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Subgrouping Leprosy Patients with Neuropathic Pain in Central Brazil Based on Pain-Related Sensory Abnormalities

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Leprosy is a significant cause of nontraumatic peripheral neuropathy and neuropathic pain (NP). Generally, patients with NP exhibit a variety of symptoms and sensory signals, creating an individual phenotypic profile of pain. This involves identifying and grouping a set of symptoms and signs that characterize an individual's pain experience. Neuropathic pain can be confirmed using the DN4 screening tool, which includes 7 items related to symptoms and 3 items related to physical examination. Identifying clusters of symptoms in patients with NP and distinguishing them into subgroups through statistical analysis of the most relevant and discriminating aspects of the pain phenotype can more robustly reflect the different mechanisms or combinations of mechanisms involved in its genesis.
Objective: To identify subgroups of leprosy patients with NP based on pain-related sensory abnormalities.
Methods: A cross-sectional descriptive study was performed on patients with NP caused by leprosy who were treated at a school hospital in Central Brazil to characterize the painful symptoms and establish NP sensorial phenotypes. The sociodemographic, clinical, and NP phenotype characterization was performed using the Neuropathic Pain Questionnaire 4 (DN4). Identifying groups of patients with similar individual phenotypic profiles was done using exploratory factor analysis.
Results: A total of 132 patients with leprosy and associated NP were evaluated during 2017 and 2018. Most patients were female (56.8%) with borderline leprosy (72.7%) and with a mean (SD) age of 48.7 (13.5) years. Signs and symptoms related to sensory deafferentation were predominant: numbness and hypoesthesia to touch and needle pinprick. The characterization of the sample by sensorial phenotypes identified four subgroups that best described the patients with leprosy NP and that corresponded to 62% of all variations found. In two subgroups, a predominance of signs and symptoms of sensorial loss corresponded to 38% of the patients. The other two were characterized by signs of hyperactivity of the somatosensory system.
Conclusions: NP phenotypes associated with leprosy are characterized by numbness, tingling, pins, needling, and hypoesthesia to touch and needle pinprick. The sensory phenotype of leprosy-associated NP has four phenotypic subgroups. There were two groups related to sensory loss that are compatible with this long-term neuropathy and the two others with signs of pathological sensory input.

Keywords: Leprosy; pain; neuropathic pain; pain phenotype.

1. INTRODUCTION

Neuropathic pain can result from injury to, or disease of the nervous system. It is notoriously difficult to treat. Peripheral nerve injury promotes Schwann cell activation and invasion of immunocompetent cells into the site of injury, spinal cord and higher sensory structures such as thalamus and cingulate and sensory cortices. Various cytokines, chemokines, growth factors, monoamines and neuropeptides effect two-way signalling between neurons, glia and immune cells. This promotes sustained hyperexcitability and spontaneous activity in primary afferents that is crucial for onset and persistence of pain as well as misprocessing of sensory information in the spinal cord and supraspinal structures [1]. Leprosy is a significant cause of nontraumatic peripheral neuropathy and neuropathic pain (NP). Between 11.0% and 85.1% of leprosy patients develop neuropathic pain (NP) despite appropriate treatment. Pain in leprosy patients is a common and multifactorial symptom that can occur before, during, and after disease treatment. Several factors are associated with leprosy pain syndromes, with the stage of neuropathy and the occurrence of reactional episodes being the most significant. Pain often persists for many years after the disease is cured, causing ongoing suffering and disability [2-10].

Patients with NP exhibit a variety of symptoms and sensory signals that constitute an individual phenotype of pain. This pattern of sensory abnormalities may provide insights into the underlying pathophysiological dysfunction. Since a single symptom can be generated by multiple pathophysiological mechanisms, it is more likely that specific groups of sensory signals and symptoms can better predict the underlying mechanisms [11-14].

Patients with the same etiology of NP often exhibit heterogeneous signs and symptoms. Several controlled clinical trials with new drugs for NP have yielded negative results, likely due to the heterogeneity of the study populations [15]. Many studies suggest that the way to reduce this heterogeneity is by stratifying patients according to their phenotypic pain profile, which is assessed through clinical examinations, NP questionnaires, and sensory tests [16]. Subgroup identification is performed through statistical analysis of the frequency and variance of pain descriptors obtained from all patients using an NP questionnaire [17].

Significant research has been conducted on the prevalence and clinical characteristics of NP in leprosy. However, no studies have yet stratified leprosy patients with NP into subgroups based on the clustering of signs and symptoms using statistical methods. Identifying distinct NP phenotypes, as has been done in other painful neuropathies, presents an opportunity to categorize subgroups within the NP leprosy patient population. Reducing the heterogeneity of study populations in clinical trials of existing or new treatments for leprosy-related NP will facilitate better pharmacological management, conserve financial resources, and alleviate the suffering caused by NP in leprosy patients [18].

2. OBJECTIVE

The aim of this investigation was to identify subgroups of leprosy patients with NP based on their sensory phenotypic profiles.

3. PATIENTS AND METHODS

This is a cross-sectional descriptive study performed with data collected from January 2017 to July 2018. All patients underwent a clinical evaluation, including a dermatoneurological examination, to establish inclusion criteria and to gather demographic, epidemiological, clinical, and laboratory characterizations of the sample. Confirmation of the pre-existing diagnosis of leprosy was made by analyzing the participants' medical records, with special attention to compliance with the definition of a case as proposed by the World Health Organization (WHO) and the Brazilian Ministry of Health [19].

Patients of both sexes who were older than 18 years, had a previous diagnosis of leprosy, and complained of pain were eligible for the study. Some patients were undergoing specific multidrug therapy for leprosy, while others were not. They were referred by the infectious disease specialist team from a school hospital in Cuiabá, Mato Grosso, Central Brazil. Patients were excluded from the study if, at the time of the evaluation, they had diagnoses of other NP-causing conditions, such as diabetes, acquired immunodeficiency syndrome, herpes zoster, hypothyroidism, cancer requiring chemotherapy, or multiple sclerosis, or if they used drugs that could potentially provoke NP.

A public domain NP screening instrument developed in France, the Douleur Neuropathique 4 (DN4), was applied to each patient [20]. This instrument was translated and validated for Brazilian Portuguese [21]. It has 10 items—seven related to symptoms and three related to physical examination signs. Each positive item received one point, and a final score of 4 or more suggested NP. Patients who had DN4-compatible scores underwent structured sensory physical examinations of the areas referred to as painful. DN4 is widely used in clinical practice and research to identify patients who may be experiencing neuropathic pain and to assist in differentiating this condition from other types of pain [22].

Data were analyzed using Stata software version 12.0 (Stata Corp., Texas, USA). Sociodemographic, clinical, and epidemiological characteristics, as well as sensory phenotypic profiles, were described through their absolute and relative frequencies. To identify phenotypic sensory groups for neuropathic pain (NP), a multivariate exploratory factor analysis was performed. This analysis aimed to reduce multiple variables into a smaller set with minimal information loss. Exploratory factor analysis was employed to uncover complex interrelationships between variables without any initial assumptions about the factors. The accuracy of the method was assessed using the Kaiser-Meyer-Olkin (KMO) measure, while Bartlett's test of sphericity was used to check whether the variables had significant correlations with each other. These tests help to ensure that factor analysis is appropriate for the data. After confirming the feasibility of the factor analysis, it was conducted using varimax rotation methods on a polychoric correlation matrix. Polychoric correlation is recommended as an alternative to product-moment correlation when variables are categorical ordinal measurements. Possible groupings of symptoms (factors) were identified by measuring their factor loadings, which indicate how strongly each factor correlates with the original variables. Higher factor loadings suggest

a stronger correlation of the factor with the related symptoms [23,24].

4. RESULTS

We enrolled 169 patients with leprosy and pain complaints were eligible for the study, of whom 150 (88.8%) had NP and 19 (11.2%) nociceptive pain. After the application of exclusion criteria, 37 patients were excluded: 18 with NP and diabetes, three with nociceptive pain and diabetes and 16 with nociceptive pain. A total of 132 subjects represented the final selected sample for this study, 56.8% (75/132) females and 43.2% (57/132) males. The mean (standard deviation [SD]) age of these patients was 48.8 (13.4) years. Adittional demographic details of these patients are shown in Table 1.

Table 1. Demographic characteristics of leprosy patients with neuropathic pain treated in Cuiabá (MT), Central Brazil, 2017-2018

Characteristics		n	%
Sex	Male	57	43.2
	Female	75	56.8
Skin color	White	43	32.6
	Brown	65	49.2
	Black	23	17.4
	Yellow	1	0.8
Occupation	Retired	19	14.4
	Active worker	65	49.2
	Sick leave	48	36.4
Marital status	Marriage	71	53.8
	Separated	24	18.2
	Single	25	18.9
	Civil union	12	9.1
Religion	Catholic	74	56.1
	Spiritualist	1	0.8
	Evangelical	49	37.1
	Other	2	1.5
	No Religion	6	4.5
Income (US$ per year)	< 2,900	76	57.6
	2,900 to 5,800	40	30.3
	5,801 to 8,700	9	6.8
	> 8,700	7	5.3
Age (years)	**Mean (SD):** 48.7 (13.5)		

Table 2. Clinical characteristics of leprosy patients with neuropathic pain treated in Cuiabá (MT), Central Brazil, 2017-2018

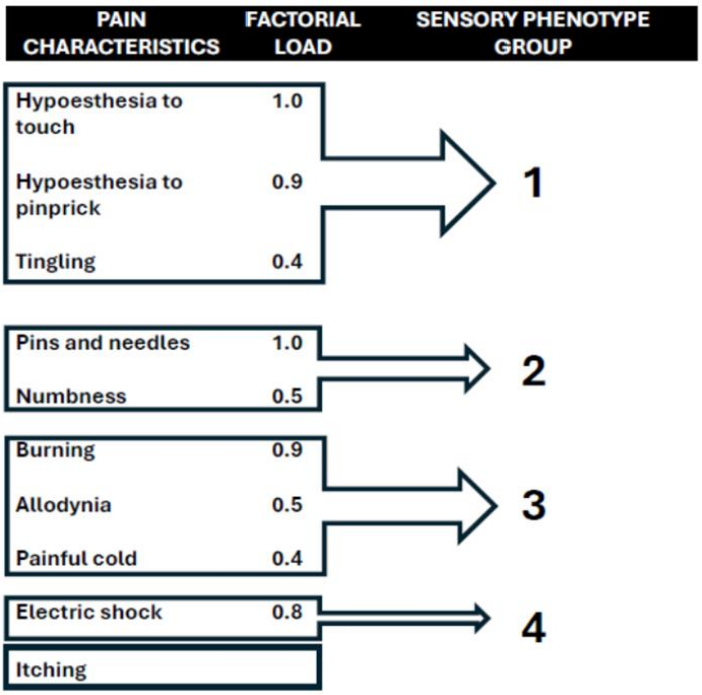
Characteristics		n	%
Ridley-Jopling leprosy classification	Borderline	96	72,7
	Indeterminate	2	1,5
	Tuberculoid	5	3,8
	Lepromatous	29	22,0
Operational classification (WHO)	Multibacillary	125	94,7
	Paucibacillary	7	5,3
Current treatment with multidrug therapy	Yes	50	37,9
	No	82	62,1
Disability degree	0	25	18,9
	1	82	62,2
	2	25	18,9
Affected nervous number	1 to 3	16	12,1
	4 to 6	88	66,7
	7 to 10	28	21,2

WHO: World Health Organization

The majority of patients had multibacillary (94.7%) and borderline (72.7%) clinical form of leprosy, according to the WHO operational and Ridley-Jopling's classifications. At the time of inclusion in the study, 62.1% of the patients had already completed treatment of the disease. The time elapsed between the end of the leprosy treatment and the medical assessment for pain ranged from 0.2 months to 492 months, with a mean (SD) of 50.4 (70.0) months. Most of the patients in the study had physical disability degrees of 1 (62.2%) and 2 (18.9%) according to the WHO classification and had four or more affected peripheral nerves (Table 2).

Most patients (64.4%) reported severe NP occurring before diagnosis and treatment, with 87.1% scoring greater than 7 on a 0-10 intensity scale. Pain occurred daily in 88.6% of patients, with 78% reporting daily analgesic use. Improvement with painkiller medication was noted by 61% of patients. Prescription painkillers were provided by physicians to 49.3% of patients who reported using drugs to relieve pain (Table 3). Numbness was the most frequent NP phenotype (93.2%), followed by tingling (86.4%), pins and needles (85.6%), hypoesthesia to touch (84.8%), and hypoesthesia to pinprick (84.8%). Itching was the least frequent pain phenotype (Table 4).

The result of KMO > 0.5 and Bartlett's test of sphericity with high statistical significance ($p < 0.0001$) indicated that the proposed factor analysis was adequate. This analysis identified four sensory phenotype groups for leprosy NP, collectively explaining 62% of all symptom variability: 22% for the first, 16% for the second, 15% for the third, and 9% for the fourth factors. The itching symptom did not exhibit a factorial load significant enough to justify its inclusion in any of these factors (Table 5 and Fig. 1).



Kaiser-Mayer-Olkin criterion		**0.52**
Bartlett's Test of sphericity	Approximate chi-square	124.12
	Degrees of freedom	45
	p-value	< 0.0001

Fig. 1. Sensory phenotype grouping of patients with NP associated to leprosy, identified by exploratory factory analysis by polychoric correlation matrix [Kaiser-Mayer-Olkin criterion > 0.5 indicates that factor analysis was adequate for interpreting the data. A p-value <0.05 indicates that there is sufficient correlation between the variables for factor analysis to be applied

Table 3. Characteristics of the neuropathic pain claimed by leprosy patients treated in Cuiabá (MT), Central Brazil, 2017-2018

Characteristics of NP		N	%
Temporal relationship with treatment	Before	85	64.4
	After	47	35.6
Intensity	Mild	3	2.3
	Moderate	14	10.6
	Severe	115	87.1
Weekly frequency (days)	1	3	2.3
	2	2	1.5
	3	3	2.3
	4	5	3.8
	5	2	1.5
	7	117	88.6
Previous use of analgesics	Yes	103	78.0
	No	29	22.0
Relief with painkillers (n=103)	Yes	44	49.3
	No	59	42.7
Painkiller prescribed by physicians (n=103)	Yes	78	75.7
	No	25	24.3

NP: Neuropathic Pain

Table 4. Phenotype characteristics of neuropathic pain claimed by leprosy patients treated in Cuiabá (MT), Central Brazil, 2017- 2018

Pain characteristics	n	%
Burning	99	75.0
Painful cold	70	53.0
Electric shock	108	81.8
Tingling	114	86.4
Pins and needles	113	85.6
Numbness	123	93.2
Itching	53	40.1
Hypoesthesia to touch	112	84.8
Hypoesthesia to pinprick	112	84.8
Allodynia	67	50.8

Table 5. Results of the factorial analysis of grouping of symptoms referred by patients with neuropathic pain associated with leprosy, Cuiabá (MT), Brazil, 2017-2018

Factors	Eigenvalue	Explained Variance (%)	Cumulative Explained Variance (%)
1	2.21	22	22
2	1.56	16	38
3	1.50	15	53
4	0.90	9	62

5. DISCUSSION

The present study describes leprosy-associated NP in 132 patients whose sociodemographic and clinical profiles were consistent with those treated at a referral center specializing in more clinically complex cases. Notably, patients with severe, frequent, and incapacitating pain were predominant. Additionally, borderline clinical forms with multiple affected nerves and high degrees of disability were prominent features in this study population.

The proportion of female patients was similar to that observed in a previous study [8]. Other available studies on leprosy pain did not report

on the sex of the patients or showed a predominance of male patients. For instance, a study conducted in India had a sample that was 72.3% men [8]. In Brazil, a multicenter epidemiological study on chronic pain found a proportion of women similar to that in the present study [25]. Psychological and social factors are important in the prevalence and incidence differences between sexes, but biological differences in the function of the immune system likely contribute to these observed effects [26].

The patient age was comparable to that reported in several studies on this subject [10, 27]. The low economic income of leprosy NP patients underscores the necessity of a governmental program to address this issue. The high number of patients on sick leave is another important social factor related to leprosy-associated NP.

The leprosy-associated NP phenotype characterized by numbness, tingling, hypoesthesia to touch, hypoesthesia to pinprick, and pinching/prickling was predominantly negative. A study in India found a prevalence of 21.8% of NP with similar phenotypes in patients who had completed multidrug therapy [27]. However, other studies showed a higher frequency of positive pain symptoms compared to our findings [9,28].

Deficits in innocuous sensory modalities of NP, such as mechanical or vibration sensitivity thresholds, may occur due to peripheral nerve injury. The resulting clinical finding could be, for example, hypoesthesia, which is defined by the International Association for the Study of Pain as decreased sensitivity to stimulation [29]. However, it is possible that pain could cause an inhibition of the innocuous impulse, particularly at the pain site, also resulting in hypoesthesia. A study on experimentally induced pain demonstrated a decrease in vibration and tactile sensitivity at the pain site. The authors referred to this phenomenon as the ‘gate of touch,’ suggesting that pain inhibits sensory input at the supraspinal level [30]. Indeed, both hypoesthesia to touch and hypoesthesia to needle pinprick involve afferent fibers A-β and A-δ, respectively [31]. Other researchers have suggested that the mechanism of pain-induced hypoesthesia could be mediated in the spinal cord [32]. A Brazilian study reported the frequency of NP-leprosy symptoms as numbness (64.9%), hypoesthesia to touch (56.8%), and needle pinprick (51.4%) [33]. The frequency of tingling, pinching, and needling symptoms, and electric shock found in this study was similar to those reported in other studies [33,34]. The activity of abnormal excitability in the afferent neurons leads to positive phenotype symptoms [35].

The symptom of burning occurred at a lower frequency in this study compared to other studies of leprosy-associated NP, which reported ranges from 24.6% to 88.5% [9,34]. Burning pain is strongly related to damage to the nociceptive system. It arises through abnormal spontaneous activity in C fibers and reflects hyperexcitability in irritable nociceptors, nerve regeneration, and nerve regeneration shoots. Alterations in the expression, distribution, and activity of voltage-dependent sodium channels result in burning pain [35]. In other painful neuropathies, the frequency of burning pain ranges from 51% to 90% [17].

Painful cold was frequent among the study patients. In another study conducted in Brazil, this pain characteristic was reported in 27% of patients [28]. The mechanism of cold pain is not fully understood, but it is probably mediated by the activation of myelinated (cold-specific) delta fibers and nonmyelinated C fibers. A central mechanism characterized by a decrease in the inhibition exerted by sensory cold channels in nociceptive fibers has been suggested [36,37].

The presence of allodynia, which is referred to as pain provoked or increased by brushing in the DN4 questionnaire, was also frequent among patients in this study, similar to the rate found (54.9%) in a study with 482 patients with NP of different etiologies [38]. Although its pathological mechanism is not yet well understood [39], some potential mechanisms have been studied, such as changes in mechanical transduction and the excitability of sensory neurons to the action of inflammatory mediators, which are associated with changes in electrical conduction in the central nervous system [40].

Although pruritus was not frequent among the studied patients, its occurrence was higher than in other studies on the same subject [27,28]. In general, pruritus occurs in about 30% of patients with peripheral neuropathies and up to 65% of patients with herpes zoster neuropathy [41]. Peripheral nerve damage can induce spontaneous pathological activities in pruriceptive neurons, leading to hyperexcitability and sensitization of the nerves. Secondary central sensitization may increase the pruritus sensation generated by hyperexcitable peripheral pruriceptors. Similar to phantom limb pain,

pruritus can be generated by central neurons mediating pruritus, which characterizes a central sensitization of the somatosensory system [42,43].

In the present study, the patients were mostly of borderline form, which, due to their immunological instability, are among those at higher risk of leprosy reactions, mainly type 1 [44]. Leprosy reactions are known to be related to neural damage, which would justify their predominance in patients with NP [2].

Most patients (64.4%) reported experiencing pain with neuropathic characteristics before their diagnosis of leprosy, consistent with the pain they experienced at the time of the research interview. This suggests that the peripheral neuropathy of leprosy in these patients was long-lasting, explaining the high frequencies of neuropathic pain and functional disability. This aspect has not been investigated in any other published study on neuropathic pain in leprosy. The presence of neuropathic pain in limbs within a leprosy-endemic area may serve as an important alert for diagnosing the disease itself. Moderate to severe pain is a major morbidity factor in patients with neuropathic pain of any etiology. Psychological stress and quality of life in leprosy patients with neuropathic pain were studied by Reis et al. [10] and Lasry-Levy et al. [8]. Patients with higher levels of psychological stress exhibited higher pain intensity and poorer quality of life [45].

The frequency of drug use for pain control among the patients was similar to that found by Ramos et al. [9]. In the present study, only half of the patients reported pain improvement with the use of analgesics, and 75.7% had analgesics prescribed by a physician. Santos et al. (2010) reported that only 28% of patients experienced relief [46], whereas Chen et al. (2012) found that 81.2% of patients reported effective pain relief from analgesics alone or in combination with corticosteroids [34].

Characterizing the sample by sensory phenotypes identified four subgroups that best describe patients with leprosy-associated NP. The hypothesis that patients with peripheral NP can be grouped into subtypes based on individual sensory phenotypes, reflecting underlying pathophysiological mechanisms, suggests clinical applicability for this grouping. A specific constellation of signs and symptoms stratified statistically could better reflect a more homogeneous sample.

The first factor (F1), or subgroup 1, presents descriptors of sensory loss (hypoesthesia to touch and needle pinprick) due to prolonged neural injury. The symptom of tingling, linked to this subgroup, is spontaneous pain caused by discharges in myelinated Aβ fibers [47].

The second factor (F2) refers to symptoms of spontaneous pain: pins and needles sensations presented a perfect factorial load. The symptom of numbness was also linked to this subgroup. Numbness is a phenotypic descriptor of sensory deafferentation of the skin, reflecting time-dependent denervation similar to that observed in studies with diabetic patients. Its presence suggests a longer and more intense duration of neural injury. Pain is generated in central medullary neurons, and central analgesics can be used for treatment [48].

The third factor (F3) grouped descriptors of spontaneous pain related to relative preservation of neural function, such as burning and painful cold, associated with allodynia, a symptom of evoked pain. Burning pain is associated with spontaneous hyperactivity of C fibers and originates from ‘irritable’ nociceptors related to peripheral sensitization. Sensitized nociceptors exhibit increased expression of ion channels and receptors in the neuronal membrane. Burning pain originates from regenerating nerves or denervated central neurons [47]. Persistent activation of normal nociceptors may lead to central sensitization at the dorsal horn of the medulla, causing tactile stimuli to activate central nociceptive neurons. The abnormal mechanical threshold reduction of nociceptors explains the peripheral mechanisms of allodynia, where an innocuous stimulus like brushing the skin is perceived as pain (allodynia) [49].

The fourth factor (F4) grouped only the symptom of electric shocks, indicating high-frequency discharges into Aβ fibers. Drugs effective in reducing neuronal discharges in nociceptors, such as sodium channel blockers, should be considered for treating these patients [50].

Existing studies on NP sensory grouping have predominantly involved patients with various pathologies, showing a predominance of groups with increased neuronal activity. This study, however, demonstrates a predominant sensory loss, characteristic of leprosy—a long-lasting neuropathy. Raicher et al. (2018) compared the sensory characteristics of NP in leprosy patients with those caused by other etiologies and did not

find significant differences. Therefore, the similarities observed between these two kinds of NP suggest that the same drugs can be used for treatment [51]. The identification of distinct subgroups of NP sensory phenotypes associated with leprosy is a promising finding. Identifying peripheral and central mechanisms in these subgroups may guide the rational choice of drugs to treat leprosy-associated NP.

The main limitation of this study is the lack of assessment of NP with complementary quantitative sensory testing, as was done in other studies subgrouping NP patients of different etiologies [52].

6. CONCLUSIONS

Patients with leprosy-associated NP were characterized by a predominance of females, multibacillary and borderline clinical forms, and having already completed multidrug therapy for leprosy. NP phenotypes associated with leprosy are characterized mainly by numbness, tingling, pins and needles, hypoesthesia to touch, and hypoesthesia to needle pinprick. This clinical feature can be stratified into four sensory phenotypic subgroups: two related to sensory loss compatible with long-term neuropathy and two with signs of pathological sensory input.

Identifying leprosy NP subgroups would enable pharmacological treatment of pain through the predominant pain phenotype rather than by etiology. Future clinical trials on the treatment of NP in leprosy patients could use this information to select samples more precisely.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

Ethics Research Committee of the Júlio Müller School Hospital at the Federal University of Mato Grosso previously approved this cross-sectional study under the document CAAE 62019516.7.0000.5541. After reading and explaining the objectives of the study, all participants signed the Informed Consent Form. Medical care was assured during the study period for all patients included.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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