Nasolacrimal Duct

For the identification of the FR, we initially used sagittal reconstructions, in which identification is easier. In the software, we were able to visualize, at the same time, the axial, coronal and sagittal reconstructions on the same screen and, by moving the cursor marking of the program for measuring structures on the image in a certain type of section, the cursor automatically moved in the two other cuts simultaneously. Thus, we were able to identify and measure the dimensions of the structures under study more precisely. In the same way, we located the AN cell and measured it anteroposteriorly, side-to-side, and vertically (craniocaudal).

We considered the AN cells, the air cells located within the frontal process of the maxillary bone, in front of and/or above the anterior end of the middle turbinate.

FB thickness and anterior-posterior (AP) length of the frontal and FR isthmus were measured in the same parasagittal plane where the FB was most prominent. The AP length of the frontal isthmus was defined as the shortest length between the most prominent portion of the FB and the posterior board of the FS. The AP length of the FR was defined as the length between the most prominent portion of the FB and the superior insertion of the ethmoidal bulla lamella.

Statistical analysis

For statistical analysis, data were tabulated in a single spreadsheet and the statistical program Jamovi (V2.5.5.0) was used. First, a descriptive analysis of the collected data was carried out. Regarding the assumption of normality of the variables BF thickness, frontal isthmus length, FR, FS height, FS width, FS length, lateral diameter of AN cells, anteroposterior diameter of AN cells and vertical diameter of cells of AN, the Shapiro-Wilk test was used. For correlation analysis between the variables, the Spearman test was used. Inter-examiner agreement was verified using the CCI. For all analyses, a confidence interval of 95% and a significance level of 5% ($p < 0.05$) were considered.

Results

Through the ICC, it was observed that the inter-examiner and intra-examiner agreement was satisfied, noting that the coefficients varied from 0.89 to 0.98,[21] indicating excellent reliability and reproducibility.

Among the 388 patients evaluated, 68.38% (n=266) were female and 31.62% (n=122) were male. The mean age of the sample was 37.51 (standard deviation ±14.58); Maximum age 86 and minimum age 18. Right (CAN-D) and left (CAN-E) AN cells were present simultaneously in all evaluated patients, regardless of gender. According to the findings, AN cells in males were found in 122 cases, and in females in 266 cases.

Table 01 demonstrates the correlation between the FS volume and the CAN-D and CAN-E volume, so that the greater the volume of the FS, the greater the volume of the CAN-D (p=0.002) and CAN-E (p <0.001). It is still possible to observe a moderate to strong correlation between the volume of CAN-D and CAN-E (p<0.001).

Table 2. Correlation between FS volume and CAN-D and CAN-E volume

		FS Volume	CAN-D Volume	CAN-E Volume
FS Volume	Rho de Spearman	-		
	p-valor	-		
CAN-D Volume	Rho de Spearman	0.158**	-	
	p-valor	0.002	-	
CAN-E Volume	Rho de Spearman	0.201***	0.663***	-
	p-valor	<.001	<0.001	-

Nota. * p < .05, ** p < .01, *** p < .001

Table 02 demonstrates the correlation between the mean FB thickness, the FS volume and the volume of the CAN-D and CAN-E, showing that the mean FB thickness does not present a significant correlation with any of the other variables. There is a moderate positive correlation between FS volume and CAN-D volume. A weak positive correlation was also found between FS volume and CAN-E volume. Positive correlations show a directly proportional relationship between the analyzed structures.

Table 3. Correlation between FB, FS and CAN-D and CAN-E volume

		Average thickness FB (frontal beak)	FS Volume	CAN-D Volume	CAN-E Volume
Average thickness FB (frontal beak)	Rho de Spearman	-			
	p-valor	-			
FS Volume	Rho de Spearman	0.241***	-		
	p-valor	> .001	-		
CAN-D Volume	Rho de Spearman	0.112*	0.158*		
	p-valor	0.027	0.002		
CAN-E Volume	Rho de Spearman	0.092	0.201***	0.663***	-
	p-valor	0.070	<0.001	<0.001	-

Nota. * p < .05, ** p < .01, *** p < .001

Table 03 demonstrates the correlations between FR length, FS volume and CAN-D and CAN-E volume. The FR length presents positive but weak correlations with the CAN-D volume (p=0.014) and the CAN-E volume (p=0.002). CAN-D volume is positively correlated with FR length, while CAN-E volume is even more strongly correlated with FR length. However, the FS did not show significant correlations with any of the variables.

Table 4. Correlation between FR length, FS volume and CAN-D and CAN-E volume.

		FR length	FS Volume	CAN-D Volume	CAN-E Volume
FR length	Rho de Spearman	-	0.260***	0.124*	0.153**
	p-valor	-	<.001	0.014	0.002
FS Volume	Rho de Spearman		-		
	p-valor		-		
CAN-D Volume	Rho de Spearman		0.158**	-	
	p-valor		0.002	-	
CAN-E Volume	Rho de Spearman		0.201***	0.663***	-
	p-valor		<.001	<.001	-

Nota. * p < .05, ** p < .01, *** p < .001

Discussion

The nasofrontal communication is a mucosa-lined canal, rather than a true ductal structure, which connects the FS with the FR of the middle nasal meatus and through which ventilation and drainage occur. The course, width, and depth of this pathway in the adult are determined by the pattern of embryological pneumatization of anterior ethmoid air cells and the develop-

ment of surrounding bony plates. Generally, the direct development of the FS from the embryological FR is associated with minimal pneumatization of the anterior ethmoid cells and wider and less tortuous communication with the middle nasal meatus,[2] but the anteroposterior dimension of the FR can be narrowed by pneumatization of the AN cell. In almost 100% of the ethmoid sinuses, there is some degree of pneumatization of the AN cells; However, the volume and pattern of development of such cells varies substantially.[2] Thus, in order to use the most appropriate approach in cases of removal of FR and FS lesions, a thorough understanding of the anatomical relationship between AN and FR and FS cells is essential.

Some anatomical variations, such as the presence of the AN cell, can induce obstruction in the drainage pathways of the maxillary and frontal sinuses. Anatomical variations of the paranasal sinuses must be evaluated to prevent serious and fatal complications secondary to sinus surgery. In addition, the identification of anatomical and morphological relationships is essential for the surgeon when approaching the skull base to avoid the risk of iatrogenic injuries in these thinner and more vulnerable structures.[22]

Determining and describing the precise anatomy, anatomical variations and pathology depends mainly on advanced imaging methods, as well as on the professional's experience and skills.[23] Many imaging modalities including radiographs, CT and CBCT are used for the evaluation of the detailed anatomy, pathology and variations of the paranasal sinuses. Although CT is established as the gold standard for diagnostic imaging of the paranasal sinuses, CBCT has advantages in terms of lower radiation dose, isotropic voxels, smaller metallic artifacts and lower cost than CT.[18,24–26]

In this study, CBCT was used to assess these structures, although there is no uniform methodology for such an analysis. In addition, the type of slice (axial, coronal or sagittal) and the thickness of the slices are different in each study, making data comparison very variable. Although Landsberg et al., 2011 reported that the identification of the AN cell is quite difficult, even with the use of sagittal reconstruction, this reconstruction was used to complement the analysis of axial and coronal sections, since it contributed to the identification of the FR, the FB and the AN Cell, as several authors report in the literature.

An important data of this analysis was the presence or not of the AN cell. In the present study, the AN cell was found in 100% of the evaluated patients, being present bilaterally. It is noteworthy that these data are presented in different ways in the literature, sometimes considering the presence of AN cell in the individual, sometimes considering the presence of AN cell on each side of the individual (right or left). In this study, we chose to use the prevalence in relation to the individual. Thus, the data found corroborate the studies by Jones, Pérez-Pinãs and Angélico Jr & Rapoport,[27,28] and the AN cell was found in 95% or more of the analyzed patients.

Another important data analyzed was the size of the BF, which varies according to the pneumatization of the AN cell and the frontal ethmoidal cells in the “beak”. A large AN cell and pneumatization of the frontal ethmoid cells often reduces the size of the beak, whereas the absence of these cells would produce a thick beak.[12] In our study, this correlation was not found, in which the mean BF thickness does not present a significant correlation with any of the other variables.

Regarding the CAN-D volume, this is positively correlated with the FR length, while the CAN-E volume presents an even stronger correlation with the FR length, indicating that the greater the FR length, the greater the AN cell volume. The presence of ethmoid cells associated with the FR and their degree of pneumatization may condition the anatomy and volume of the FR,

and may be responsible for the existence of FS pathologies. Endoscopic surgery in the FR without removing these cells is one of the most frequent reasons for the persistence of pathologies after surgery.[29]

Proper identification and characterization of accessory cells through imaging studies is essential for a safe and effective surgical approach.[29] According to Bent,[30] these cells can be differentiated from other ethmoid cells by means of serial analyzes of CT scans of the facial sinuses, so that it is of great importance that both the clinical professional and the radiologist become aware of the main anatomical variations of the paranasal sinuses.

The knowledge allows avoiding errors and surgical complications, especially related to endoscopic surgeries, and preventing diseases, since the correlation between anatomical variations and the predisposition of individuals with the appearance of associated pathologies is not known for sure.[31]

Conclusion

The study indicates the presence of AN cells in 100% of the individuals analyzed, being present bilaterally. There was no significant correlation between FB and the AN cell. Significant positive correlations were found relating CNA-D and CAN-E with FR and FS. It is noticed the fundamental importance of anatomical knowledge on the part of professionals for a surgery to access the FS in a precise and uncomplicated way.

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Positron emission tomography/computed tomography (PET/CT) as a predictor of sarcoidosis activity: a case series

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Abstract

Introduction: Sarcoidosis is a multisystemic granulomatous disease that can present different clinical and radiological manifestations, while nospecific exams exist to monitor its activity and spontaneous or drug-induced remission. Objective: This study aimed to evaluate the degree of consistency between patients' symptoms and Positron emission tomography/computed tomography (PET/CT) results in patients with sarcoidosis. Methods: Patients with sarcoidosis underwent two PET/CT scans, which were performed at the nuclear medicine sector of the National Cancer Institute (INCA) at two different times during a four-year period, to assess disease activity. The maximum standardized uptake (SUVmax) value was noted and its consistency with the clinical status of the disease was checked. The analysis was performed using the SUVmax value. Results and Discussion: Twenty-seven patients were recruited, totaling 54 exams. The median SUVmax was 8.1 (range 3.5–16.1). Most examinations that showed hypermetabolism included both lung and extrapulmonary sarcoidosis sites in the same patient. The most affected sites with uptake by PET/CT were the lungs, followed by the intra-abdominal, pelvic, and peripheral lymph nodes. Other organs with glycolytic hypermetabolism included the spleen, subcutaneous tissue, bones, and heart. In 44% of the patients, the PET/CT scans and clinical status were not consistent. This result occurred mainly in: patients with cutaneous manifestations that exhibited no metabolic correspondence on PET/CT; patients with pulmonary fibrosis and dyspnea not attributable to disease activity; extrapulmonary sites such as the spleen, abdominal and peripheral lymph nodes, and bone without symptoms; and patients with pulmonary uptake on PET/CT despite being asymptomatic. Conclusions: The applicability of PET/CT should be discussed in each case to ensure that the information will assist the patient's diagnosis and management.

Keywords: PET/CT; pulmonary sarcoidosis; nuclear medicine.

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Introduction

Sarcoidosis is a multisystemic granulomatous disease that, in the majority of patients, affects the lungs but can occur in most organs. A major challenge to monitoring these patients is identifying disease activity. Biomarkers—such as angiotensin-converting enzyme, chitotriosidase, and interleukin-2 receptor—have already been studied.[1]

Positron emission tomography/computed tomography (PET/CT) has gained relevance in the treatment of sarcoidosis since the 1990s, when Lewis and colleagues[2] reported two cases of tracer uptake at various sites. Studies have shown its usefulness for various purposes, such as identifying possible biopsy sites, detecting extrapulmonary and pulmonary active disease, identifying inflammatory activity in fibrosing disease and assessing myocardial involvement. In addition, PET/CT scans are useful in the detection of metabolic treatment response.[3-9]

Some authors have proposed associating the metabolic activity found in PET/CT with patients' clinical symptoms. Teirstein and colleagues[9] reported on 137 patients with sarcoidosis who underwent PET/CT and observed tracer uptake mainly in the mediastinal and extrathoracic lymph nodes and lungs, with SUVmax ranging from 2.0 to 15.8.[9] In their sample, 15% of tests with PET/CT tracer uptake did not correspond to the diagnoses suggested by clinical examinations or other imaging tests. A comparable situation was observed by Guleriaand colleagues[6]who reported a complete clinical response and evidence of uptake on PET/CT in 22% of patients, showing moderate consistency between clinical findings and metabolic expression.

Despite many decades of studying tools that help identify sarcoidosis activity, we remain unsure about the applicability of complementary exams, such as PET/CT, in the management ofsarcoidosis. Since it is a heterogeneous disease, with diverse clinical and radiological presentations, the group of patients who stand to benefit from PET/CT must be better understood.

This study aimed to describe cases of patients who underwent PET/CT and the applicability of this tool in the management of sarcoidosis.

Methodology

This is a prospective and observational study consisting of a case series of sarcoidosis patients, selected by convenience sampling, diagnosed with sarcoidosis treated and monitored at the interstitial diseases outpatient clinic of the Piquet Carneiro University Polyclinic (UERJ), during four years (2016 to 2020). Patients with infectious insults detected at the time of assessment were excluded, as were those who did not remain in follow-up care at the facility due to abandonment or death (Figure 1). All participants consented to participate in the study, which was approved by the Research Ethics Committee (CAAE: 46767915.8.00005259). Patients were diagnosed at the time of inclusion in the study or up to 48 months beforehand. Sarcoidosis diagnosis was determined according to the American Thoracic Society (ATS), European Respiratory Society (ERS), and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines on sarcoidosis.[10] Individuals underwent two PET/CT scans. The median interval between the two exams was 19 months (15-33). During this period, the patient continued to be monitored by medical appointments, underwent complementary tests and received treatment with immunosuppressive drugs as sarcoidosis activity was identified. All patients were examined by a pulmonologist for clinical assessment of the signs and symptoms of pulmonary and extrapulmonary sarcoidosis.

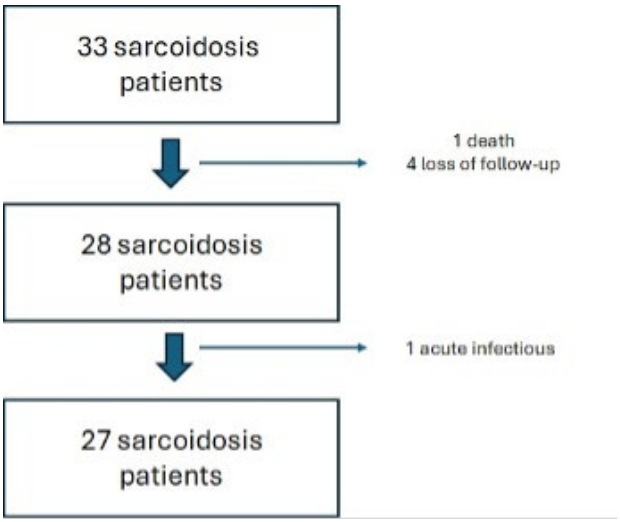

Figure 1. Recruitment and follow-up of sarcoidosis patients

Non-contrast tomography images and then three-dimensional volumetric PET images were obtained by PET/CT, in the nuclear medicine sector of the National Cancer Institute (INCA), both from the vertex of the skull to the middle of the thighs using Philips Gemini TF w/ToF 64 equipment (Cleveland, OH, USA). Images were reviewed in the transaxial, coronal and sagittal planes. The patients' metabolism was assessed via whole-body PET/CT scans that used 18 F-fluorodeoxyglucose (FDG) with tomography and PET images acquired 60 minutes after tracer infusion andsemi-quantitative analysis using the maximum standardized uptake value (SUVmax).[11] Reports were prepared after evaluation by two radiologists from the nuclear medicine service.

During follow-up, we collected data on clinical features, clinical manifestations and patients' evolution according to treatment. Respiratory clinical manifestations included chest pain, dyspnea, coughing and wheezing. The constitutional symptoms were fever, weight loss, fatigue, arthralgia, and night sweats. Palpitations and angina were listed as cardiac symptoms. Facial palsy and balance disturbance were considered as neurological symptoms.

All data were entered in spreadsheets (MS Office/Excel 2010, Microsoft Co., CA, USA) by the first author of the present study. GraphPad Prism version 10.0 (GraphPad Software Inc., La Jolla, CA, USA) was used for the statistical analysis. The chi-square test (with Fisher's correction when necessary) and the Mann-Whitney test were used to compare the differences between categorical variables and the differences between continuous unpaired variables, respectively. The paired t-test and Wilcoxon's test were used to compare continuous paired variables. A significance level of 5% was used. Concordance was measured by use of the Kappa coefficient.

Results

Twenty-seven patients with sarcoidosis were evaluated (Table 1). The reported respiratory symptoms were dyspnea and coughing. The cutaneous lesions compatible with sarcoidosis included plaques, papules, subcutaneous nodules, erythema nodosum, and scars (tattoos) (Figure 2 A, 3C).

Table 1. Data of sarcoidosis patients

Data	All patients (n. 27)
Age	51.35 (SD 10.29)
Sex (female: male)	22:5
Smoker	
Former	7
Never	20
PET CT +	15
Findings of thoracic CT:	
Ground glass opacities	5
Reticular opacities	8
Small nodules	20
Mediastinal and hilar lymph node	17
Thickened peribronchovascular bundles	5
Consolidation	3
Fibrosis	6
Signs and symptoms	
Dyspnea	9
Cough	3
Skin lesions	12
Fever	1

Legend: PET-CT – Positron Emission Tomography and Computed Tomography

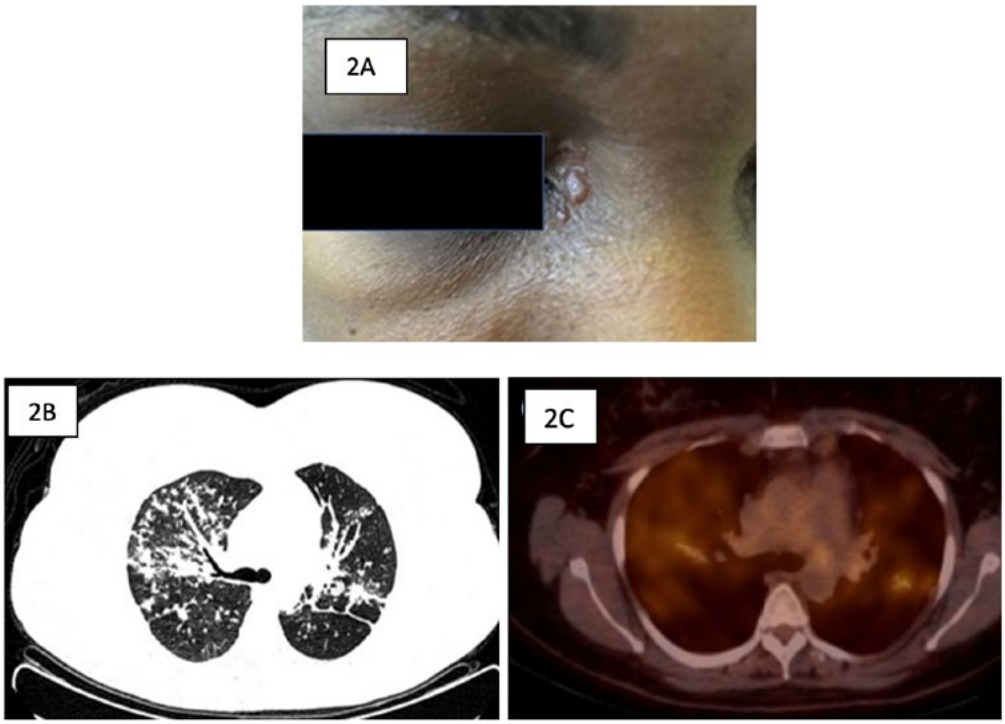

Figure 2. Consistency of CT and PET/CT

Legend: 2A: Woman, 36 years, papule in the corner of the eye; 2B and 2C: bilateral micronodules and nodules in fissures with metabolic activity.

Fifty-four PET/CT scans were performed, 24 of which showed tracer uptake (SUVmax, 8.439; range 3.5–16.1; SD 3.013; 95%CI 7.13 6-9.742). Five scans revealed uptake in extrapulmonary sites only, 8 in pulmonary sites only, and 11 in both extrapulmonary and pulmonary sites. (Figure 3, Table 2)

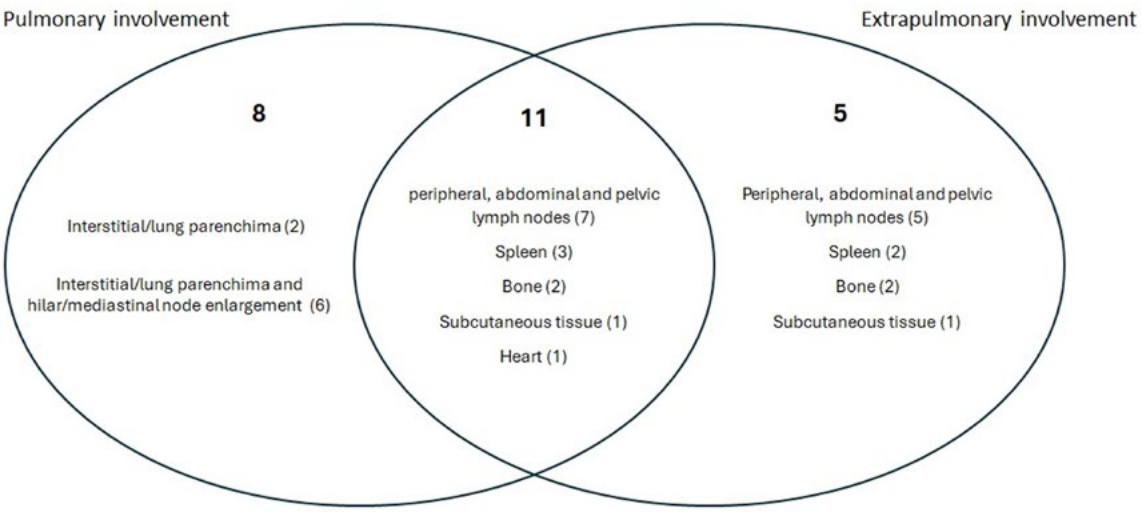

Figure 2. Activitity of sarcoidosis detected by PET/CT

Legend: Observation: 11 patients had pulmonary and extrapulmonary involvement.

Twenty-five PET/CT scans revealed discrepancies with the clinical status (Table 3), since the Kappa indexes disagreed. Three asymptomatic patients showed infiltrates with metabolic activity (Figure 2B - 2C). Four patients showed uptake in extrapulmonary sites, such as the spleen, bone, and abdominal and retroperitoneal lymph nodes, without clinical correlation (Figure 4A - 4B). However, 8 patients with skin lesions suggestive of active sarcoidosis (Figure 4C) and 4 individuals who complained of dyspnea showed no expression on PET/CT. Of these, 3 had characteristic infiltrates of sarcoidosis on tomography, such as micronodules, peribronchovascular bundle thickening, ground-glass nodules, and fibrotic areas.

Table 2. Activitity of sarcoidosis detected by PET/CT

PET/CT+	Number
Pulmonary sites	8
Extrapulmonary sites	5
Abdominal/pelvic lymph node	1
Peripheral lymph node	5
Spleen	2
Subcutaneous tissue	1
Bone	2
Pulmonary and extrapulmonary sites	10
Abdominal/pelvic lymph node	7
Peripheral lymph node	4
Spleen	3
Bone	2
Subcutaneous tissue	1
Heart	1

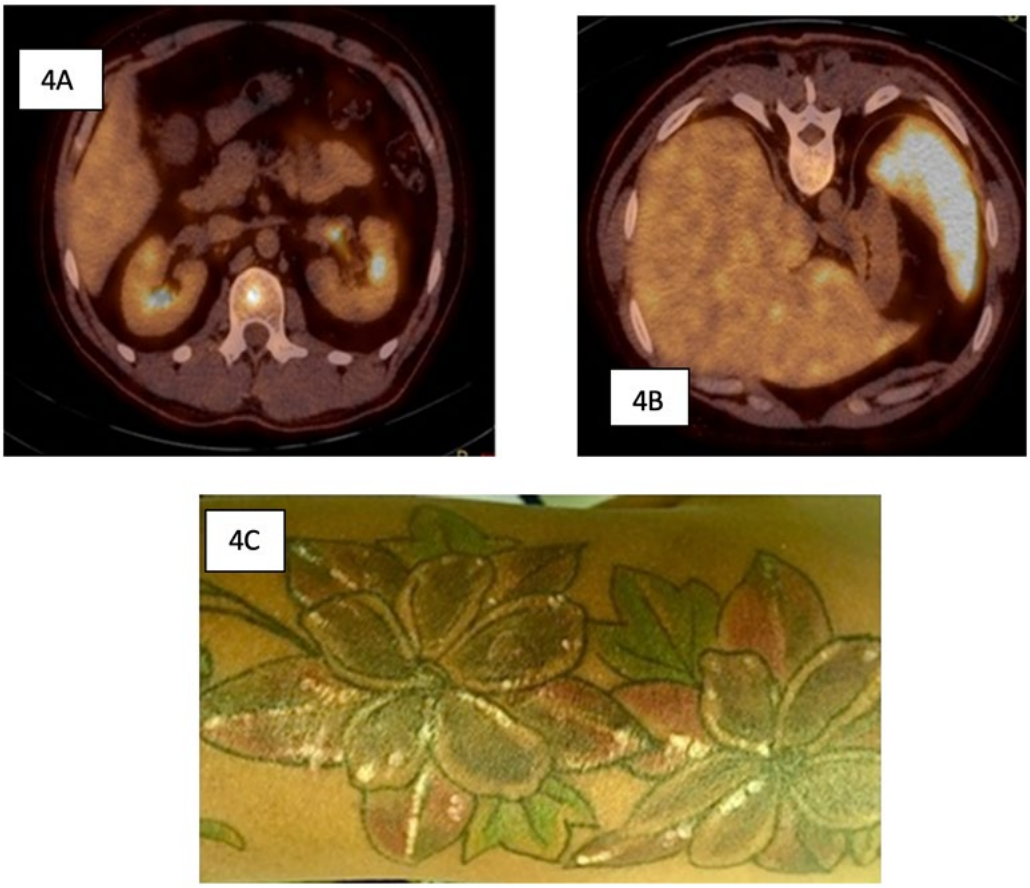

Figure 4. PET/CT and extrapulmonary disease

Legend: 4A-4B: man, 36 years, bone (vertebra) and spleen intense uptake (SUVmax 8,4), without associated symptoms. 4C: woman, 39 years, papular lesions on the arm tattoo.

Table 3. Clinical and radiological dissociation

	PET/CT +	PET/CT -
Symptom +	13 patients	14 patients
Symptoms -	11 patients	16 patients

Legend: PET-CT = Positron Emission Tomography and Computed Tomography. The Kappa agreement was 0.074 (SE 0.135, 95%CI -0.190 to 0.338)

The number of observed correlations was 29 (53.70% of the observations) and the number of correlations expected by chance was 27 (50% of the observations), with Kappa = 0.074 (SE 0.135, 95%CI -0.190to 0.338) (Table 3).

Discussion

The definition of disease activity progression in sarcoidosis is important for the therapeutic management of patients, including choice of drugs, changes in treatment, and assessment of patient response to the proposed therapy.[6]

In this case series, we studied the degree of consistency between sarcoidosis activity evaluated using signs and symptoms on physical examination as well as PET/CT. We found a weak consistency between these two variables but evaluated each case to identify situations in which PET/CT proved useful.

Among the PET/CT scans that disagreed with the clinical assessment, skin lesions were observed on physical examination but not identified on PET/CT. However, these patients were treated with either prednisone or methotrexate. Skin lesions may not show metabolic expression, especially when undergoing treatment.[12,13]

Nonetheless, PET/CT can greatly contribute to the definition of metabolic activity in pulmonary fibrosing disease.[14] This prospect was observed in this series of cases, in which two patients had dyspnea that was considered to be a consequence of pulmonary fibrosis, while PET/CT did not identify pulmonary metabolic activity.

The identification of extrapulmonary sites may be important for determining biopsy sites when a definitive diagnosis has not been made. However, this procedure is questionable as a screening tool because the clinic defines the need for treatment in most cases.[5]In our patients, the lesions in the spleen and bone showed no clinical correspondence and did not require therapeutic interventions.

Patients with asymptomatic metabolic pulmonary activity should be evaluated with pulmonary function tests for therapeutic purposes. Keijsers and colleagues[15] demonstrated that patients with metabolic activity in the lung parenchyma exhibit significant improvements in vital capacity (VC), forced expiratory volume in 1[st] second (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO) when treated.[15]This group of patients often presents an exuberant image with clinical dissociation and is challenging to define, whether by use of pharmacological treatment or other means. We opted to treat asymptomatic patients with alterations in pulmonary function tests (FVC, FEV1, and DLCO) and pulmonary infiltrates with hypermetabolic activity on PET/CT.

We observed discrepancies between clinical status and PET/CT scans in cases of extrapulmonary disease, pulmonary fibrosis, and asymptomatic respiratory patients. Therefore, PET/CT is useful in the study of heart disease, in which cases even asymptomatic patients should be encouraged to undergo treatment since it is one of the main causes of sarcoidosis mortality.[16] In patients with pulmonary fibrosing disease with symptoms of dyspnea, PET/CT is a helpful tool to guide treatment decision.

Despite PET/CT's high sensitivity and accuracy in assessing the evolution of sarcoidosis, its applicability should be questioned, when considering its high cost and low availability in treatment centers. Nonetheless, its use to detect sarcoidosis activity in individuals with fibrosis and heart diseases seems promising, since it can change the therapeutic plan.

The limitations of this study include the lack of a cardiac protocol for PET/CT, which prevents the implementation of an adequate cardiological study. Therapeutic interventions between the two PET/CT scans were not evaluated for possible metabolic changes.

Conclusion

The disease course of patients with sarcoidosis must be followed up at specialized facilities by a professional trained to identify clinical signs of disease activity and the use of PET/CT in selected cases.

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Brazilian Journal of Health and Biomedical Sciences
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Keywords: three to six terms related to the subject must be given, separated by semicolons, according to MeSh (Medical Subjects Headings) for English.

Full text

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Methodology and resources: this section must briefly present all the information needed for other researchers to replicate the study. Adopted procedures must be clearly described, as must the analyzed variables and tested hypotheses. Definitions must be given whenever necessary. Population, sample, and measurement instruments must be described and information about data gathering and processing must be given. If possible, validity scores must be included. Methods and techniques used must be duly detailed, including statistic methods. New or substantially modified methods must be described, with a justification for its use and mention of its limitations. Research ethics must be observed. Authors must explicitly state that the research was done within ethical standards and with the approval of an ethics committee.

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Acknowledgments: must be concise and limited to people and institutions that contributed to the research in some degree, but could not be included as authors.

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the order in which they are referenced in-text. All abbreviations must be explained with a legend below the table. There must be the source from which the table was extracted and/or the authorship of it, this information must be written below the table, after the legend for the abbreviations, if any.

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Case report: usually it describes one to three patients or a family case. The text must be up to 2,000 words long, with up to three tables or images and up to 25 references. The abstract must be no more than 100 words long.

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It must be about subjects relevant to medical practice. These will form a section about the common theme of each issue. These are limited to 5,000 words (excluding abstract and references) and a maximum of five images and/or tables. Maximum of 40 listed references. Literature reviews will be submitted for the editorial board analysis under invitation by the guest editor of this section, and must conform to the following standards:

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Abstract: must be written in English with a maximum of 250 words. Must follow the structured abstract model, with mandatory introduction, objective(s), methodology and resources, results and discussion, conclusion(s). It is well known that the abstract gets more visibility and distribution than the full text of the paper. Therefore, it must contain the essential information in the paper, but cannot be just a patchwork of sentences from it. It must be succinct and direct, highlighting what is most important in the full text in order to encourage a full reading. In the conclusion, all results must be related to the objectives of the study. The discussion must assert the contribution of the results to the body of knowledge about the subject of research.

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several conditions of..."; and up to two authors can be named: "Handel and Matias[15] conducted a study about..." However, when the number of authors is three or more, the first author must be named along with the expression "and cols.": "Silveira and cols.[13] have proposed a new methodology..."

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