THE ASSOCIATION OF PROCALCITONIN, LACTATE, WBC COUNT, AND INTERLEUKIN-10 MAY BE HELPFUL IN THE EARLY DIAGNOSIS OF SEPSIS IN BRAZILIAN PATIENTS

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ABSTRACT: Introduction: Sepsis is a set of clinical symptoms resulting from inflammation and infection. Several biomarkers are used for early diagnosis and improved management of sepsis. Objectives: This study evaluated the performance of procalcitonin (PCT), interleukin-10 (IL-10), interleukin-6 (IL-6), and classic inflammatory markers in hospitalized patients with suspected sepsis. Sixty-one patients were assessed. The participants were monitored over a three-day period: baseline (Day 0, D0), 24 hours (Day 1, D1), and 48 hours (Day 2, D2). The hospital's clinical team classified them as "sepsis" or "non-sepsis". Results: On the first day (D0), PCT, lactate, leukocyte count, IL-10, and IL-6 were elevated in patients with sepsis compared to those without. On Day 1, all of these biomarkers remained elevated in the sepsis group except for IL-6. By Day 2, none of the parameters differed between the sepsis and non-sepsis groups. AUC analyses demonstrated that PCT, lactate, leukocyte count, and IL-10 could

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discriminate between sepsis and non-sepsis patients, with IL-10 showing the best sensitivity and specificity at D0 and D1. Conclusion: When combined, the biomarkers performed better in diagnosing sepsis in the Brazilian population.
KEYWORDS: Procalcitonin; Interleukin-10; Interleukin-6; Sepsis.

ASSOCIAÇÃO DE PROCALCITONINA, LACTATO, CONTAGEM GLOBAL DE LEUCÓCITOS E INTERLEUCINA-10 PODE SER ÚTIL NO DIAGNÓSTICO PRECOCE DA SEPSE EM PACIENTES BRASILEIROS

RESUMO: Introdução: Sepse é um conjunto de sintomas clínicos resultantes de inflamação e infecção. Vários biomarcadores são usados para um diagnóstico precoce e melhor manejo da sepse. Objetivos: Este estudo avaliou o desempenho da procalcitonina (PCT), interleucina 10 (IL-10), interleucina 6 (IL-6) e marcadores inflamatórios clássicos em pacientes hospitalizados com suspeita de sepse. Sessenta e um pacientes foram avaliados. Os participantes do estudo foram acompanhados por um período de três dias: primeiro dia (D0), 24h (D1) e 48h (D2). A equipe clínica do hospital os classificou como "sepse" ou "não sepse". Resultados: Os resultados mostraram que no primeiro dia, PCT, lactato, contagem de leucócitos, IL-10 e IL-6 apresentaram aumento na sepse em comparação aos pacientes sem sepse. No D1, os biomarcadores anteriores permaneceram elevados nos pacientes com sepse, exceto IL-6. No D2, nenhum dos parâmetros analisados diferiu entre os grupos com sepse e sem sepse. As análises de AUC mostraram que PCT, lactato, contagem de leucócitos e IL-10 puderam discriminar entre pacientes com sepse e sem sepse, com IL-10 apresentando melhor sensibilidade e especificidade no D0 e D1. Conclusão: Quando combinados, os biomarcadores tiveram desempenho melhor no diagnóstico de sepse na população brasileira.
PALAVRAS-CHAVE: Procalcitonina; Interleucina-10; Interleucina-6; Sepse.

LA ASOCIACIÓN DE PROCALCITONINA, LACTATO, RECUENTO DE LEUCOCITOS E INTERLEUCINA-10 PUEDE SER ÚTIL EN EL DIAGNÓSTICO PRECOZ DE LA SEPSIS EN PACIENTES BRASILEÑOS

RESUMEN: Introducción: La sepsis es un conjunto de síntomas clínicos resultantes de la inflamación y la infección. Varios biomarcadores se utilizan para un diagnóstico temprano y un mejor manejo de la sepsis. Objetivos: Este estudio evaluó el rendimiento de la procalcitonina (PCT), la interleucina 10 (IL-10), la interleucina 6 (IL-6) y los marcadores inflamatorios clásicos en pacientes hospitalizados con sospecha de sepsis. Se evaluó un total de sesenta y un pacientes. Los participantes fueron seguidos durante un periodo de tres días: día inicial (D0), 24 h (D1) y 48 h (D2). El equipo clínico del hospital los clasificó como “sepsis” o “no sepsis”. Resultados: En el primer día (D0), PCT, lactato, recuento de leucocitos, IL-10 e IL-6 mostraron niveles elevados en los pacientes con sepsis en comparación con aquellos sin sepsis. En D1, los biomarcadores mencionados permanecieron elevados en los pacientes con sepsis, excepto la IL-6. En D2, ninguno de los parámetros analizados mostró diferencias entre los grupos con y sin sepsis. Los análisis de área bajo la curva (AUC) indicaron que PCT, lactato, recuento de leucocitos e IL-10 pudieron discriminar entre pacientes con sepsis y sin sepsis, siendo la IL-10 la que presentó mejor sensibilidad y especificidad tanto en D0 como en D1. Conclusión: Cuando

se combinan, los biomarcadores mostraron un mejor rendimiento en el diagnóstico de la sepsis en la población brasileña.
PALABRAS CLAVE: Procalcitonina; Interleucina-10; Interleucina-6; Septicemia.

1. INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is an exaggerated defense response of the body to a noxious stressor. SIRS with a suspected source of infection is termed sepsis, a clinical syndrome with biochemical and immunological abnormalities induced by an infection (WHO, 2020).

The sooner the diagnosis is made and the correct care is applied, the reduction of mortality and a better outcome for the patient may be observed (Srzić; Nesek Adam; Tunjić Pejak, 2022). At present, there are no specific tests for sepsis. Cultures take 2–3 days and may be negative in 40–50% of cases under antimicrobial treatment (Vincent *et al*., 2020). There is a score that measures the association between organ dysfunction and subsequent mortality, the Sequential Organ Failure Assessment (SOFA) score. Sepsis diagnosis is confirmed with a SOFA score ≥ 2, and septic shock is defined by hypotension requiring therapy with vasopressor to maintain the mean arterial pressure > 65 mmHg and serum lactate level > 2 mmol/L (Singer *et al*., 2016). The qSOFA scoring system, a more straightforward clinical screening tool, includes altered mental status (Glasgow Coma Scale < 15), a respiratory rate greater than 22, and systolic blood pressure (SBP) less than 100 (Singer *et al*., 2016). However, combining biomarkers with SOFA may enhance diagnostic accuracy.

The markers commonly used for sepsis identification are procalcitonin (PCT), lactate and white blood cell (WBC) count (Ackerman *et al*., 2021). Most organs and macrophages produce PCT, a precursor of calcitonin (Póvoa *et al*., 2023). PCT rises within 3-4 hours after inflammation and helps monitor antibiotic effectiveness, though caution is needed when using it to diagnose sepsis. Lactate reflects disease severity and mortality risk, while WBC is a low-cost marker influenced by many factors, including infection (Liu *et al*., 2019; Klein *et al*., 2023). Cytokines released during infection/inflammation may provide diagnostic quickness and better clinical management of sepsis in association with established clinical criteria. Interleukin 10 (IL-10) is an anti-inflammatory cytokine produced by immune cells Peng *et al*. (2021) and IL-6 is a proinflammatory cytokine released by leukocytes and several other cells (Van Snick, 1990). IL-6 is the primary inducer of C-reactive protein (CRP) from the hepatocytes

during the acute phase of an inflammatory/infectious process. Elevations in IL-6 and IL-10 have been identified in critical illnesses such as sepsis (Mcelvaney *et al*., 2021).

This study aimed to correlate classical tests (PCT, CRP, WBC, lactate) with IL-10 and IL-6 levels in Brazilian patients hospitalized with suspected sepsis over three days.

2. PATIENTS AND METHODS

2.1 Patients

We conducted a prospective study between July and November 2016. During screening, patients with at least one infectious focus and two or more SIRS criteria were included, a strategy adopted to broaden protocol enrollment and minimize the likelihood of missed sepsis cases. Patients were subsequently classified using SOFA or qSOFA. Throughout the study period, patient evaluation at H.M.T. was based primarily on SIRS criteria, reflecting local screening practice. Although Sepsis-3 (SOFA ≥2) is now widely accepted, it was not applied systematically at that time.

The inclusion criteria were: age over 18 years, suspected sepsis, request for examinations within two consecutive days after the opening of the Sepsis Protocol, and initiation of antibiotic therapy only after collection of the first sample (protocol opening day). Exclusion criteria were: age under 18 years, absence of hospitalization despite suspected sepsis, and lack of blood collection on the first and subsequent two days after protocol initiation.

After applying the exclusion criteria, 61 participants were eligible. The study population comprised 30 women and 31 men, ranging in age from 22 to 95. All the patients were hospitalized at H.M.T., and their clinical data were accessed by the medical records. According to H.M.T., the subjects were classified into two different clinical groups: (I) Nonsepsis (N=38) and (II) Sepsis (N=23). The imbalance between the groups with and without sepsis (23 vs. 38) reflects the profile of cases during the study period and highlights the need for validation in a larger and more balanced cohort in the future.

2.2 Sample and tests

Samples were collected in heparin or EDTA-containing tubes on the day of hospitalization (D0) and the two subsequent days after the Sepsis Protocol opening. Plasma levels of PCT (VIDAS® B.R.A.H.M.A.S. PCT ™ kit), IL-10 (ImmunoTools® kit), and IL-6 (ImmunoTools® kit) were determined by ELISA. Manufacturer's protocols

were followed, and readings were processed at 450 nm using the VIDAS® immunoanalyzer or a microplate spectrophotometer.

The Madre Tereza Hospital's Clinical Analyzes laboratory performed laboratory exams (CRP, global leukocyte count, and lactate) during the patient's hospitalization as part of the routine. The hospital nursing team determined clinical data, heart and respiratory rates, blood pressure, and body temperature. The clinical evolution (discharge or death) and the results of routine exams were obtained by reading each patient's medical record.

2.3 Statistical analyzes

Statistical analyses were performed using the GraphPad Prism 9.0 software (San Diego, CA). Data were analyzed for normal distribution using the Shapiro-Wilk test. The Mann-Whitney test was used to compare the two groups. Correlation analyses were performed using the Spearman linear correlation coefficient. Categorical variables were compared using the Chi-Square test. Receiver operating characteristic (ROC) curves were used to assess the sensitivities and specificities of analyzed biomarkers. Statistically significant differences were considered $p < 0.05$.

2.4 Ethical considerations

The present work was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais (53353816.0.0000.5149) and Hospital Madre Tereza (H.M.T.), in Belo Horizonte, Minas Gerais, Brazil (57781416.8.0000.5127). All participants in this study signed a written informed consent.

3. RESULTS

3.1 Clinical characterization of participants

All 61 patients met at least two SIRS criteria. The cohort comprised 31 males (50.8%) and 30 females (49.2%), with no significant age difference between sepsis and non-sepsis groups (mean age ≈ 72 years). There was also no difference in admission setting (hospital vs. emergency department) at sepsis protocol initiation. Blood culture positivity was significantly higher in the sepsis group (89% vs. 11%) (Table 1).

No significant differences were observed between groups regarding hypotension ($p = 0.558$), tachycardia ($p = 0.979$), tachypnea ($p = 0.869$), or fever ($p = 0.204$) (data not

shown). Additionally, qSOFA scores did not differ significantly (p = 0.295) (data not shown).

Regarding outcomes (discharge vs. death), no statistical difference was found between groups. Overall mortality was 25%, with 21.7% in the sepsis group and 26.3% in the non-sepsis group (Table 1).

Table 1: Clinical and demographic data of the study participants.

	SIRS Positive (n= 61)	Sepsis (n=23)	Non-sepsis (n=38)	p-value
Gender				
Female, n	30	14	16	
Male, n	31	9	22	0.155
Age (Years)				
Mean ± SD	72.6 ± 18.2	75.3 ± 15.6	71.8 ± 19	0.54
Protocol origin, n				
Hospitalization	18	4	14	
Emergency care	43	19	24	0.106
Blood culture, n				
Positive	9	8	1	
Negative	51	15	36	**0.001***
No	42	14	28	
Outcome, n				
Discharge	46	18	28	0.687
Death	15	5	10	

Non-parametric data are presented as mean ± S.D. and were evaluated using the Mann-Whitney test. Categorical data are presented as frequency and were assessed using the Chi-Square test. $p<0.05$ was considered significant.
Note: qSOFA: quick SOFA; SIRS: Systemic Inflammatory Response Syndrome.

3.2 Parameters evaluated in sepsis and non-sepsis patients

PCT levels in sepsis patients were significantly higher than in non-sepsis patients on D0 (5.2±2.5 ng/mL vs. 0.53±0.2 ng/mL, p=0.03) and D1 (2.3±0.82 ng/mL vs. 0.36±0.12 ng/mL, p=0.04). No significant difference was observed on D2 (3.2±1 ng/mL vs. 0.52±0.21 ng/mL, p=0.09) (Figure 1A).

Lactate levels were also elevated in sepsis patients compared to non-sepsis individuals on D0 (2.9±0.3 mmol/L vs. 1.9±0.4 mmol/L, p<0.0001) and D1 (1.98±0.2 mmol/L vs. 1.2±0.1 mmol/L, p=0.01), with no difference on D2 (1.7±0.2 mmol/L vs. 1.3±0.1 mmol/L, p=0.16) (Figure 1B).

WBC counts differed significantly between groups, sepsis and non-sepsis, on all days: D0 (15.7±1.4 x10^3/mm^3 vs. 11±0.8 x10^3/mm^3, p=0.003), D1 (14.2±1.9 x10^3/mm^3

vs. 9.6±0.8 x10³/mm³, p=0.02), and D2 (12.1±1.4 x10³/mm³ vs. 9.1±0.7 x10³/mm³, p=0.04) (Figure 1C).

CRP levels showed no significant differences: D0 (57.6±7 mg/L vs. 50.3±5.2 mg/L, p=0.4), D1 (52±14 mg/L vs. 62±9 mg/L, p=0.6), and D2 (67.2±9 mg/L vs. 61.3±7.5 mg/L, p=0.5) (Figure 1D).

Sepsis patients had higher IL-10 levels than non-sepsis individuals on D0 (71.5±20.7 pg/mL vs. 50.8±13.3 pg/mL, p=0.03) and D1 (50.5±6.8 pg/mL vs. 36.6±6.4 pg/mL, p=0.003), with no significant difference on D2 (38.7±2.2 pg/mL vs. 32±2.6 pg/mL, p=0.2) (Figure 1E).

On D0, IL-6 expression was higher in sepsis patients (4±0.6 pg/mL) compared to non-sepsis individuals (3±0.2 pg/mL, p=0.04), with no differences on D1 (3±0.2 pg/mL vs. 3±0.3 pg/mL, p=0.7) and D2 (2.8±0.1 pg/mL vs. 2.7±0.1 pg/mL, p=0.7) (Figure 1F).

3.3 Potential to discriminate between sepsis and non-sepsis patients

On D0, lactate and WBC count effectively discriminated between non-sepsis and sepsis patients (Figure 2A and 2B). In contrast, PCT (AUC=0.68, p=0.06), CRP (AUC=0.57, p=0.36), IL-10 (AUC=0.69, p=0.065), and IL-6 (AUC=0.68, p=0.09) demonstrated inadequate sensitivity and specificity to discriminate non-sepsis or sepsis patients (data not shown).

On D1, PCT, lactate, WBC count, and IL-10 were adequate for discrimination between non-sepsis and sepsis patients (Figure 2C-F). However, CRP (AUC=0.59, p=0.54) and IL-6 (AUC=0.53, p=0.69) showed insufficient sensitivity and specificity to discriminate the analyzed groups (data not shown).

On D0, PCT, lactate, and WBC count exhibited similar sensitivities, while IL-10 demonstrated outstanding sensitivity (Table 2). On D1, PCT and lactate showed significantly lower sensitivity for predicting sepsis, whereas the sensitivities and specificities of WBC count and IL-10 remained consistent with D0. WBC count and IL-10 outperformed PCT and lactate in predicting sepsis on both D0 and D1 (Table 2).

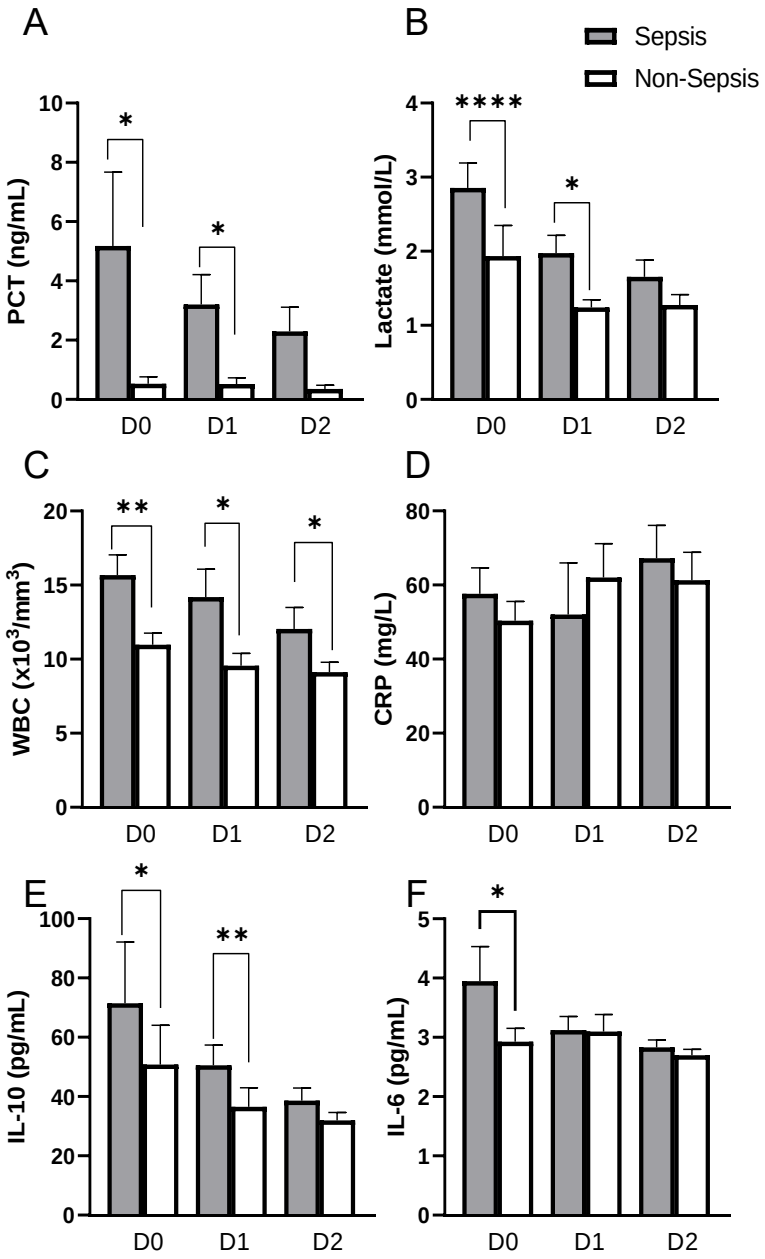

Figure 1: Assessment of procalcitonin (PCT), Lactate, leukocyte count (WBC), C-reactive protein (CRP), interleukin-10 (IL-10) and interleukin-6 (IL-6) on D0 (day of the opening of the sepsis protocol) and on the following 2 days, D1 and D2. (A) Plasma levels of PCT, (B) Lactate, (C) WBC count, (D) CRP, (E) IL-10 and (F) IL-6 in sepsis patients (n = 23) and non-sepsis individuals (n=38). Significant differences between groups are indicated by connecting lines. The Mann-Whitney test compared two groups ($p < 0.05$).

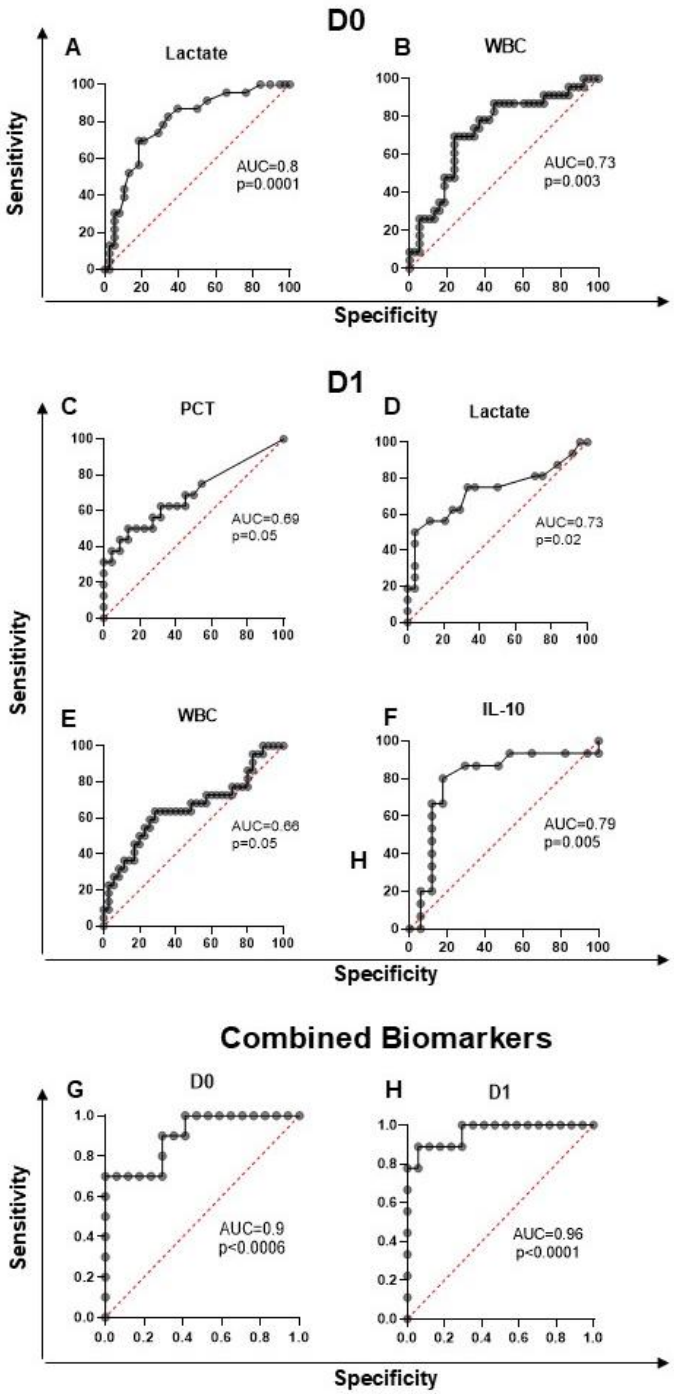

Figure 2: Measurement of parameters performance as potential biomarkers. Receiver operating Characteristics (ROC) curve analyses were calculated to determine the potential to segregate analyzed groups, sepsis, and non-sepsis on D0: (A) Lactate ROC curve and (B) WBC count ROC curve. On D1: (C) Procalcitonin (PCT) ROC curve, (D) Lactate ROC curve, (E) WBC count ROC curve and (F) Interleukine-10 (IL-10) ROC curve. (G) Combination of increased parameters on D0 (PCT, WBC count, Lactate, IL-10, and IL-6). (H) Combination of increased parameters on D1 (PCT, WBC count, Lactate, and IL-10). The area under the curve (AUC) measurement with a 95 % confidence interval and statistical significance ($p \leq 0.05$) are presented in the graphs.

Table 2: Diagnostic accuracy of biomarkers

	Cutoffs D0	Prediction of sepsis (%)		Cutoffs D1	Prediction of sepsis (%)	
		Sensitivity	Specificity		Sensitivity	Specificity
PCT (ng/mL)	>0.08	70.6	68.2	>1.03	50	86.4
Lactate (mmol/L)	>1.9	69.6	81.6	>1.8	50	95.8
WBC Count ($x10^3/mm^3$)	>12.35	69.6	76.3	>10.4	63.6	71.4
IL-10 (pg/mL)	>33.04	81.2	66.7	>31.93	80	82.4

PCT: procalcitonin; WBC Count: White blood cells count; IL-10: interleukin 10.

3.4 Correlation between analyzed biomarkers

In D0, it was observed positive correlations between PCT and WBC count, PCT and IL-10, IL-10 and WBC count, and IL-6 and WBC count in sepsis group (Table 3). On D1, a positive correlation was observed only between PCT and leukocyte count in the sepsis group (Table 3). Although the following correlations have been evaluated: PCT and lactate, WBC count and lactate and IL-10 versus lactate; there were no correlations between such parameters for the sepsis group in D0 or D1 (data not shown).

The same parameters were subjected to correlation analysis on D0 and D1 with the non-sepsis group, and none were statistically significant (data not shown).

Table 3: Correlation between analyzed parameters to sepsis group in D0 and D1

D0 Sepsis			D1 Sepsis		
Parameters	Spearman r	P Value	Parameters	Spearman r	P Value
PCT x WBC	0.6	**0.02**	PCT x WBC	0.6	**0.03**
PCT x IL-10	0.6	**0.01**			
IL-10 x WBC	0.5	**0.03**			
IL-6 X WBC	0.6	**0.01**			

Correlation coefficient data (r) obtained by the Spearman correlation test are presented. $p<0.05$ was considered significant. PCT: procalcitonin; WBC: White blood cells count; CRP: C-reactive protein; IL-10: interleukin 10, IL-6: interleukin 6.

4. DISCUSSION

Early diagnosis of sepsis remains a global challenge. Its initial signs are often nonspecific and frequently go unnoticed by both patients and healthcare providers. This study aimed to evaluate and correlate traditional tests used for assessing sepsis—PCT, CRP, total leukocyte count, and lactate—as well as serum levels of IL-10 and IL-6 in

Brazilian patients hospitalized with suspected sepsis. The objective was to determine whether combining these biomarkers could enhance early sepsis diagnosis. The study received ethical approval and informed consent in 2016, which remains valid to date. Although conducted in 2016, the data still adhere to ethical standards and retain scientific and clinical relevance, as sepsis continues to be a leading cause of hospital mortality in Brazil.

There was no statistically significant difference in sepsis prevalence between genders in this study. Our findings align with recent research characterizing Brazilian sepsis inpatients, which reported no gender differences in hospitalization rates or mortality from sepsis[12]. Conversely, another study indicated a higher mortality rate among males within the Brazilian sepsis population (Moura *et al*., 2017). However, a systematic review analyzing ten years of literature found no definitive conclusions regarding the relationship between gender and sepsis mortality (Failla; Connelly, 2017), thus highlighting the lack of consensus on this issue.

The average age of the sepsis group was approximately 75 years, underscoring the prominence of older adults in this population. It is well established that the highest incidence of sepsis in Brazil occurs among the elderly (Almeida *et al*., 2022). Additionally, after age 65, individuals often present with comorbidities that can mimic sepsis symptoms, and advanced age is considered a risk factor for the development of, and higher mortality from, sepsis (Gotts; Mattay, 2016).

This study also examined the origin of the protocol, dividing patients between hospital admission and emergency care. No significant differences were observed between these groups at the time of protocol initiation. However, it is noteworthy that a high proportion of sepsis cases originated from the emergency room. In 2017, the Latin American Sepsis Institute (ILAS) surveyed 2,000 Brazilians about sepsis, and only 14% had heard of the condition (ILAS, 2017). These data highlight the urgent need to promote awareness of sepsis among healthcare professionals and the general population.

During the study, patients were screened using the SIRS criteria. Mortality among SIRS patients was approximately 25%. For the sepsis group, mortality was 21.7%, while in the non-sepsis group it was 26.3%. The lower mortality among sepsis patients may reflect that many individuals exhibited SIRS symptoms due to other underlying conditions, leading to death from complications unrelated to sepsis. A recent study analyzing septic patient survival reported mortality rates of 13.7% for sepsis, 27.5% for

severe sepsis, and up to 80% for septic shock (Silva *et al*., 2019). Importantly, early recognition of suspected sepsis and well-established management protocols can minimize adverse outcomes by ensuring prompt, appropriate care—potentially reducing mortality.

As expected, a significant difference was observed in positive blood culture rates between sepsis and non-sepsis patients. Of nine patients with positive blood cultures, eight were classified as septic. The patient classified as non-septic, who had a positive blood culture, died on the day of admission; *Staphylococcus aureus* was isolated in this case, suggesting a possible misclassification. The rate of positive blood cultures in septic patients was 35%, consistent with the literature, which indicates that 30–50% of severe sepsis cases are blood culture positive (Diament *et al*., 2011). Conversely, it is also known that isolating the causative pathogen is often challenging, with positive results obtained in only approximately 25–50% of sepsis cases (Taeb; Hooper; Marik, 2017).

This study observed a significant difference in PCT levels on D0 and D1 between the sepsis and non-sepsis groups. Research by Angeletti *et al*. (2015) demonstrated higher PCT levels in septic patients compared to those with SIRS or controls (Angeletti *et al*., 2015). Similarly, Zeng *et al*. (2022) reported increased PCT in septic patients experiencing hyperinflammatory responses (Zeng *et al*., 2022). Our findings support the diagnostic utility of PCT for early sepsis identification and monitoring progression toward septic shock (Heredia-Rodríguez *et al*., 2017). Although PCT levels tended to be higher in septic patients, regression analysis showed borderline significance ($p \approx 0.06$ on D0 and 0.05 on D1). Regarding diagnostic performance, PCT showed a sensitivity of approximately 71% and specificity of 68% on D0, with sensitivity decreasing to 50% on D1. Other studies have reported similar sensitivity and specificity (~63%), reinforcing PCT's role as an adjunct marker for early sepsis detection (Karon *et al*., 2017).

An increased lactate level was observed in sepsis patients on D0 and D1, demonstrating lactate's potential value in differentiating between sepsis and non-sepsis groups; this finding was reinforced by the AUC analysis for both days. Consistent with our results, higher lactate levels were found in patients with confirmed sepsis compared to those without the diagnosis. The study by Singer *et al*. (2014) showed that elevated serum lactate levels are more indicative of sepsis severity (Singer *et al*., 2014). Similarly, Karon and colleagues reported higher lactate levels among patients classified as septic (Karon *et al*., 2017). The sensitivity and specificity of lactate for distinguishing sepsis from non-sepsis were 55.1% and 62.7%, respectively. In our study, these values were

higher, with a sensitivity of 69.6% and a specificity of 81.6% on D0 at a cutoff of 1.90 mmol/L. On D1, sensitivity decreased. Since elevated lactate levels are not specific solely to sepsis, it is important to note that lactate serves as a valuable prognostic biomarker, as numerous studies have linked high lactate levels to increased mortality (Vincent; Bakker, 2021).

Our data also showed a significant rise in WBC count in sepsis patients compared to non-sepsis controls over the three days of evaluation (D0, D1, D2). The AUC analysis confirmed that higher WBC counts were associated with sepsis, particularly on D0 and D1. Elevated WBC levels during the initial three days of hospitalization, combined with PCT concentrations, have been shown to help differentiate infected postoperative patients. In our study, on D0, the sensitivity and specificity at a threshold of 12,350 cells/mm³ were 69.6% and 76.3%, respectively. These parameters decreased on D1, indicating that WBC count remains a useful parameter, especially in early diagnosis. Our findings align with previous research reporting a sensitivity and specificity of around 66% for WBC count. Although expected, these results highlight the importance of classical markers like WBC in diagnosing and monitoring severe conditions such as sepsis.

No significant differences in CRP levels were observed between sepsis and non-sepsis groups across the three days evaluated. CRP's response to IL-6 begins approximately six hours after inflammatory stimuli, with serum levels doubling every 8 hours and peaking at 36–50 hours, with a half-life of around 19 hours (Póvoa *et al*., 2023). Because our data were collected 48 hours after the initiation of sepsis management, this timing may have influenced the results. Additionally, the participants' advanced age and comorbidities could have contributed to elevated CRP levels, potentially confounding the findings. Previous studies in postoperative patients also found no significant differences in CRP levels between infected and non-infected groups[22]. Similarly, some research in adults found no correlation between CRP levels and sepsis severity or scores like APACHE II and SOFA (Ali *et al*., 2021). Conversely, a recent study in children indicated increased CRP levels in septic patients versus those with other infections (Wang; Lu; Li, 2022). Variability in results may be due to factors such as age and ethnicity.

Regarding cytokines, IL-10 levels were significantly higher in sepsis patients compared to non-sepsis individuals on D0 and D1. On D1, IL-6 levels were also higher in sepsis patients. By D2, however, no significant differences in IL-6 or IL-10 were observed between groups. IL-10 proved useful for discriminating sepsis from non-sepsis

cases on D1, with a cutoff of approximately 32 pg/mL and good sensitivity and specificity (80% and 82.4%, respectively). While IL-10 was also evaluated in relation to outcomes such as discharge or death, no significant differences were found across the three days.

These findings are consistent with previous research. A study involving 62 Brazilian ICU patients demonstrated that increased levels of IL-6 and IL-10 correlated with disease severity, with significantly higher levels observed in septic shock patients compared to those with severe sepsis (Nobre *et al*., 2016). Other studies likewise report elevated IL-10 in septic patients compared to SIRS patients or healthy controls (Angeletti *et al*. 2015). Several investigations also highlight the importance of IL-6 as a diagnostic marker in sepsis (Song *et al*., 2019). Nevertheless, larger studies remain necessary to confirm the diagnostic and prognostic value of IL-6 and other cytokines. From an immunological perspective, IL-10 plays a key role in modulating the immune response, whereas IL-6 is predominantly pro-inflammatory. In sepsis, IL-10 production may be enhanced as a compensatory mechanism to control the exaggerated inflammatory response, which likely explains its more discriminative role in the early phase of sepsis observed in our cohort. In Brazil, most hospitals follow the recommendations of the Instituto Latino-Americano de Sepse (ILAS), relying mainly on biomarkers that are already technically well established and widely available in routine clinical laboratories. Although IL-10 and IL-6 show promise for improving early sepsis diagnosis, their routine implementation is unlikely in the short term due to cost constraints, which remain a practical limitation in most healthcare settings.

The combination of PCT, WBC count, lactate, IL-10, and IL-6 outperforms individual biomarkers in diagnosing sepsis (Zeng *et al*., 2022). Monitoring these biomarkers is crucial for early detection in suspected cases, potentially improving prognosis. Correlation analyses revealed positive relationships between PCT, WBC, IL-10, and IL-6 in septic patients—all on D0. Specifically, PCT correlated positively with WBC and IL-10, and WBC correlated positively with IL-10 and IL-6. On day 1, the only persistent correlation was between PCT and WBC. These findings suggest that PCT, WBC, IL-10, and IL-6 could serve as helpful adjuncts for early sepsis diagnosis. Our results support existing evidence that combining biomarkers enhances early detection and treatment effectiveness (Song *et al*., 2019; Feng *et al*., 2024).

This study has several limitations, such as its conduction at a single health center, patient evaluation based on SIRS criteria, the lack of a control group, and a moderately

small sample size. Based on our findings, we propose that PCT, WBC, lactate, and IL-10 should be jointly evaluated for the clinical assessment of patients with sepsis. However, it is important to emphasize the need for data validation in a larger cohort of individuals from multiple health centers.

5. CONCLUSION

Sepsis continues to pose a significant global health challenge. In this study, we observed early elevations in the biomarkers procalcitonin (PCT), white blood cell count (WBC), lactate, and interleukin-10 (IL-10) among Brazilian patients with sepsis. These biomarkers, when used collectively, may aid in the early diagnosis of sepsis within this population. However, given the study's limitations—including its sample size and single-center design—these findings should be considered suggestive rather than definitive. To validate and generalize these results, further large-scale multicenter studies are essential. Such research will be crucial in establishing the clinical utility of these biomarkers across diverse populations and healthcare settings.

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