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Review Article

Sepsis biomarkers: a review of the diagnostic value of presepsin

Biomarcadores de sepse: uma revisão do valor diagnóstico da presepsina

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RESUMO: A sepse é uma síndrome prevalente e com alta morbimortalidade, sendo necessário um método diagnóstico precoce e eficaz. Estudos recentes sugerem que a presepsina pode ser um potencial biomarcador para o diagnóstico de sepse e que tem um desempenho melhor do que outros biomarcadores mais consolidados, como procalcitonina e PCR. Esta revisão sistemática tem como objetivo avaliar a acurácia da presepsina para o diagnóstico de sepse e comparar com a procalcitonina e a proteína-C-reativa. Uma pesquisa sistemática abrangente foi conduzida no PubMed e na Biblioteca Virtual em Saúde para coletar estudos publicados nos últimos dois anos com foco na precisão diagnóstica da presepsina para sepse. Oito estudos foram selecionados. Todos eles sugeriram que a presepsina tem algum valor diagnóstico para sepse. Em quatro estudos, a presepsina teve um desempenho melhor do que a procalcitonina e em dois a presepsina teve um desempenho melhor do que a PCR. Dois estudos não mostraram diferenças significativas entre a presepsina e os outros biomarcadores. Esta revisão indica que a presepsina pode ter valor significativo para o diagnóstico precoce da sepse, corroborando para aumentar a eficiência de ferramentas existentes, como a PCR e a procalcitonina. No entanto, mais estudos são necessários para confirmar sua eficácia como um único marcador de diagnóstico.

Palavras-chave: Biomarcadores; Sepse; Diagnóstico; Presepsina; Procalcitonina; PCR.

ABSTRACT: Sepsis is a prevalent syndrome with high morbimortality, so an efficient early diagnostic method is needed. Recent studies suggest that presepsin could be a potential biomarker to sepsis diagnosis and has a better performance than other more consolidated biomarkers, such as procalcitonin and CRP. This systematic review aims to develop assess the accuracy to sepsis diagnosis of the presepsin and compare with procalcitonin and C-reactive protein. A comprehensive systematic research was conducted in the PubMed and Virtual Health Library to collect studies published in the last two years that focused on presepsin diagnostic accuracy for sepsis. Eight studies were selected. All of them suggested that presepsin has some diagnostic value for sepsis. In four studies presepsin had a better performance than procalcitonin and in two studies presepsin performed better than CRP. Two studies did not show significant differences between presepsin and the other biomarkers. This review indicates that presepsin may have significant value for the early diagnosis of sepsis, corroborating to increase the efficiency of existing tools, such as CRP and procalcitonin. However, more studies are needed to confirm its efficiency as a single diagnosis's marker.

Keywords: Biomarkers; Sepsis; Diagnosis; Presepsin; Procalcitonin; CRP.

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INTRODUCTION

According to the Latin American Sepsis Institute[1], the sepsis is an extremely prevalent syndrome with high morbimortality and high cost. Thus, early recognition and treatment are of vital importance for changing this scenario. For this purpose, definitions and diagnostic tools are required to provide the best aid in patient management[1].

The most updated definition of sepsis (sepsis 3) is the life-threatening organ dysfunction in consequence of a dysregulated host response to infection[2]. Dysregulated response can be understood as both inflammation imbalance and immune dysfunction due to organism action against infectious agents. These factors are important elements of sepsis pathogenesis, which also include coagulopathy, neuroendocrine immune network abnormalities, endoplasmic reticulum stress, autophagy, and other pathophysiological processes, and ultimately leads to organ dysfunction[3].

Until 2016, sepsis diagnosis was based on leukocyte count, body temperature, heart and respiratory rates, which are SIRS symptoms[4]. In turn, SIRS (systemic inflammatory response syndrome) can be defined as an exacerbated defensive response of the immune system in an attempt to locate and eliminate a harmful stressor agent from the body, which can be an infection, acute inflammation, trauma, malignancy, surgery, ischemia, in addition to other possible etiological, endogenous or exogenous causes[5]. Over time, some studies indicated that SIRS is not an efficient criteria to diagnose sepsis, for example, 1 in 8 severely ill patients with sepsis does not develop SIRS' criteria[6] and almost half of patients hospitalized on the ward developed SIRS during their ward stay[7].

Currently, the sepsis diagnosis is clinical and based on the Sequential Organ Failure Assessment (SOFA). The diagnosis of sepsis is established in a patient in the presence of infection and a SOFA score of 2 or more points[2,8]. It is important to note that although SIRS is not enough to diagnose sepsis, septic patients may have characteristic manifestations included in the SIRS criterias, such as increased heart rate, increased respiratory rate, and leukocytosis; however, not all patients with all symptomatic manifestations of SIRS will, in fact, have sepsis[6]. Although the SIRS criteria were considered to be a tool of good sensitivity for identifying patients with altered organic inflammatory response, as it could not include 1 in 8 patients with infection and organ dysfunction, there was a need for a tool with greater specificity to sepsis identification. Therefore, despite the relative loss in sensitivity, the definition of Sepsis-3 was adopted as a predictor of mortality and ICU stay, with an increase in specificity in the detection of patients with a higher probability of mortality[9]. In addition, the new definitions' accuracy improved progressively with severity[10].

Nevertheless, a negative point is the decrease of the sensitivity to identify cases that could have an unfavorable evolution, especially in low-income and middle-income countries[11]. Moreover, delays in recognition and treatment are the main cause of sepsis-associated deaths that were potentially preventable[12].

The diagnosis of infection is often difficult to establish. In older patients admitted from the emergency department (ED), the provisional ED diagnosis and the inpatient diagnosis of an acute infection often disagree. In a prospective, observational, convenience sampling of a cohort conducted in a hospital, 18% of older ED patients diagnosed with infection during an ED stay were not diagnosed as infected by the inpatient physician[13]. These data show the importance of having more instruments that assist in the differential diagnosis of sepsis. A possible alternative to obtain early recognition and to promote a balance between sensitivity and specificity in screening are sepsis biomarkers. Estimates point to about 180 different biomarkers used in the sepsis process, but only a few could be useful for diagnosing[14].

Among the sepsis biomarkers, two of them have stood out in the literature: C-reactive protein (CRP) and procalcitonin. Both are infection-related biomarkers that are widely used in clinical practice. Procalcitonin (PCT) is an acute-phase protein, characterized as a pro-hormone of calcitonin. In infections, it is secreted into various organs of the body in response to endotoxins and inflammatory mediators. Its serum levels, whose values correlate with infection severity, start to rise between 2 and 6h with a peak between 6 and 24h during sepsis. Currently, it has been a biomarker widely used for early diagnosis of sepsis and septic shock, as well as a tool to aid in the decision to initiate and continue antibiotic therapy. Its levels can be elevated in situations other than infection, such as in patients after severe trauma. C-reactive protein (CRP), in turn, is an acute phase protein produced by hepatocytes in response to tissue aggression or inflammation. In response to infection, serum CRP levels start to increase between 6 to 8 h, peaking between 36 to 50 h, resulting in a moderate potential for sepsis detection when compared to other biomarkers mainly due to its low specificity. Despite this, its initial analysis can be used to support decision making for initiation of antibiotic therapy as well as its temporal evaluation can be used to monitor the organism's response to therapeutic measures[3, 14].

However, a newer biomarker, the presepsin, is being described by some studies as more efficient to diagnosis, prognostic, and severity assessment of sepsis than CRP and procalcitonin[3, 15-18]. Presepsin, unlike PCT and PCR, is a biomarker related to the activation of the innate immune system response. Presepsin consists of an N-terminal fragment of 64 amino acids (sCD14-ST) obtained after cleavage of a soluble subtype (sCD14) of

a cell surface glycoprotein called CD14 present on the cell surface of monocytes and macrophages, belonging to the Toll-like receptor family. Thus, when this receptor is activated, presepsin is released into the plasma, raising its serum levels within 2 hours, with a peak in 3 hours after the beginning of the infection. It is important to emphasize that in a healthy organism, free of infection, the serum levels of presepsin are very low, virtually imperceptible, a fact that changes markedly when there is invasion by microorganisms, and thus a promising biomarker in the rapid identification of patients with sepsis[3, 19]. Therefore, a systematic review is needed to consolidate the knowledge about the presepsin efficiency to diagnose sepsis compared with other traditional biomarkers, like procalcitonin and CRP.

OBJECTIVE

To perform a systematic review on the diagnostic accuracy of the presepsin for sepsis and to compare it with other biomarkers such as procalcitonin and c-reactive protein.

METHODS

Search strategy and eligibility criteria

We developed search strategies for two databases: PubMed and VHL - Coordinated by BIREME (Latin American and Caribbean Center on Health Sciences Information or also Regional Library of Medicine), WHL consists in an operational platform of technical coordination of the Pan American Health Organization (PAHO) for the administration of health information and knowledge in the region. We used the same search terms for PubMed and the VHL, "(presepsin [Title/Abstract]) AND (sepsis [Title/Abstract])". We restricted the publication period of the articles to the last two years (2018/01/01 to 2020/08/01) on both platforms. For the VHL, we added the following filters: "full text available", "English" and "limit of study in humans". For PubMed, we use the filters: "full text" and "free full text".

Two reviewers (TF and MC) independently assessed the inclusion of studies in the review by analyzing the abstract, objectives and methods. Duplicated studies were excluded. The inclusion criteria were: (1) sepsis-related studies; and (2) studies with presepsin as a diagnostic biomarker. The exclusion criteria were: (1) systematic reviews and meta-analyzes; (2) articles focusing on children and adolescents; (3) post-mortem analyzes; and (4) in vitro analyzes.

RESULTS

In the PubMed database, we found 346 articles by searching with the terms. Using time restriction (last 2 years) we obtained 187 articles. The restriction for studies with "free full text" allowed us to view 160 articles, of which 4 were selected according to the eligibility criteria. In the VHL database, 198 articles were found by searching with the terms. Using the filters, we obtained 45 studies (74 with the publication interval filter; 68 with "full text available"; 63 with "English language" filter; and finally, 45 with the "human study limit" filter), of which 4 new articles were selected according to the inclusion and exclusion criteria.

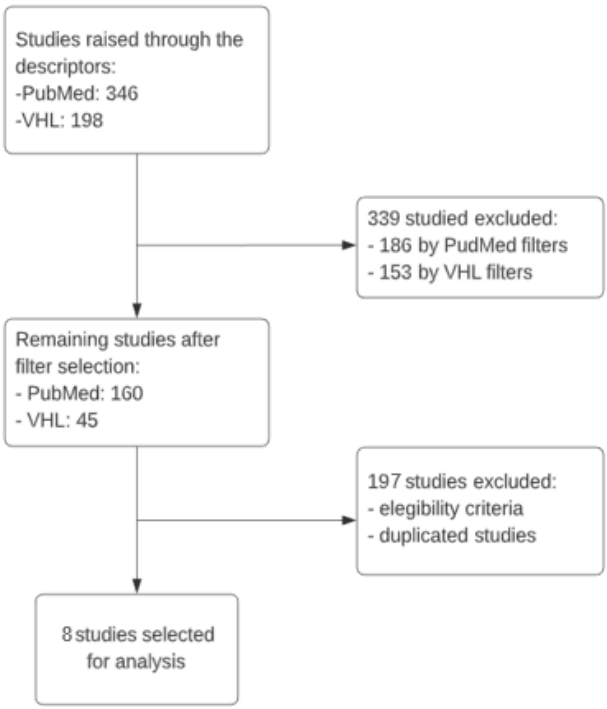

Figure 1: Flow chart of study selection

Basic characteristics of the included studies

Table 1: Basic characteristics of the studies

Author	Publication	Country	Sepsis/ Control (n)	Mean age case/control	Controls	Tests	Study design	Sepsis definition
Zhao et al.[20]	June, 2020	China	168/157	Sepsis: 58; HC: 51; Non-Sepsis ARDS: 59	Non-Sepsis related ARDS (n=57) and healthy control (n=100)	ELISA	Prospective	Sepsis 2
Imai et al.[21]	Dec., 2019	Japan	46/30	78.93/77.30	Not reported	PATHFAST	Prospective	Sepsis 2
Venugopalan et al.[22]	July, 2019	India	26/22	Not reported	ICU and emergency department patients	ELISA	Prospective	Sepsis 2
Brodska et al.[23]	Nov., 2017	Czech Republic	30/30	66/68	SIRS	PATHFAST	Prospective	Sepsis 2
Lu et al.[24]	Dec., 2017	China	33/43	Sepsis: 54.1; HC: 60.6; SIRS: 59.7	SIRS (n=23) and healthy control (n=20)	PATHFAST	Prospective	Sepsis 2
Tambo et al.[25]	March, 2020	Japan	11/50	73/61	Obstructive APN associated with upper urinary tract calculi	Not reported	Retrospective	Sepsis 3
Yamamoto et al.[26]	Jan., 2019	Japan	29/29	63/66	Non-sepsis	Not reported	Prospective	Sepsis 3
Nakamura et al.[27]	Sept., 2018	Japan	146/660	73/65	Non-AKI (n=393) and AKI (n=267)	PATHFAST	Retrospective	Sepsis 3

Among the 8 selected studies, 5 were carried out in an intensive care unit (ICU)[20,22,23,26,27], 1 in a ward for the treatment of acute obstructive pyelonephritis[25], 2 in the emergency room ward for suspected sepsis[21,22] and 1 in the emergency department[24].

A total of 1452 patients were evaluated between 2014 and 2019, among which, 494 were classified according to the "sepsis 2" criteria, which defines sepsis as the presence of a systemic inflammatory response (SIRS) related to a presumed or probable infection[4]. The other 958 patients[25-27] were analyzed according to the "sepsis 3" criteria, considering sepsis as a life-threatening organ dysfunction in consequence of a dysregulated host response to infection[2].

Regarding the characteristics of the sample, Zhao et al.[20] included patients with ARDS and sepsis, Tambo et al.[25] included patients with acute obstructive pyelonephritis and sepsis, Imai et al.[21] included elderly patients with bacteremia, Venugopalan et al.[22] included patients in different stages of sepsis, Brodska et al.[23] included patients over 18 years old admitted to the ICU for more than 3 days, Lu et al.[24] included patients in the emergency department with sepsis and non-infectious SIRS, Yamamoto et al.[26] included patients who met SIRS criteria, and Nakamura et al.[27] included patients with and without acute kidney injury.

The methods for determining the concentration of presepsin in plasma were performed by an enzyme-linked immunosorbent assay (ELISA) in 2 studies[20, 22], by chemiluminescent enzyme immunoassay (PATHFAST immunoassay analytical system) in 4 studies[21,23,24,27] and was not reported by others 2 trials[25,26].

Quality of the articles

It is important to highlight some characteristics of the selected studies that may influence the discussion of results and future conclusions. Eight articles were selected for this systematic review, of which five used Sepsis-2 criteria[20,21,22,23,24] and three used Sepsis-3 criteria[25,26,27], a fact that may influence the clinical criteria for admission and classification of the analyzed patients.

The selected studies grouped different amounts of people to compose the analysis sample (n). In some of them, this sample represents a small number[22,25,26], a fact that makes generalizations difficult. In total, the eight studies contributed 1452 analyzed patients, which is still a modest number.

About the allocation of patients and selection of control groups, there was an important difference among the studies: some selected healthy patients as reference; others, however, admitted as control patients who did not meet criteria for sepsis, regardless of the underlying disease[20, 24, 25, 27], a fact that could influence the levels of markers.

Methodological quality of articles

Additionally, some authors have adopted different methodological strategies to conduct their investigations. Tambo et al.[25] and Nakamura et al.[27] had performed single-center retrospective studies using patients with nephron-

urinary pathologies, while the other authors designed observational prospective studies. Zhao et al.[20] analyzed the presepsin uses in sepsis-related acute respiratory distress syndrome and Imai et al.[21] evaluated the biomarker uses specifically in elderly patients. The other studies had included patients with different profiles and underlying pathologies.

Diagnostic accuracy of presepsin

Table 2: Diagnostic accuracy of presepsin

Presepsin				
Studies	Thresholds (pg/mL)	AUC	Sensitivity %	Specificity %
Zhao et al.[20]	454.3	0.81	64.3	89.5
Imai et al.[21]	285	0.69	93.7	41.3
Venugopalan et al.[22]*	93.7 pg/dL	0.69	65.4	68.2
Brodska et al.[23]**	NR	0.67	NR	NR
Lu et al.[24]	407	0.95	98.6	90.7
Tambo et al.[25]	NR	NR	NR	NR
Yamamoto et al.[26]	557	0.90	93	86
Nakamura et al.[27]	240	0.88	80.9	83.2

* Data regarding the cut-off value defined as best for diagnosis by the authors.
** Data regarding the patient's admission day (D1).
NR= not reported.

The results of the Zhao et al.[20] essay demonstrated higher levels of presepsin in patients with sepsis-related ARDS compared to patients with non-sepsis-related ARDS. With a cut-off value of 454.3 pg/ml, the specificity and sensitivity values found were, respectively, 89.5% and 64.3%. The positive predictive value (PPV) was 94.7% and the negative predictive value (NPV) was 45.9%. The area under the receiver operating characteristic (AUROC) found was 0.81 (95% CI 0.76–0.87) e p <0.01.

In the Imai et al.[21] study, presepsin values were also significantly higher in cases (patients with bacteremia) compared to controls (866.6 ± 184.6 vs 639.9 ± 137.1 pg/mL, p=0.03). The sensitivity and specificity found were 93.7% and 41.3% respectively. The positive and negative predictive values were 46.8% and 92.3%, respectively. The AUC found for presepsin was 0.69 for a cutoff value of 285 pg/mL.

Venugopalan et al.[22] analyzed the diagnostic efficiency of presepsin from two cutoff values: 200 pg/dL and 93.71 pg/dL. The 200 pg/dL cutoff provided the following parameters: sensitivity of 46.2%, specificity of 100%, PPV of 100% and NPV of 61.1%. The 93.71 pg/dL cutoff applied as normal for presepsin provided the best values for sensitivity and specificity (65.4% and 68.2%, respectively), with PPV of 70.7% and NPV of 62.5%. For this presepsin value, the AUC was 0.688.

In Brodska et al.[23], for the differentiation between patients with sepsis and SIRS at the admission, presepsin was higher in patients with sepsis, with AUC=0.674 (p <0.021), other information was not reported.

Lu et al.[24], using a cutoff point of 407 pg/mL for the diagnostic determination of sepsis and differentiation with SIRS, observed that presepsin levels were significantly higher among patients with sepsis compared to those with SIRS. The AUC was 0.954 (95% CI 0.910-0.998; p<0.001). The sensitivity, specificity, PPV, and NPV were 98.6%, 90.7%, 94.67% and 97.48% respectively.

Tambo et al.[25] compared presepsin levels of the sepsis group and the control group. The authors observed presepsin levels were significantly increased in the sepsis group (1080 pg/dL [696–1550] vs 387 pg/dL [313-558]; p<0.001). Descriptive measures (specificity, sensitivity, AUC, etc.) were not provided in the study.

In Yamamoto et al.[26] study, using a presepsin cutoff value of 557 pg/mL, the area under the curve (AUC) values to distinguish sepsis without shock (sepsis group) from non-sepsis (non-sepsis group) were 0.90 (95% CI, 0.76–0.96) for presepsin. The sensitivity, specificity, PPV, NPV, and accuracy of presepsin to diagnose sepsis without shock were 93%, 86%, 87%, 93%, and 90%, respectively. The outcomes were statistically significant (p<0.05).

In Nakamura et al.[27], for sepsis in patients without acute kidney injury, the presepsin AUC was 0.88 (p=0.525) with a cutoff value of 240 pg/mL. The sensitivity was 80.9% and the specificity was 83.2%. For sepsis in patients with stage 3 kidney injury, the AUC was 0.768 (p<0.001) with an ideal cutoff value of 500 pg/mL (sensitivity: 89.7%, specificity: 59.7%).

Comparison of presepsin and other biomarkers

Table 3: Diagnostic accuracy of procalcitonin

PCT				
Studies	**Thresholds (ng/mL)**	**AUC**	**Sensitivity %**	**Specificity %**
Zhao et al.[20]	NR	0.62	NR	NR
Imai et al.[21]	15.5	0.61	43.7	86.7
Venugopalan et al.[22]	0.5 mg/dL	NR	46.2	31.8
Brodska et al.[23]*	0.05 µg/L	0.79	NR	NR
Lu et al.[24]	NR	0.87	NR	NR
Tambo et al.[25]	NR	NR	NR	NR
Yamamoto et al.[26]	0.79	0.71	69	66
Nakamura et al.[27]	0.10	0.90	85.1	79.1

* Data regarding the patient's admission day (D1).
NR= not reported.

Table 4: Diagnostic accuracy of C-reactive protein

CRP				
Studies	**Thresholds (mg/L)**	**AUC**	**Sensitivity %**	**Specificity %**
Imai et al.[21]	34.6	0.53	25.0	93.3
Brodska et al.[23]*	5.0	0.90	NR	NR
Lu et al.[24]	NR	0.86	NR	NR
Nakamura et al.[27]	11.9	0.67	66.0	62.0

* Data regarding the patient's admission day (D1).
NR= not reported.

In Zhao et al.[20], PCT average levels were higher in the group with sepsis-related ARDS compared to patients with non-sepsis-related ARDS, but there was an overlap in the range of serum levels of procalcitonin in these two groups {[5.13 (1.21–15.49) vs 2.73 (1.33–4.04); p=0.006]. Furthermore, the AUROC of presepsin [0.81 (95% CI, 0.76–0.87)] was significantly greater than that of procalcitonin [0.62 (0.55–0.70)] ($p < 0.01$).

In Imai et al.[21,] biomarkers such as procalcitonin (p=0.18) and C-reactive protein (p=0.66), did not present a statistically significant p value for differentiation between the control group (without bacteremia) and the studied group (with bacteremia). However, for cutoff values of 15.8 ng/mL for PCT and 34.6 mg/L for CPR, the AUC values of these biomarkers did not differ markedly from the value found for presepsin, being 0.61 (p=0.30) to PCT and 0.53 (p=0.07) to CRP. The sensitivity, specificity, PPV and NPV values for PCT were, respectively: 43.7%, 86.7%, 63.6% and 74.2%. For CRP, the values of sensitivity, specificity, PPV and NPV were, respectively: 25%, 93.3%, 66.6% and 70%.

In Venugopalan et al.[22], for procalcitonin cutoff of 0.5 mg/dL, it was less efficient diagnostic biomarker than presepsin, and present the following outcomes: sensitivity of 46.2%, specificity of 31.8%, PPV of 44.4% and NPV of 33.3%.

In Brodska et al.[23], when comparing presepsin with other biomarkers, presepsin was not superior in relation to the diagnostic differentiation of patients with sepsis and patients with SIRS at the admission: presepsin (AUC=0.674; p<0.021), PCT (AUC=0.791; p<0.001), CRP (AUC=0.903; p<0.0001).

On the other hand, the study by Lu et al.[24] suggested that presepsin can be a promising diagnostic biomarker compared to the others. The authors obtained the following statistic significant (p<0.05) results for the area under the ROC curve of biomarkers: 0.954 (95% CI, 0.910–0.998) to presepsin; 0.874 (95% CI, 0.793–0.955) to PCT; 0,859 (95% CI, 0.782–0.936) to CRP.

In Tambo et al.[25], as well as presepsin, PCT was also higher in the group with sepsis (31.57 ng/mL [1.83-134.40]) than in the group without sepsis (0,54 ng/mL [0.14–4.86]) (p <0.001). However, the study did not provide other measures of association or parameters for comparison and characterization of the findings.

Yamamoto et al.[26] found the following outcomes to distinguish sepsis without shock (sepsis group) from non-sepsis (non-sepsis group): for PCT, with a cut-off values of 0.79 ng/mL, AUC=0.71 (95% CI, 0.57–0.83), sensitivity=69%, specificity=66%, PPV= 67%, NPV=68%, and accuracy of biomarker to diagnose=67%; for CRP, with a cut-off values of 11.9 mg/L, AUC=0.67 (95% CI, 0.52–0.79), sensitivity=66%, specificity=62%, PPV=63%, NPV=64%, and accuracy of biomarker to diagnose=64%.

In Nakamura et al.[27], the diagnostic accuracy of sepsis in patients with severe acute kidney injury (AKI) was better with PCT than with presepsin. In the group without AKI, the PCT AUC was 0.897 (p = 0.525), with ideal cut-off value of 0.10 ng/ml (sensitivity: 85.1%, specificity: 79.1%). For stage 3 AKI, the PCT AUC was 0.946 (p<0.001) with a cutoff value of 4.07 ng/ml (sensitivity: 87.2%, specificity: 93.5%).

DISCUSSION

Sepsis represents an important health problem, both because of its prevalence, morbimortality and costs to the health systems[1] and because of the difficulty it imposes on early diagnosis methods, which are fundamental for adequate therapeutic conduct and change in the natural history of the disease process.

The measurement of procalcitonin and C-reactive protein is an increasingly common practice in the clinic to support the early diagnosis of patients with suspected sepsis. However, these biomarkers lack sufficient precision and predictive accuracy to inform diagnosis of infections[28]. In this way, the present systematic review collected recent publications in the literature to analyze the diagnostic capacity of an alternative biomarker, presepsin.

Among the eight studies selected, in all of them, the mean level of presepsin was higher in patients with sepsis compared to patients without sepsis. The studies used different cutoff values of presepsin, which varied between 93.71 pg/mL and 557 pg/mL. Other parameters to presepsin found varied within the following ranges: area under the ROC curve: 0.674–0.954; sensitivity: 64.3–98.6%; specificity: 41.3–90.7%; positive predictive value: 46.8–94.7%; and negative predictive value: 45.9–97.48%.

Of the studies that used the "sepsis 2" definition, the area under the ROC curve of presepsin was between 0.674–0.954, sensitivity 64.3–98.6%, specificity 41.3–90.7%, PPV 46.8–94.7%, and NPV 45.9%–97.48%. Among the studies that conceptualized sepsis according to the "sepsis 3" definition, obtained the following variations to presepsin: AUC: 0.768–0.90; sensitivity: 80–93%; and specificity: 59–86%.

In comparison with the other biomarkers, in the eight studies selected, presepsin showed better efficiency in differentiating between groups with sepsis and groups without sepsis in relation to procalcitonin in 4 studies[20, 22, 24, 26]; compared to C-reactive protein, this advantage was observed in 2 studies[24, 26]. Two other studies[21, 23] did not show significant differences between presepsin and the other biomarkers, PCT and CRP. In Nakamura et al.[27], procalcitonin showed greater AUC and greater sensitivity than presepsin for sepsis identification in patients with stage 3 AKI, but it was not observed in patients without AKI. In Tambo et al.[25], both presepsin and PCT levels were higher in the sepsis group, but many parameters were not provided for comparative analysis between these biomarkers.

In addition, three[20,22,23] of the selected studies also assessed the prognostic value of presepsin and two[23, 24] the association with the severity of the disease. Zhao et al.[20] observed that presepsin levels were associated with increased mortality, being a promising biomarker for predicting in-hospital mortality in sepsis-related ARDS. Venugopalan et al.[22] identified that presepsin is a better indicator of 28-day mortality than procalcitonin. Lu et al.[24] found that presepsin levels increased significantly with sepsis severity. Brodska et al.[23] identified that presepsin obtained the best association with mortality among the analyzed markers but did not correlate with severity of disease.

The results obtained by the present systematic review are compatible with those observed by previous reviews and meta-analyzes[17,29,30], which pointed to a potential diagnostic value of presepsin and a good performance in relation to other diagnostic methods.

LIMITATIONS

This study has some limitations. Not all selected articles have all the parameters required for diagnostic analysis. In addition, most use an earlier definition of sepsis ("sepsis 2") and not the most up-to-date definition ("sepsis 3"). Another point is that there is a wide range of limit values for the biomarkers analyzed. Finally, we did not aim to develop an extensive statistical analysis of the data collected.

CONCLUSION

Our review indicates that presepsin may have significant value for the early diagnosis of sepsis, corroborating to increase the efficiency of existing tools, such as CRP and procalcitonin. As a single marker, more studies are needed, supported by the new definitions of sepsis ("sepsis 3"), with relevant standards and samples so that limitations and biases are minimized in verifying the benefits of this promising diagnostic instrument.

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