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Role of Presepsin and Comparison with Conventional Markers for Early Diagnosis and Differentiation of Sepsis

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Abstract: Sepsis is a fatal condition that contributes to most deaths in health care setups worldwide. Early diagnosis of sepsis could alleviate this growing mortality rate. However, it remained a challenging task due to the lack of specific biomarkers. This study aimed to analyze the utility of novel Presepsin to indicate the early onset of sepsis and distinguish it from systemic inflammatory response syndrome compared to conventional markers. We have conducted a cross-sectional study on 38 patients who recently developed septicemia and 90 systemic inflammatory syndrome cases. Demographic data and results of initial laboratory workup for sepsis, blood culture, procalcitonin, and C-reactive protein were obtained for comparison. The plasma levels of Presepsin were significantly higher in the sepsis patients ($p<0.001$) with the highest sensitivity (81.6%), specificity (70%), and area under the curve (0.87). Strong statistical association of C-reactive protein and sepsis was determined despite lower validity and area under the curve. Relatively lower validity indices and receiver operating curve were found for procalcitonin, while culture appeared to be the least effective marker for early diagnosis of sepsis. Conclusively, the study showed that Presepsin could serve as a new biomarker for sepsis. Hence, we recommend revision in current management guidelines of sepsis for inclusion of Presepsin to already existing biomarkers for accurate early diagnosis and differentiation of sepsis.

Keywords: sepsis, systemic inflammatory response syndrome, soluble CD14-subtype, presepsin.

前蛋白酶在脓毒症早期诊断和鉴别中的作用及与常规标志物的比较

摘要：脓毒症是一种致命疾病，导致全球医疗机构中的大多数死亡。脓毒症的早期诊断可以缓解这种不断增长的死亡率。然而，由于缺乏特定的生物标志物，这仍然是一项具有挑战性的任务。本研究旨在分析新型前蛋白酶的效用，以指示脓毒症的早期发病，并将其与传统标志物相比，将其与全身炎症反应综合征区分开来。我们对最近发生败血症的38例患者和90例全身炎症综合征病例进行了横断面研究。获得人口统计学数据和脓毒症、血培养、降钙素原和C反应蛋白的初步实验室检查结果以进行比较。脓毒症患者的血浆前蛋白酶水平显着升高($p<0.001$)，敏感性(81.6%)、特异性(70%)和曲线下面积(0.87)最高。尽管有效性和曲线下面积较低，但仍确定了C反应蛋白和脓毒症的强统计关联。降钙素原的有效性指数和受试者工作曲线相对较低，而培养似乎是败血症早期诊断最无效的标志物。最终，该研究表明前蛋白酶可以作为脓毒症的新生物标志物。因此，我们建议修订现行的脓毒症管理指南，将前蛋白酶纳入现有的生物标志物，以准确早期诊断和区分脓毒症。

关键词: 脓毒症，全身炎症反应综合征，可溶性光盘14 亚型，前蛋白酶.

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1. Introduction

Sepsis is the most commonly encountered life-threatening condition in medical ICUs caused by the dysregulated host response to infection. Approximately 6 million deaths were reported from sepsis worldwide. In contrast, systemic inflammatory response syndrome (SIRS) is a clinical response to an insult of noninfectious origin [1]. Early and accurate diagnosis is the key to improving survival in sepsis patients. Besides that, early distinction of sepsis and SIRS is equally important to avoid unnecessary use of antibiotics, which is largely responsible for growing resistance against antibiotics [2].

Presently, clinical findings, biological markers, and isolation of microorganisms constitute the basis for diagnosing sepsis. Unfortunately, most of these assays are time-consuming and have limited sensitivity, which contributes to false negative results in most instances. Apart from routine investigations, some new markers such as procalcitonin (PCT) and recently discovered Presepsin (P-SEP) had shown promising results for early diagnosis of sepsis in comparative studies [3].

P-SEP, the newly identified marker for bacterial infection, is a 13kDa fragment of the N-terminal of soluble CD14, released into the bloodstream in response to bacterial engagement with CD14-bacterial specific monocyte receptor [4]. The utility of P-SEP to differentiate sepsis from other noninfectious causes of systemic inflammation has been reported in several studies [3]. Besides that, qualities such as; early response time, better sensitivity, cost-effectiveness, and prognostic value, further endorsed its superiority [3]. At the same time, PCT is the inactive propeptide of calcitonin released by C cells of the thyroid gland, hepatocytes, and peripheral monocytes [4]. However, high cost and delayed response are the major disadvantages of PCT when compared to P-SEP [2].

Although many authors support P-SEP diagnostic value for advanced sepsis and its differentiation from SIRS, prognostication, and survival prediction, there is a dearth of literature on its role in the early developmental stages of sepsis. Thus, we aimed to evaluate the independent diagnostic potential of P-SEP and other markers for early sepsis and compared these characteristics with conventional markers. Our findings may provide insight on early markers of sepsis which in turn prove useful in accurately identifying cases that are in transition to develop sepsis and hence guide therapeutic decisions in the early stages of sepsis, eventually leading to improved outcomes in patients.

2. Materials and Methods

2.1. Study Design and Inclusion Criteria

A single-center, cross-sectional study was conducted in Ziauddin University Hospital, Karachi, Pakistan, after seeking ethical approval (1701219 FHPAT). We identified 128 new admissions in ICU who were clinically suspected with early onset of sepsis and followed for confirmatory diagnosis. All patients were receiving care during 2020 and 2021. Fig. 1 presents the workflow of this research.

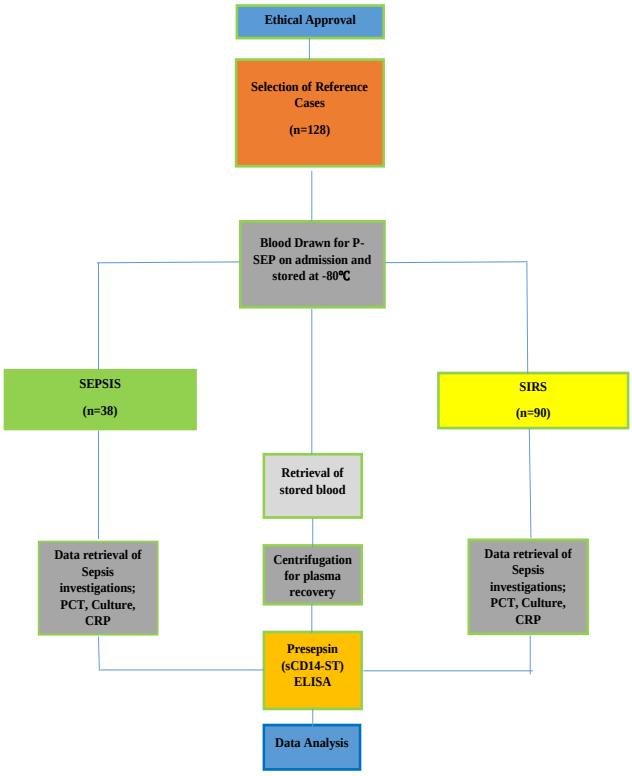

Fig. 1 Flowchart depicting the overview of the research plan

Early sepsis was diagnosed if at least two or more prescribed laboratory investigations were positive and CDC described clinical parameters were encountered [3]. Among laboratory parameters, positive blood culture, PCT ≥ 24.3 ng/ml, CRP≥179 mg/L, and lactate >2mmol/L were considered the primary indicators of early sepsis. Clinical findings include; temperature >38℃ or < 36℃, pulse rate >90 beats/min respiratory rate of >20 breaths/min or hyperventilation with a partial pressure of arterial carbon dioxide (PaCO2) of <32 mmHg and white blood cell (WBC) count of >12,000 /μL, or < 4000 /μL, or >10% immature cells [5]. Patients with SIRS were characterized on clinical parameters though the sepsis-related laboratory workup was negative.

2.2. Data Collection and Procedure

The patients were divided into two groups following the diagnosis: Sepsis and SIRS. Multiorgan failure, prior steroid use, and immunosuppression were exclusion criteria. Written informed consent was obtained from all subjects included in this research. Data from day 0 lab investigations, blood culture, PCT, and CRP, along with demographic, age and gender, were obtained. The leftover blood from day 0 investigations was used for P-SEP analysis. According

to manufacturer instructions, P-SEP was analyzed using a commercially available ELISA kit (Biotech Cat # E3754Hu). A plasma level greater than or equal to 200 ng/L was considered standard for a positive test in compliance with [6].

For the procedure, a standard solution along with streptavidin-HRP was added to the standard well. Plasma and anti-IgA antibodies were then transferred to the well. The plate was covered with a sealer and incubated for 60 min at 37℃, and washed with buffer. Substrate solutions A and B were added to each well and blotted onto the paper towel. After applying the sealer, the plate was incubated for 10 minutes at 37℃. Stop solution was added to each well, and optical density was calculated at 450nm using a microplate reader.

2.3. Statistical Analysis

The statistical analysis was performed using SPSS version 25. Data were analyzed for normality using the Shapiro-Wilk test, and the median for numerical variables was determined. The indices for validity measures, i.e., sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were estimated for all markers. The receiver operating curve (ROC) was generated to estimate the area under the curve (AUC) and optimum cut-offs for all studied markers, whereas the strength of association with sepsis was calculated by employing the Chi-Square test. The value of $p < 0.05$ was considered for statistical significance, and a confidence interval of 95% was used for all assessments.

3. Results

On clinical characterization, 38 cases were classified in the sepsis group, and the remaining 90 cases were categorized in the SIRS group. Overall, male cases were predominant in our series. All participants were aged from 18 to 90 years; their median age was 67 years. The biomarker profile revealed values above the laboratory reference range for all studied markers. The observed median values were 51 ng/L, 0.4 ng/ml, and 117.2 mg/ml for P-SEP, PCT, and CRP, respectively. Coagulase-negative staphylococci were the most frequently isolated organisms on culture.

We came across 31 cases positive for the P-SEP test in the sepsis group on laboratory investigations compared to 27 in SIRS. This number accounts for a significant statistical difference ($p<0.05$). Also, P-SEP showed the highest odds (81.6%) for predicting the onset of sepsis in patients. For the CRP test, the 12 positive cases in the sepsis group were observed while 51 cases were in SIRS. Also, a strong statistical relationship (0.009) for CRP was found despite lower sensitivity (31.6%) and specificity (43.3%) for CRP.

In comparison, PCT and culture were positive in 12 and 11 cases of sepsis, respectively, with no statistical difference. Relatively, lower sensitivity (31.6%) and specificity (67.8%) of PCT were noted, while culture showed the lowest rates for validity parameters. The results of all investigations and statistical assessments are presented in table 1.

Table 1 Statistical estimates and distribution of cases for all markers for sepsis and SIRS

Investigations (Cut-off) †	Disease		p-value* (p≤ 0.05)	Sensitivity (%)	Specificity (%)	PPV§ (%)	NPV‡ (%)	AUC ǂ
	Sepsis ¶ (n = 38)	SIRS (n = 90)						
Blood Culture (Positive)	11	25	0.893	28.9	72.2	27.8	71.1	0.494
CRP (179 mg/L)	12	51	0.009	31.6	43.3	56.7	68.4	0.532
PCT (24 ng/ml)	12	29	0.943	31.6	67.8	32.2	68.4	0.702
P-SEP (200 ng/L)	31	27	0.001	81.6	70	30	18.4	0.870

Notes:

† Described cut-off for Sepsis ¶ Early Sepsis according to CDC Guideline

* Chi-Square Test

§ Positive Predictive Value

‡ Negative Predictive Value

ǂ Area Under Curve

On ROC analysis, we found the highest AUC (0.870) for P-SEP, followed by PCT (0.702), CRP (0.532), and culture (0.494). Fig. 2 shows the ROC plot for all studied markers. We recommend 126 ng/L as the cut-off level of P-SEP, indicating the onset of sepsis with the corresponding sensitivity of almost 80%.

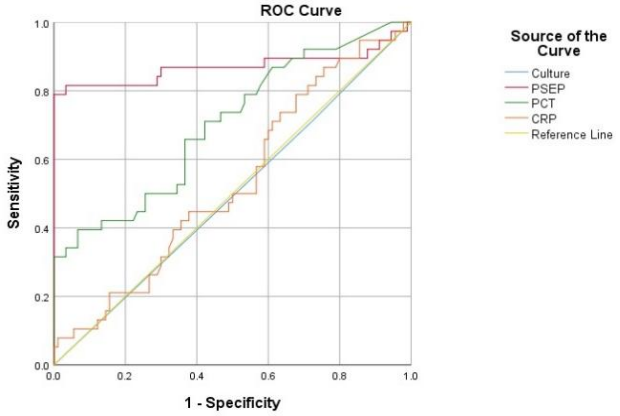

Fig. 2 Receiver operating curve (ROC) comparing levels of P-SEP (red), PCT (green), C-reactive protein (orange), and culture (blue) in patients with sepsis

4. Discussion

Accurate and early diagnosis of sepsis is crucial for timely therapeutic intervention and reducing mortality. At present, 2001 International Sepsis Definition and management guidelines are being followed in most of our clinical setups for routine diagnosis. The criteria are based on blood culture findings, which is time-consuming and could be influenced by factors such as; prior antibiotic use and poor sensitivity [7]. Recently, a more robust definition for sepsis has been published, which outlined the prerequisite to rule out infection in suspected patients [8]. Thus, the evaluation of numerous molecules for early detection of infection had gained support and enthusiasm. P-SEP or soluble

CD14 subtype is a protein suggested to have promising implications in the management of sepsis and its distinction from other inflammatory conditions [9]-[10]. Although many researchers have studied the role of P-SEP in sepsis and its differential properties, most of them investigated its utility in advanced or progressive septicemia, leaving a gap in knowledge for the role in early disease [3]. In this study, we intended to evaluate the value of monitoring P-SEP level in patients on the initial state of septicemia for diagnosis and differentiation from non-septicemic pathologies compared to the widely used PCT and CRP markers.

Recent clinical literature suggested the reference points for sepsis which are described as 200 pg/ml for P-SEP, 24.3 ng/ml for PCT, and 179 mg/L for CRP [6], [11]. Considering the values as reliable indicators, we have employed these limits as reference levels of studied markers for sepsis. We found that P-SEP levels were significantly higher on the day of admission in patients fulfilling the criteria of early sepsis. P-SEP also proved useful in the early differentiation of SIRS. In line with our findings, it was noted in [12] that P-SEP levels were significantly raised among sepsis patients than healthy control or SIRS subjects. Previously, as also observed in [13], the plasma concentration of P-SEP was 333.5 ± 130.6 pg/mL in the SIRS group, while 817.9 ± 572.7 pg/mL, 1992.9 ± 1509.2 pg/mL, and 294.2 ± 121.4 pg/mL in sepsis, severe sepsis and healthy controls, respectively. Also, a sequential rise in P-SEP concentration with the progression of septicemia in a single-center prospective study was reported in [14], which further strengthened our findings. We believe that increased levels of P-SEP in sepsis could be explained by widespread bacteremia triggering its release in greater proportion. We also found a good overall sensitivity (81.6%) and specificity (70%) of P-SEP compared to conventional markers. This observation is also in line with the pooled sensitivities and specificities of P-SEP documented in a recent meta-analysis [15].

Concurrently, we found PCT concentration above predefined reference levels in most clinically confirmed cases of sepsis; however, this rise was not statistically significant ($p>0.05$). Similarly, we also observed lower sensitivity and specificity of PCT compared to what has been documented by previous authors [16], [17]. We suspect that a steady increase in PCT, which usually peaks on the 2nd or 3rd day of admission, might be a reason for this negative association. In the past, a systematic review and meta-analysis determined that PCT levels typically start to rise by 6-12 hours after infection [18]. Therefore, the rise in PCT is relatively slow and more dependent on the infection dose. Numerous studies investigating early sepsis observed similar results [19].

Despite being nonspecific, serum CRP is still considered a useful investigation in the workup of sepsis. In the current research, we evaluated the levels of serum CRP on the day of admission and found a significant difference in sepsis versus SIRS groups. In agreement, a significant relationship between raised serum CRP and sepsis was found in [20]. Contrary to this, no association of elevated CRP and sepsis was determined in [21]. We further noted a low sensitivity of CRP analysis for sepsis, suggesting that the test merely reflects an inflammatory response rather than an infectious etiology.

In our comparative analysis, traditional culture proved to be the least sensitive of all. Previously, lower sensitivity rates for culture were documented by numerous authors [22]-[23]. Although our findings showed that culture is unreliable and redundant, we still recommend this investigation for its additional quality of antibiotic susceptibility testing.

We have employed the ROC curves to evaluate the accuracy of biomarkers for predicting early sepsis and determined that the AUC value for P-SEP on the day of admission (0.870) was the highest among conventional tools. This indicates that P-SEP has a better ability to predict sepsis and an edge over other molecules in the early discrimination of sepsis from SIRS. Our inference is parallel to previous authors suggesting the superiority of P-SEP in early diagnosis of sepsis [24].

Furthermore, we estimated 126 ng/L as an optimum cut-off for P-SEP to determine the onset of sepsis which might also serve as a point for early differentiation from noninfectious conditions. Previously, most authors estimated cut-off concentration on cases with progressive septicemia using values from serial monitoring of P-SEP and thus documented higher reference levels (3). Contrary to that, we evaluated cases of early septicemia, and hence our proposed cut-off is relatively lower. Similar findings were reported in [11], where 88 ng/L effectively indicated early sepsis [11]. In general, there is a dearth of literature on P-SEP concentration in early sepsis; therefore, we recommend more research to address these discrepancies to establish a single cut-off value for P-SEP in early disease.

Besides our main objective, the clinical data revealed a higher baseline temperature in the sepsis group. This result was in agreement with [25] reporting a positive association of raised temperature and risk of sepsis. In contrast, according to [26], fever is an indigenous response to many noninfectious inflammatory conditions, and thus it is not pathognomonic to sepsis. Moreover, our data showed a large number of male subjects with no comparable difference in terms of demographic and co-morbidities.

This study has some limitations. Firstly, there was a limited number of cases in the sepsis group. Therefore, we recommend non-probability quota sampling for a more balanced grouping in future studies. Secondly, due to budget constraints, our objectives were restricted

to early sepsis, and distinguishing it from SIRS and serial monitoring of P-SEP was not performed, which could have provided us an opportunity to evaluate the prognostic value of this molecule. Lastly, P-SEP potential to predict mortality was not assessed. We recommend a large-scale cohort for this purpose.

5. Conclusion

SEP monitoring alongside other inflammatory markers could be vital in the accurate early sepsis diagnosis and can also distinguish infections of bacterial origin from non-bacterial ones. The value of P-SEP was demonstrated in past studies as well. However, previous conclusions were drawn on serial monitoring of P-SEP, reflecting its utility in full-blown and progressive disease while missing out on investigating its role in early sepsis. We observed elevation in plasma level of P-SEP, which was evident in patients on the day of admission corresponding to the onset of sepsis. Hence, we suggest that P-SEP is a promising marker that seems to play an important part in the early diagnosis of sepsis and recommend including this novel molecule in the diagnostic workup of patients suspected of bacterial septicemia.

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