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Routine laboratory parameters of newly diagnosed pulmonary tuberculosis patients: a single center study in Brazil

Parâmetros laboratoriais de rotina de pacientes recém-diagnosticados com tuberculose pulmonar: um estudo em um único centro no Brasil

Parámetros de laboratorio de rutina de pacientes con tuberculosis pulmonar recién diagnosticada: un estudio de un solo centro en Brasil

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Abstract

Objective: Evaluate the severity of tuberculosis and its association with laboratory tests before antituberculosis treatment. Methodology*:* Patients with pulmonary tuberculosis were evaluated for severity using data available in medical records (Clinical; Excretion of mycobacteria; and Diagnostic imaging) and associated with biochemical and hematological parameters requested at the time of diagnosis and before antituberculosis treatment. Results*:* The evaluation of the severity showed a predominance of smear AFB (+), fever associated with other symptoms and infiltrative tuberculosis. Only a positive correlation between mycobacteria excretion and imaging diagnosis (rho=0.47; p=0.023) was observed. The patients presented hyponatremia (9/21), hypomagnesemia (6/13), and hypercalcemia (1/13), unrelated to the severity. The presence of fever influenced the number of non-segmented neutrophils (p=0.0142) and the total leukocyte count correlated with the increase in total neutrophils (rho=0.9631; p<0.0001). Conclusion*:* Different severity characteristics of tuberculosis, although they reflect the degree of commitment of the patient, are not always correlated; the evaluation of electrolytes could contribute to clinical behavior; and non-segmented neutrophils are associated with a worse clinical prognosis in patients with tuberculosis.

Keywords: Diagnostic imaging; Water-electrolyte imbalance; *Mycobacterium tuberculosis*; Neutrophil; Signs and symptoms.

Resumo

Objetivo: Avaliar a gravidade da tuberculose e sua associação com testes laboratoriais antes do início do tratamento antituberculose. Metodologia: Pacientes com tuberculose pulmonar foram avaliados quanto à gravidade usando dados disponíveis em prontuários (Clínica; Excreção de micobactéria; Diagnóstico por imagem) e associado a parâmetros bioquímicos e

hematológicos solicitados no momento do diagnóstico e antes do tratamento antituberculose. Resultados: A avaliação da gravidade mostrou predomínio de esfregaço de BAAR (+), febre associada a outros sintomas e tuberculose infiltrativa. Observou-se apenas correlação positiva entre excreção de micobactérias e diagnóstico por imagem (rho = 0,47; *p* = 0,023). Os pacientes apresentavam hiponatremia (9/21), hipomagnesemia (6/13) e hipercalcemia (1/13), sem relação com a gravidade. A presença de febre influenciou o número de neutrófilos não segmentados (*p* = 0,0142) e a contagem total de leucócitos correlacionou-se com o aumento dos neutrófilos totais (rho = 0,9631; *p* <0,0001). Conclusão: As diferentes características de gravidade da tuberculose, embora reflitam o grau de comprometimento do paciente, nem sempre estão correlacionadas; a avaliação de eletrólitos pode contribuir para o comportamento clínico; e os neutrófilos não segmentados estão associados a um pior prognóstico clínico em pacientes com tuberculose.

Palavras-chave: Diagnóstico por imagem; Desequilíbrio hidroeletrolítico; *Mycobacterium tuberculosis*; Neutrófilo; Sinais e sintomas.

Resumen

Objetivo: Evaluar la gravedad de la tuberculosis y su asociación con pruebas de laboratorio antes del tratamiento antituberculoso. Metodología: Se evaluó la gravedad de los pacientes con tuberculosis pulmonar utilizando los datos disponibles en los registros médicos (Clínica; excreción de micobacterias y diagnóstico por imagen) y asociado a parámetros bioquímicos y hematológicos solicitados en el momento del diagnóstico y antes del tratamiento antituberculoso. Resultados: La evaluación de la gravedad mostró un predominio de BAAR frotis (+), fiebre asociada a otros síntomas y tuberculosis infiltrativa. Solo se observó una correlación positiva entre la excreción de micobacterias y el diagnóstico por imágenes (rho = 0,47; *p* = 0,023). Los pacientes presentaron hiponatremia (9/21), hipomagnesemia (6/13) e hipercalcemia (1/13), sin relación con la gravedad. La presencia de fiebre influyó en el número de neutrófilos no segmentados (*p* = 0,0142) y el recuento total de leucocitos se correlacionó con el aumento de neutrófilos totales (rho = 0,9631; *p* <0,0001). Conclusión: Las diferentes características de gravedad de la tuberculosis, aunque reflejan el grado de compromiso del paciente, no siempre están correlacionadas; la evaluación de electrolitos podría contribuir al comportamiento clínico; y los neutrófilos no segmentados se asocian a un peor pronóstico clínico en pacientes con tuberculosis.

Palabras clave: Diagnóstico por imagen; Desequilibrio hidroelectrolítico; *Mycobacterium tuberculosis*; Neutrófilo; Signos y sintomas.

1. Introduction

Tuberculosis is an infectious disease mainly caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and according to the World Health Organization (WHO), 1,7 billion people (a quarter of the world's population) are infected with the bacillus, and 10.4 million develop the active form every year, with an estimate of 1,7 million deaths. The highest incidences of tuberculosis are in developing countries, such as Brazil, and constitute a serious public health problem. Every year, around 80,000 new cases and 5,000 deaths from tuberculosis are identified in Brazil, ranking it among the 22 countries with the highest incidence of the disease (WHO, 2019).

Tuberculosis diagnosis is based on three main axes: clinical, radiological, and acid-alcohol resistant bacilli (AFB) search. The symptomatology of tuberculosis is influenced by its form, pulmonary (more frequent), extrapulmonary, or miliary. In general, the main symptoms are fever developed in the late afternoon, night sweats, food apathy, and marked weight loss (Bertolozzi et al., 2014). In association with the clinical diagnosis, radiological diagnosis has been shown to be of great value, in which X-ray and/or Computed Tomography can demonstrate opacities and mainly cavitation characteristics suggestive of active pulmonary tuberculosis. It should be noted that in Brazil, approximately 26.7% of patients are treated without bacteriological confirmation of pulmonary tuberculosis, based only on the clinical radiological profile (Giacomelli et al., 2017).

Several authors have evaluated the severity of tuberculosis through diagnostic criteria of the three main axes, but few have correlated with laboratory data from the diagnostic routine (Panteleev et al., 2017). In general, diagnostic routine exams, such as electrolytes and hematological parameters, are accessible to most of the population, because they tend to be not expensive and can be performed by a variety of equipment. Thus, the objective of this study was to evaluate the severity of tuberculosis through the evaluation of clinical, bacteriological, and imaging diagnosis and its association with laboratory tests before antituberculosis treatment.

2. Methodology

This is a primary, cross-sectional, retrospective study (Hochman et al., 2005; Pereira et al., 2018) performed at the Tisiology Outpatient Clinic of the “Profª Ana Cardoso Maia de

Oliveira Lima" Ambulatory of Presidente Prudente. Patients with tuberculosis treated during the period between 2017 and 2018 were invited to participate in the study.

The study included patients with tuberculosis of both sexes, over 18 years of age, without HIV/Aids, with information on the medical records of diagnostic symptoms, images (X-ray and/or computed tomography) and laboratory results of mycobacteria search (bacilloscopy and/or culture). Patients who belong to the penitentiary system were excluded due to ethical issues.

The severity of tuberculosis was analyzed and stratified after the review of data available in the medical records in three categories: 1) Clinical: evaluation of the presence of fever and other symptoms, such as cough, fatigue, night sweats and weight loss, and after analysis, stratified as: Asymptomatic; No fever; Fever; 2) Excretion of mycobacteria: bacilloscopy and/or culture results were evaluated, and after analysis, stratified as: Negative; Positive (+); Positive (++); 3) Diagnostic imaging: X-ray and/or computed tomography results were evaluated and, after analysis, stratified as: Tuberculoma (presence of granuloma); Infiltrated tuberculosis (presence of opacities, bronchial tree); Cavitation (Panteleev et al., 2017).

For the association of tuberculosis severity with the laboratory data requested at the time of diagnosis and before antituberculosis treatment, the biochemical and hematological parameters present in the medical records were selected, although not all the patients had all the studied variables.

The correlation between the different severity categories of tuberculosis was performed using Spearman's test and the association of the stratification of each category with the biochemical parameters before the antituberculosis treatment was performed by the Kruskal-Wallis test, followed by Dunn's test. Significant results were considered with $p<0.05$.

The study protocol was designed in compliance with the Declaration of Helsinki. All participants were informed about the study and signed a free and informed consent form. The research was approved by the Research Ethics Committee (protocol nº 72754017.4.0000.5515).

3. Results

During the period of the study, 59 patients were invited to the study, but after the evaluation of the medical records, only 23 patients with pulmonary tuberculosis met the

inclusion diagnosis criteria, of which three were females, mean age 52.67 (±18.45) years and 20 males, mean age 45.70 (±15.22) years.

The assessment of the severity of tuberculosis showed that most of the patients had mycobacteria detected, and 52.18% were classified as positive (+). Only four patients were negative for both bacilloscopy and culture (17.39%) but were confirmed with tuberculosis by the presence of clinical signs and radiological alterations. Regarding the clinical signs, most of the patients presented fever (56.52%), and only two patients were asymptomatic (8.7%). The evaluation of the imaging diagnosis demonstrated that all the patients presented alterations suggestive of active tuberculosis, most of them characterized as infiltrative tuberculosis (60.87%). Table 1 shows the distribution of tuberculosis patients characteristics and the criteria used to classify the severity of the disease.

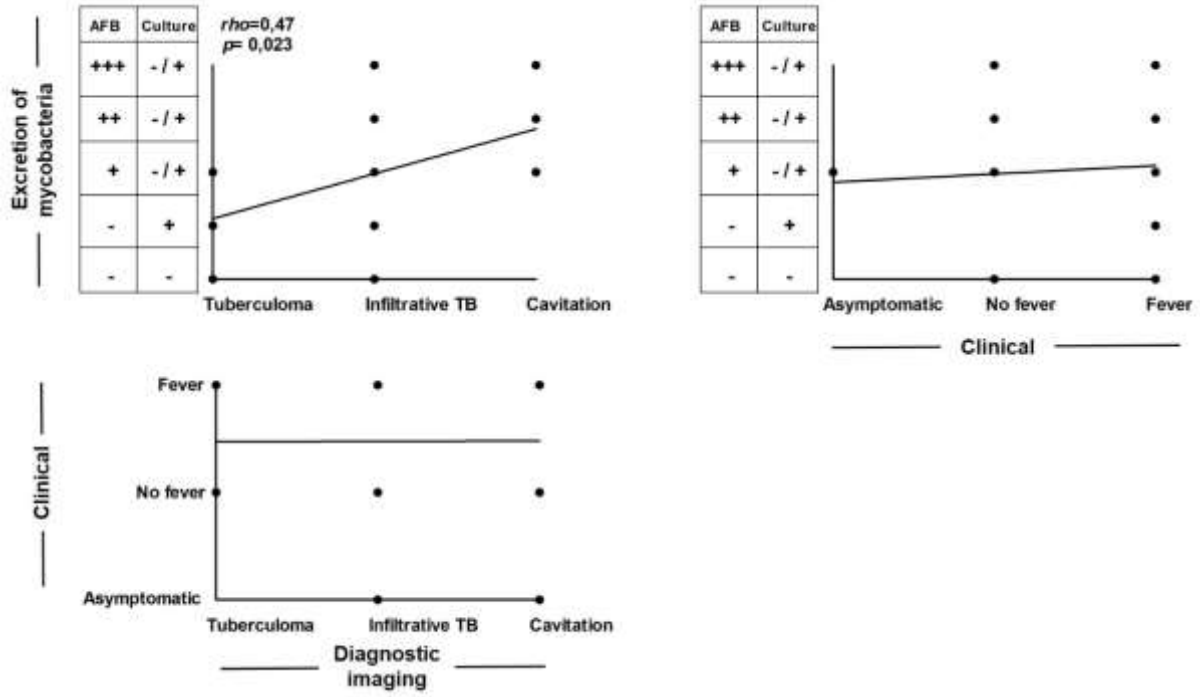
Table 1. Pulmonary tuberculosis patient's characterization according to stratification of severity categories of mycobacterial excretion, clinical and diagnostic imaging.

Tuberculosis severity			**n (%)**	**Severity stratification for association with laboratory aspects**
Mycobacteria excretion	AFB	Culture		
	-	-	4 (17,39)	Negative
	-	+	2 (8,70)	Positive (+)
	+	- / +	10 (43,48)	
	++	- / +	3 (13,04)	Positive (++)
	+++	- / +	4 (17,39)	
Clinical signs	Fever	Other symptoms[a]		
	-	-	2 (8,70)	Assintomatic
	-	+	8 (34,78)	No fever
	+	+	13 (56,52)	Fever
Image diagnosis	Normal		0	
	Tuberculoma		5 (21,74)	Tuberculoma
	Infiltrative tuberculosis		14 (60,87)	Infiltrative tuberculosis
	Cavitation		4 (17,39)	Cavitation

AFB (Acid fast bacilli). [a] Cough, fatigue, night sweats and weight loss. Source: Authors.

Analysis of the severity of tuberculosis showed that there was a positive correlation between mycobacteria excretion and imaging diagnosis (rho=0.47; p=0.023), but no correlation between clinical signs and mycobacterial excretion nor diagnostic imaging. Figure 1 shows the correlation of different criteria of severity (defined in Table 1) of tuberculosis patients.

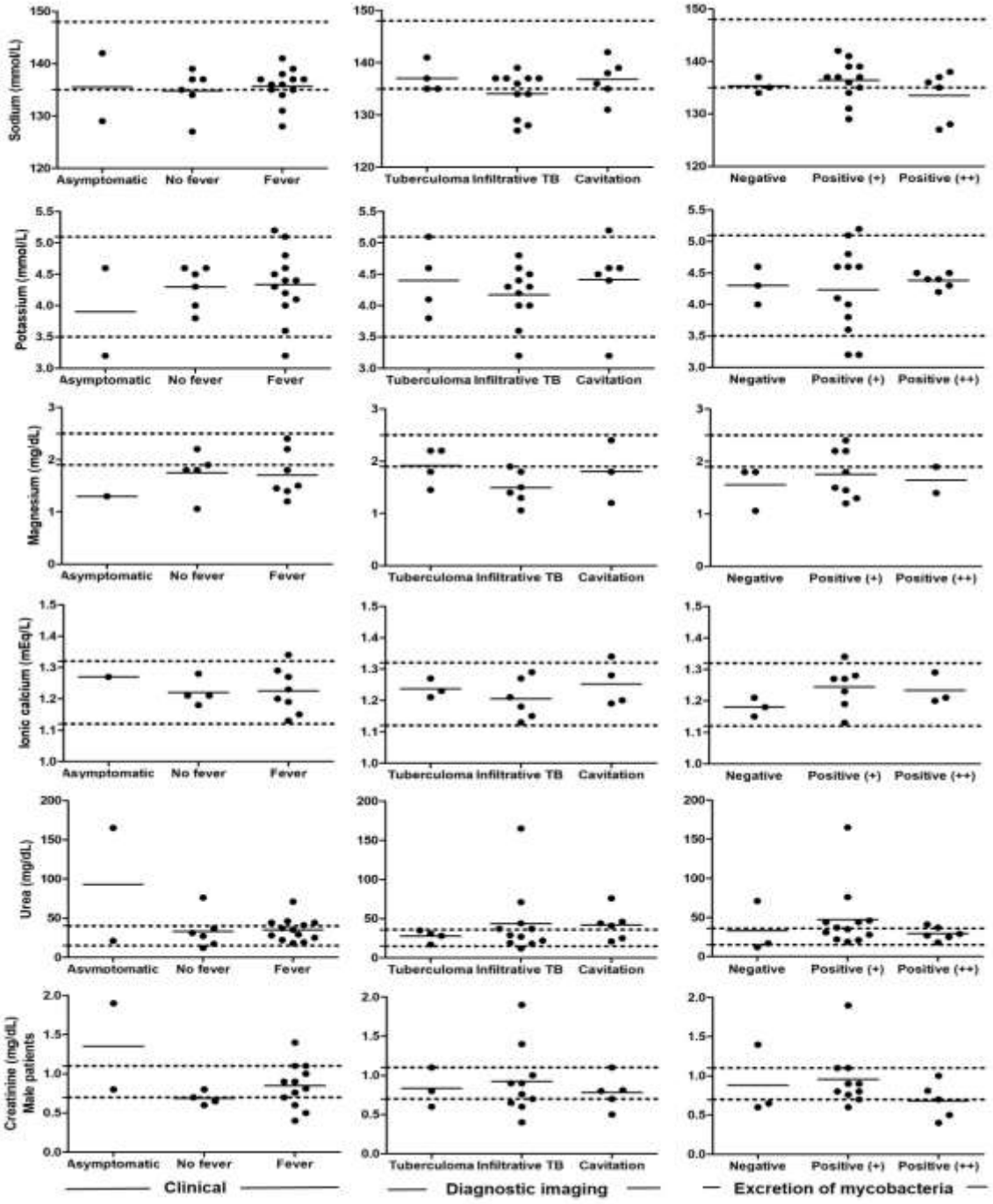
Figure 1. Correlation of clinical, imaging and mycobacterial excretion severity characteristics of pulmonary tuberculosis patients. Correlation between the variables was performed by the Spearman test, and was considered significant when $p<0,05$.



Source: Own authorship.

Among the biochemical variables analyzed, the most requested at the time of diagnosis were urea (n=21), potassium (n=21), sodium (n=21), and creatinine (n=21), the latter evaluated only in male patients (n=18), and ionic calcium (n=13). The results showed that 9/21 patients presented hyponatremia, 6/13 presented hypomagnesaemia, and 1/13 hypercalcaemia. The association of these variables with the tuberculosis severity parameters demonstrated no difference in any of the stratifications evaluated. Figure 2 shows the comparison of biochemical routine parameters stratified by each criteria of severity (defined in Table 1) of tuberculosis patients.

Figure 2. Biochemical evaluation of patients with pulmonary tuberculosis according to the stratification of the severity characteristics clinical, imaging and mycobacterial excretion. The comparison between the different groups was performed by the Kruskal-Wallis test, followed by the Dunn test, and was considered significant $p<0,05$. The median for each variable is represented and dotted lines represent the reference values of each variable.

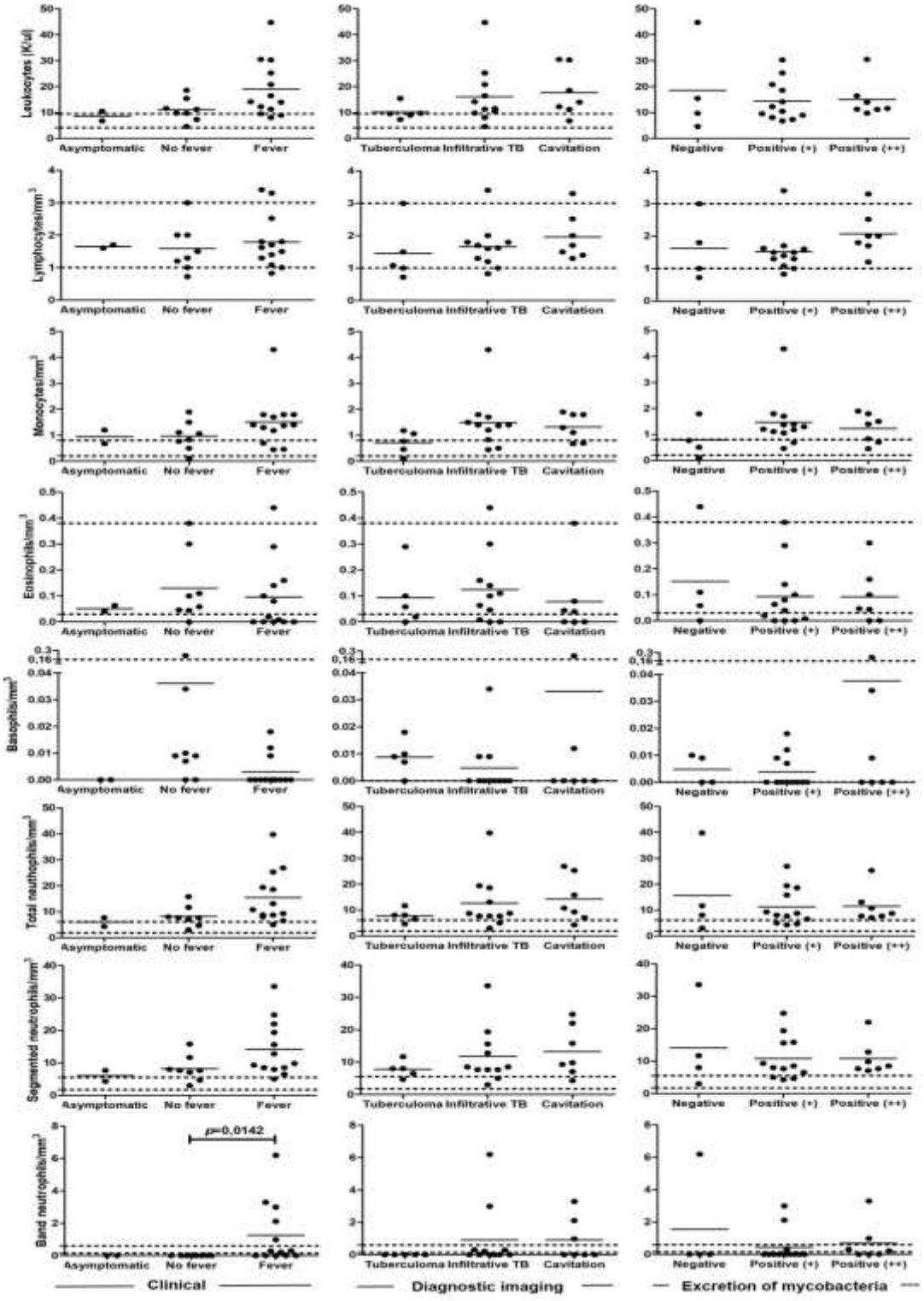


Source: Own authorship.

All patients with tuberculosis presented leukogram results, with normal values for lymphocytes (n=19), basophils (n=20), eosinophils (n=14) and non-segmented neutrophils

(n=19). Total leukocytes (n=15), monocytes (n=15), total neutrophils (n=18), and segmented neutrophils (n=19) were above the reference values in most patients. Analysis of the leukogram distribution demonstrated that only the clinical stratification had an influence on the number of non-segmented neutrophils, which was higher in patients presenting fever and other symptoms when compared to patients presenting only other symptoms, with absence of fever (p=0.0142). Figure 3 shows the comparison of leukocyte routine parameters stratified by each criteria of severity (defined in Table 1) of tuberculosis patients.

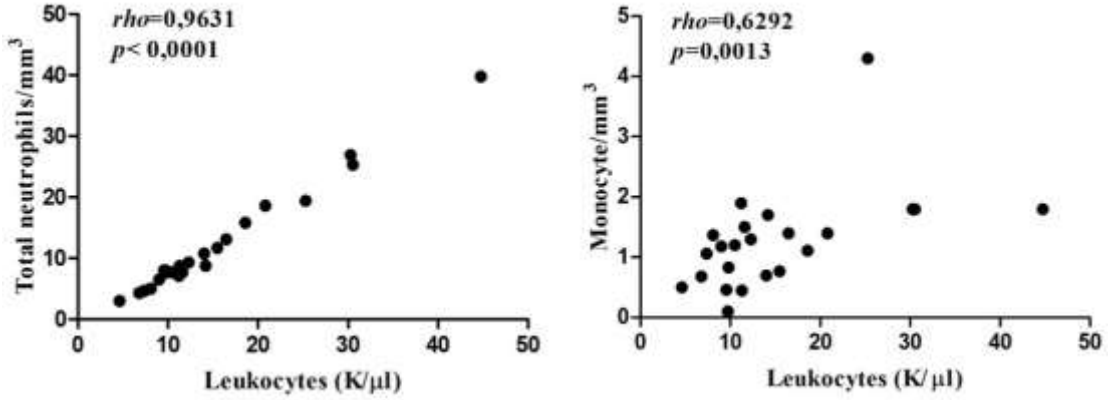
Figure 3. Leukocyte evaluation of pulmonary tuberculosis patients according to stratification of severity of clinical characteristics, image and mycobacterial excretion. The comparison between the different groups was performed by the Kruskal-Wallis test, followed by the Dunn test, and was considered significant p<0,05. The median for each variable is represented and dotted lines represent the reference values of each variable.



Source: Own authorship.

The correlation between the total leukocyte count and the monocytes and total neutrophils showed that both cells were correlated with the total leukocytes increase, with total neutrophils presenting a very strong correlation (rho=0.9631; $p<0.0001$) compared to monocytes (rho=0.6292; $p=0.0013$). Figure 4 shows the correlation between neutrophils and leukocytes and between monocytes and leukocytes to understand which cell would be related with tuberculosis.

Figure 4. Correlation of total neutrophils and monocytes in relation to leukocytes in patients with pulmonary tuberculosis. Correlation between the variables was performed by the Spearman test, and was considered significant when $p<0,05$.



Source: Own authorship.

4. Discussion

Tuberculosis is an infectious disease in which progression depends on the immune response of its host, in its health. Several laboratory tests used in the diagnostic routine are capable of evaluating the general condition of the patient, such as renal function, however, few studies have associated their results to the severity of tuberculosis, evaluated in the present study through routine tests for the diagnosis of tuberculosis, such as imaging and AFB search, as well as the clinical evaluation of the patient.

Supposedly, different manifestations of tuberculosis can similarly assess the severity of the disease, so it would be expected to have a strong correlation with each other (Panteleev et al., 2017). In the present study, however, only the stratification of excretion of mycobacteria and evaluation of the diagnosis by imaging were correlated, showing no correlation with the clinical evaluation.

Results different from those expected in the assessment of tuberculosis severity were also observed in another study, which showed a correlation between the forms of tuberculosis and the extent of the disease and clinical severity; tissue destruction and extent of the disease with the presence of *M. tuberculosis* and between them; however, there was no association between tissue destruction, presence of *M. tuberculosis* and extent of disease (Panteleev et al.,k 2017). Although the present study evaluated some manifestations of tuberculosis similar to the aforementioned study, the authors did not have access to refined data, such as a very detailed interpretation of the imaging diagnosis, which would allow to evaluate the tissue destruction and the extent of the disease, since the original X-rays or CT scans of patients were not available.

Another recent study found a weak association between the presence of *M. tuberculosis*, through the smear microscopy positivity and the extent of alterations present in the chest X-ray, not observing the same association in the absence of cavitation. The authors caution clinicians not to over interpret the results of imaging diagnosis, despite generally reflecting the severity of tuberculosis (Murthy et al., 2018).

Most patients with active tuberculosis are in a catabolic state and present weight loss associated with vitamin and mineral deficiency at the time of diagnosis (Mohamed-Hussein et al., 2016). Hyponatremia is defined as a serum sodium level below 135 mmol/L and is a common problem among hospitalized patients, reported in both acute and chronic diseases (Korzelius et al., 2013). Pulmonary tuberculosis is one of the few pulmonary infections that can induce hyponatremia, attributing this finding to dehydration, promoted by vomiting, loss of muscle mass, fever, and sweating, due to the sweat being considered hypotonic when compared to plasma (Jonaidi Jafari et al., 2013; Olalekan et al., 2015).

The present study demonstrated that 9/21 patients with tuberculosis had hyponatremia, presenting concordant data with the prevalence observed in a study carried out in Iranian patients with pulmonary tuberculosis, in which hyponatremia was associated with older age, a fact not observed in our evaluation (Jonaidi Jafari et al., 2013). In the present study, no differences were observed between the levels of sodium according to the severity of tuberculosis and no studies were found with this approach.

A study evaluating patients newly diagnosed for pulmonary tuberculosis showed that 72% had hyponatremia, and that the chance of manifesting the change was 2.57 times higher for newly diagnosed patients than in the treated cases. Other authors observed that patients with pulmonary tuberculosis had lower sodium levels when compared to controls (Patil & Mrudula, 2019; Purohit et al., 2017). However, a study conducted with patients newly

diagnosed with tuberculosis demonstrated higher sodium levels in the patients compared to the control subjects and associated antituberculosis treatment with the development of hyponatremia, demonstrating that hyponatremia is still a controversial aspect during antituberculosis treatment (Olalekan et al., 2015).

The stress present in severe and chronic diseases promotes an increase in the catabolism of proteins, leading to the movement of potassium from the intracellular compartment into the plasma, and, consequently, the secretion of this electrolyte in the urine, sweat and vomit, leading to the loss of potassium in situations that do not have a compensatory replacement through feeding, such as anorexia, a common symptom in pulmonary tuberculosis, being hypokalemia defined as below normal potassium levels (Olalekan et al., 2015; Patil & Mrudula, 2019; Purohit et al., 2017; Kardalas et al., 2018). The present study did not observe a significant loss of potassium in patients with pulmonary tuberculosis, as well as a difference according to the severity of tuberculosis. Other studies with patients with pulmonary tuberculosis have demonstrated lower potassium levels in patients when compared with controls and the presence of hypokalemia in 48% of patients newly diagnosed for tuberculosis, however no assessment of tuberculosis severity has been reported (Olalekan et al., 2015; Patil & Mrudula, 2019).

Although magnesium is involved in several vital physiological functions, few studies have evaluated hypomagnesemia, defined as magnesium levels below 1.6 mg/dL, but which do not promote signs and symptoms until levels decrease to 1.2 mg/dL, and low levels of magnesium have been associated with the presence of malnutrition in patients with pulmonary tuberculosis (Pham et al., 2014; Agrawal et al., 2017). The present study demonstrated that 6/13 of the patients presented hypomagnesemia, among them only two with risk values (≤1.2 mg/dL), a fact that was not influenced by the severity of tuberculosis (Pham et al., 2014).

A study performed with pulmonary tuberculosis showed that patients with positive smear microscopy had decreased levels of magnesium, although not levels of hypomagnesemia, when compared to patients with negative smear microscopy and controls. In addition, the same authors associated decreased levels of magnesium with delayed bacilloscopy conversion in positive AFB patients (Agrawal et al., 2017). Another study that correlated magnesium levels with tuberculosis severity demonstrated an inverse relationship between magnesium levels and duration of disease (months), extent of disease (minimal, moderate, advanced, and very advanced), and the presence of symptoms, such as hemoptysis and weight loss, concluding that the magnesium level may be a reasonable indicator to assess the severity of pulmonary tuberculosis (Irfan et al., 2017).

Calcium can be found in plasma in three different forms, free as ionized calcium (50%), bound to proteins, mainly albumin (35-40%), and in combination with low molecular weight molecules such as bicarbonate, phosphate, lactate, citrate, among others, but only the free portion has relevant physiological function (Basseto et al., 2013). Tuberculosis is one of the granulomatous diseases that alter the concentration of calcium in the plasma, with an incidence of varied hypercalcemia among distinct populations, mainly due to the differences in vitamin D and calcium consumption and in the time of sun exposure (Rohini et al., 2014; Roussos et al., 2001; Memon, Shah & Kazi, 2014). Some authors, on the other hand, reported hypocalcemia in patients with tuberculosis and associated this finding with malnutrition and malabsorption during the active disease (Rohini et al., 2014). In the present study, only one patient presented hypercalcemia and calcium levels were not associated with the severity of tuberculosis. Another study evaluating patients with pulmonary tuberculosis concluded that the hypocalcemia present was associated with an increase in the concentration of AFB, suggesting that *M. tuberculosis* would be the cause of the change (Chandra & Sowjanya, 2018).

In addition to electrolyte dosage, renal function may be evaluated in conjunction with quantification of serum creatinine and urea. Creatinine levels may be influenced by muscle function, muscle composition, activity, diet, and health status of the individual and their levels are indicative of renal failure when it is above the reference values (Edmund & David, 2006; Banfi & Del Fabbro, 2006). Urea is associated with protein and amino acid catabolism, and when elevated (uremia) is indicative of renal failure, however, other factors such as diet may influence its levels (Badar, Arif, & Alam, 2018). The present study demonstrated that only two patients had high levels of creatinine and six of uremia, and the levels of both were not associated with the severity of tuberculosis and there were no studies that presented this approach.

The hematopoietic system is severely affected during active tuberculosis, influencing the myeloid and lymphoid lineages, as well as plasma components, and these alterations can be used as diagnostic markers, prognosis and response to antituberculosis treatment (Morris, Bird, & Nell, 1989). The present study demonstrated that the elevation of leukocytes in patients with tuberculosis is mainly related to the increase of total neutrophils, a fact observed by other authors (AL-Omar, Al-Ashban, & Shah, 2009). A study that evaluated patients before and after treatment reported an increase in neutrophil differential counts after completion of the intensive phase of antituberculosis treatment, in relation to pretreatment counts (Kassa et al., 2016).

Regarding the association of severity parameters of patients with pulmonary tuberculosis and leukogram evaluation, a study showed that neutrophils may be mediators of tissue damage, associating with the impact of tuberculosis on the bone marrow, suggesting that non-segmented neutrophils would be indicators and not cause of pulmonary destruction in tuberculosis (Panteleev, et al., 2017). Another study concluded that neutrophil counts are positively correlated with bacilliferous load, associating neutrophilia with the risk of mortality in patients with tuberculosis (Lowe et al., 2013). In the present study, a relationship was observed between the non-segmented neutrophils and the presence of fever, a symptom associated with the stimulation of the inflammatory process.

Neutrophils can contribute to the pathological process of tuberculosis through different mechanisms. One of them is a concept applied not only to tuberculosis, but also to other infectious diseases, such as visceral leishmaniasis, which consists of neutrophil theory acting as a Trojan horse, harboring *M. tuberculosis* inside it, rendering it inaccessible to macrophages for elimination (Lowe et al., 2012; Santos-Mateus et al., 2016). In addition, neutrophils are associated with the transition from latent tuberculosis to the active form of the disease and can act as mediators of tissue destruction, severity and progression of tuberculosis (Lyadova, 2017).

5. Final Considerations

The evaluation of different characteristics of tuberculosis severity, although they reflect the degree of commitment of the patient, is not always correlated, fact that could be explained by the lack of standardization of the information present in the medical records, which could be improved by the application of a standard form for clinical, radiological and microbiological evaluation. The presence of alterations in the electrolytes of patients with pulmonary tuberculosis before antituberculosis treatment, although did not correlate with the severity stratification, may be associated with the patient's general condition and could contribute to the clinical course. In addition, the association between non-segmented neutrophils and a worse clinical prognosis in patients with tuberculosis suggests that the neutrophil should be evaluated for the diagnosis and evaluation of the prognosis of antituberculosis treatment.

We suggest future evaluations of the electrolytes and non-segmented neutrophils in different moments of the antituberculosis treatment and the association with the severity of

the disease to better elucidate the utility of these routine parameters in the diagnosis, prognostic and treatment follow-up of tuberculosis patients.

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