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Review article

Presepsin Versus CRP and Procalcitonin as Biomarker of Sepsis: A Meta-analysis

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Abstract

Background: Despite advances in therapy, sepsis is the leading cause of death in critical care settings, so early diagnosis of sepsis is a must, so we performed a meta-analysis to compare the accuracy of presepsin versus CRP and procalcitonin as biomarker of sepsis. **Methods:** This analysis performed using MEDLINE, EMBASE, PubMed and Cochrane to identify all published randomized, and prospective clinical trials, comparing the accuracy of Presepsin versus Procalcitonin and CRP in diagnosis of sepsis. **Results:** The Database of our meta-analysis included 13 studies with 2679 participants meeting definitive criteria of sepsis, The pooled sensitivity and of presepsin, procalcitonin and CRP was 0.84, 0.80, 0.69 respectively which shows that presepsin is stronger than procalcitonin and CRP, the pooled specificity of presepsin, procalcitonin, CRP was 0.73, 0.69, 0.68 respectively. The PLR and NLR of presepsin were 2.7 and 0.2, respectively and of procalcitonin were 2.6 and 0.29, respectively and of CRP were 2.6 and 0.41, respectively. The DOR of presepsin, procalcitonin and CRP was 11.8, 8.8, 6.2, respectively. **Conclusions:** This study demonstrated that presepsin is a reliable biomarker of sepsis because of its higher sensitivity and specificity than procalcitonin and CRP.

Keywords: Presepsin; CRP; Procalcitonin; Sepsis

Introduction

Sepsis is a medical emergency currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. With a recent estimate of 11 million sepsis-related deaths out of 48.9 million yearly sepsis cases, it is a global health priority (1). Current sepsis treatment guidelines recommend general measures, such as antibiotic treatment, source control, and resuscitation. The heterogeneity of the sepsis syndrome however makes early and consistent diagnosis difficult and has resulted in a lack of sepsis-specific treatments. An essential factor limiting our ability to detect sepsis is the lack of clinically relevant biomarkers for the early phases of the syndrome (2).

Despite advances in therapy, sepsis is the leading cause of death in critical care

settings and critically ill patients are more predisposed to sepsis due to many risk factors as older age, compromised immune system, diabetes, longer hospital stays, invasive devices as CVL, risk of mechanical ventilation, SO to improve the survival, early recognition of severe sepsis and septic shock and subsequent introduction of an aggressive supportive therapy are mandatory (3, 4).

The benefits of early diagnosis and treatment have been well-studied and protocolized in specialties such as trauma medicine, cardiology (e.g., myocardial infarction and cardiac arrest) and neurology (e.g., stroke management), but less so in the field of sepsis (5).

This can potentially lead to longer time-to-antibiotics and higher mortality. Sepsis patients often undergo their first extensive evaluation in the emergency room. Decisions made at this stage, such as choice of antibiotic treatment and discharge destination, are likely to highly impact the rest of the hospital stay. Biomarkers are able to reduce the heterogeneity among sepsis patients in the ER and could improve their care (6).

Various biomarkers have been reported useful in sepsis diagnosis, such as procalcitonin and C-reactive protein. However, these biomarkers may also be elevated in non-septic conditions such as trauma, burn and postoperative settings. Some are slow to rise after the onset of sepsis. It thus remains necessary to find reliable biomarkers to replace or improve those that are currently available (7).

More recently, the soluble CD14 subtype, presepsin, appears to be an accurate sepsis diagnostic marker and rises up a great clinical interest. Levels of presepsin were found significantly higher in septic than in non-septic patients. Moreover, a specific increase was reported in the early stage of sepsis that also well correlated with severity. Accordingly, plasma presepsin levels could be useful for diagnosis and prognosis of sepsis and also for monitoring the course of the disease (8).

This study aimed to compare the accuracy of presepsin versus CRP and procalcitonin as biomarker of sepsis.

Patients and Methods

This study was a meta-analysis; it was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement it was conducted at the Department of Critical Care Medicine in Benha University Hospital, Benha, Egypt from December 2021 to May 2023.

This study was approved by the ethical committee of Benha University **(Ms.6.12.2021).**

This analysis was performed using MEDLINE, EMBASE, PubMed and Cochrane to identify all published randomized, and prospective clinical trials, comparing the accuracy of Presepsin versus Procalcitonin and CRP as biomarker of sepsis (9). Relevant articles were distinguished using the following search terms: Presepsin, Procalcitonin and CRP.

Inclusion criteria: included studies which were chosen to meet the definitive criteria of sepsis, additionally the studies included data to compare the accuracy of prespsin versus CRP and procalcitonin as biomarker of sepsis, and enough data to calculate the

outcome data (true positive (TP), false positive (FP), true negative (TN), false negative (FN).

Exclusion criteria: Any studies conducted on animal models or other non-human subjects or published in languages other than English were excluded.

The following descriptive data were extracted from the included studies: the name of the first author, publication year, country of origin, study design, clinical setting, sample size, and the true positive (TP), false positive (FP), false negative (FN), and true negative (TN) rates, sensitivity (SEN) and specificity (SPE) of the data.

Four researchers analysed and assessed risk of bias and applicability of diagnostic accuracy for the included studies based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) by RevMan (version 5.2, Cochrane Collaboration, Oxford, UK). QUADAS-2 consists of four sections: patient selection, index test, reference standard, and flow and timing. The studies included were graded as low risk, high risk, or unclear bias based on the following criteria: (1) if the answers to all of the questions for a section were "yes," then the risk of bias was judged as "low;" (2) if any answer to a question in a section was "no," then risk of bias was judged as "high;" (3) the unclear bias was only to be used when insufficient information was provided.

Applicability was judged as low, high, or unclear with the above criteria. Deek's funnel plot also was used to detect publication bias and it was performed using STATA software version 17.0.

Statistical analysis:

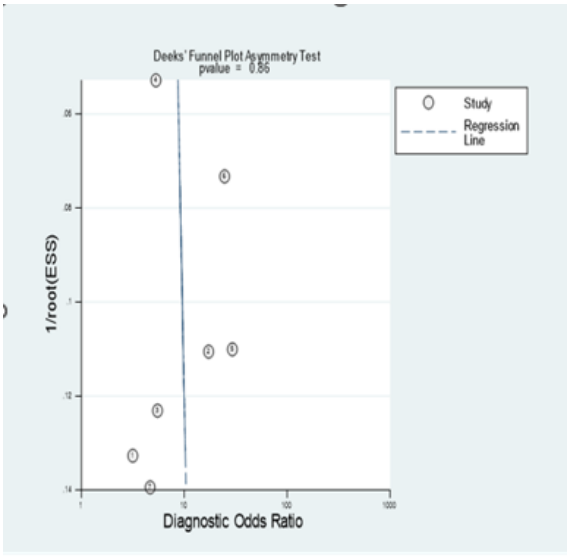
All statistical analyses were performed using RevMan (version 5.2, Cochrane Collaboration, Oxford, UK) and Midas and Metandi modules for STATA software version 17.0. It was used to calculate the pooled SEN, SPE, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR), also we constructed summary receiver operator characteristic (SROC) curve to assess overall diagnostic accuracy of presepsin, CRP and procalcitonin.

Results:

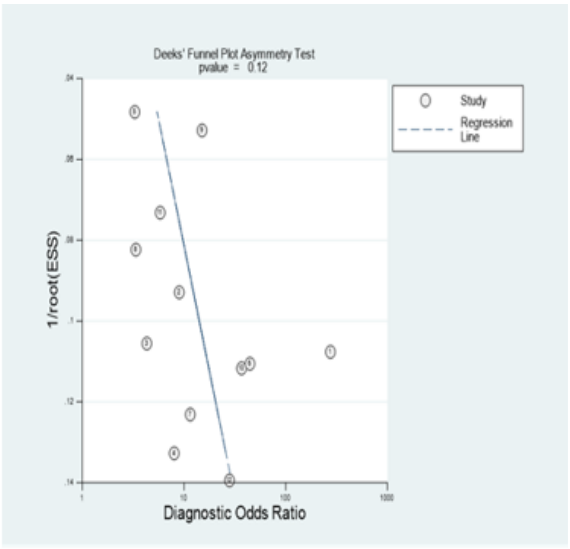
Table 1 lists the criteria of the included studies. The Database of this analysis included 13 studies with 2679 participants meeting definitive criteria of sepsis, 12 included studies analyzed the diagnostic accuracy of presepsin and 7 studies analyzed procalcitonin accuracy and 5 studies analyzed CRP. Our included studies were published between 2012 to 2021 and 3 studies conducted in Japan, 2 in Italy, 2 in Egypt, 1 in Germany, 1 in Iran,1 in China,1 in France, 1 in Coroatia, 1 in Korea. Overall, 1891 participants were assigned to the sepsis group and 788 participants were assigned to the healthy group.

Table 1: criteria of included studies.

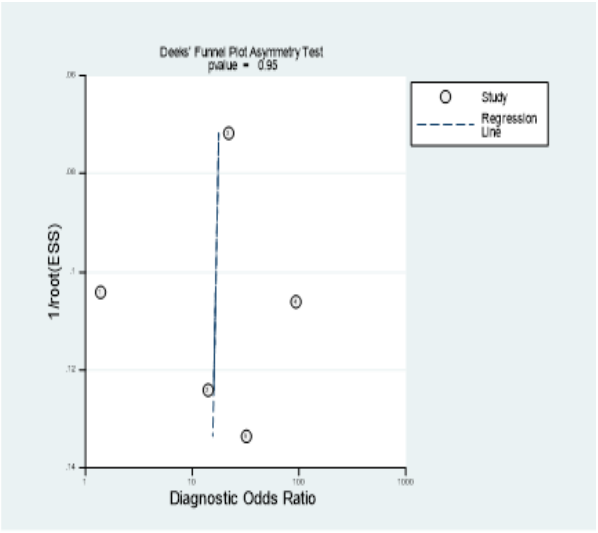
Study Id	country	Total number	Pathology	Study duration	parameters	Study design
Abdollahi et al 2012	Iran	95	sepsis	between January 2009 to January 2010	CRP Procalcitonin Interleukin 6	prospective cross sectional study
Ulla etal. 2013	Italy	189	SIRS Sepsis Septic shock	. Between January 2012 and January 2013,	Presepsin procalcitonin	multicenter prospective study
Liu etal 2013	China	959	sepsis in emergency department	2011 -2012	presepsin , procalcitonin , MEDS score , APACHE11 score	prospective study
Behnes etal 2014	Germany	116	Severe sepsis and septic shock	October 2011-2014	presepsin, procalcitonin interleukin 6 (IL-6), CRP WBC	mono-centric prospective controlled study
Ishikura et al.2014	Japan	82	SIRS	from June 2010 to June 2011	Presepsin CRP Procalcitonin WBCs IL6	prospective single-center observational study w
Klouche etal 2016	France	144	community acquired pneumonia	2016	presepsin , procalcitonin	observational prospective study
AMER etal 2018	Egypt	100	Sepsis and septic shock	between November 2016 and March 2017.	Presepsin CRP TLC	Case control study
TSUJIMOTO etal2018	Japan	126	Sepsis in rheumatoid arthritis	2014-2015	presepsin - CRP - PCT	observational study
Yao etal 2019	Japan	105	bacterial infection following hepato-biliary-pancreatic surgery	Between 2017 and 2019	Presepsin NLR CRP procalcitonin	A prospective observational study
Bejta etal 2020	Kosovo , Croatia	100	Sepsis	2015 -2016 , 2018	presepsin , CRP , Procalcitonin , SOFA score	prospective observational study
Ferrarese etal 2020	Italy	448	bacterial infection in cirrhosis	2016 -2019	presepsin , CRP , Procalcitonin	observational study
El Kady etal 2021	Egypt	62	Sepsis	from November 2017 to February 2018.	Presepsin CRP procalcitonin	prospective cohort study
Koh etal 2021	korea	153	Sepsis or septic shock	July 2019 to August 2020.	Presepsin Lactate CRP Procalcitonin	Retrospective cohort study



Deek 's funnel plot of procalcitonin



Deek 'funnel plot of presepsin



Deek's funnel plot of CRP

Figure 1: Deek's funnel plot of presepsin, procalcitoin and CRP.

In **Figure 1**, Deek's funnel plot of presepsin, procalcitonin and CRP it was of asymmetry test and of *p* value 0.12, 0.86, 0.72 respectively which indicated there is no significant risk of publication bias.

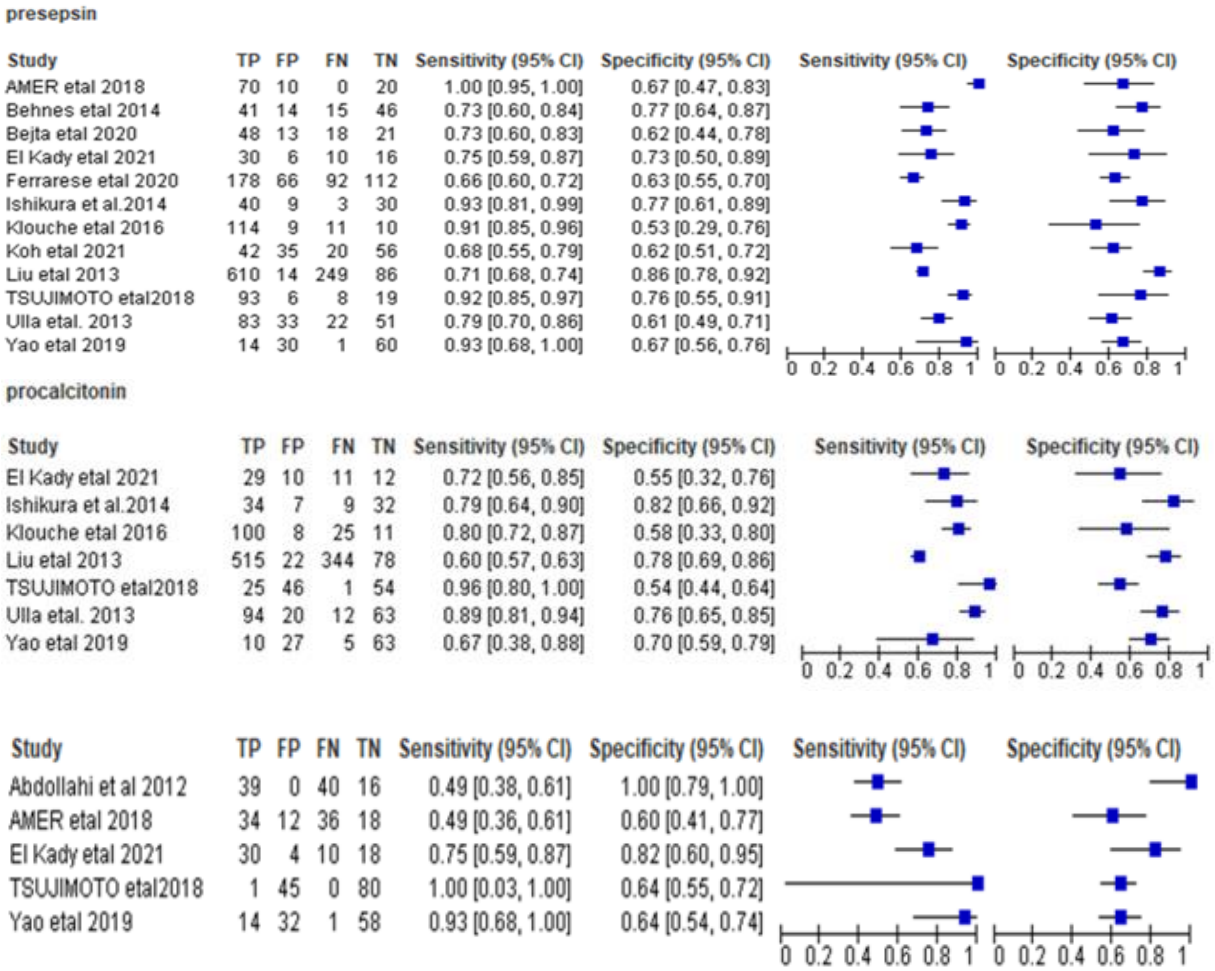
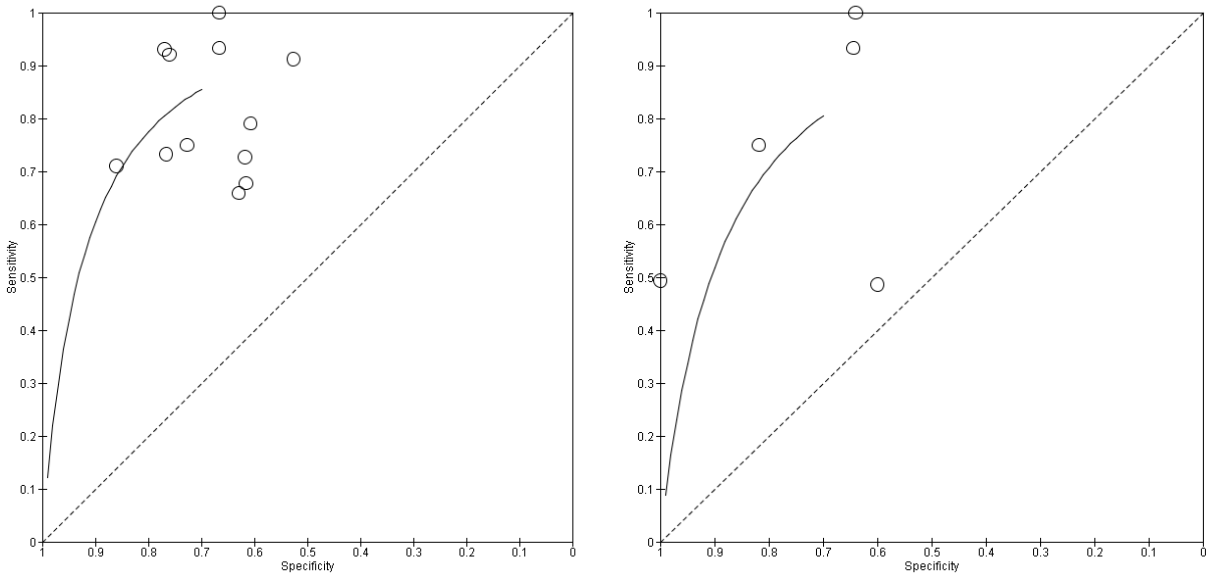
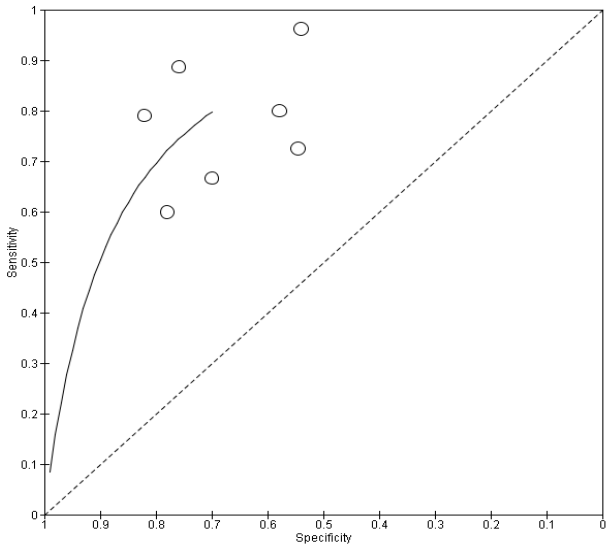


Figure 2: Forestplot of presepsin, Procalcitonin and CRP.

Figure 2 shows forestplot of presepsin, procalcitonin and CRP. The pooled sensitivity of presepsin, procalcitonin and CRP was 0.84(95% CI: 0.75 – 0.90) , 0.80 (95% CI: 0.69 – 0.87), 0.69 (95% CI: 0.46 – 0.86) respectively which shows that presepsin is stronger than procalcitonin and CRP, the pooled specificity of presepsin, procalcitonin, CRP was0.73 (95% CI : 0.56 – 0.85) , 0.69 (95% CI: 0.62 – 0.76), 0.68 (95% CI: 0.63 – 0.74)respectively, The PLR and NLR of presepsin were 2.7 (95 % CI: 2.2, 3.3) and 0.22 (95 % CI: 0.14, 0.37), respectively and of procalcitonin were 2.6 (95 % CI: 2, 3.2) and 0.29 (95 % CI: 0.19, 0.44), respectively and of CRP were 2.6 (95 % CI: 1.4, 4.6) and 0.41 (95 % CI: 0.21, 0.81), respectively. The DOR of presepsin, procalcitonin and CRP was 11.8 (95 % CI: 6.3, 22.2), 8.8 (95 % CI: 5.1, 15.2), 6.2 (95 % CI: 2, 18.8) respectively.

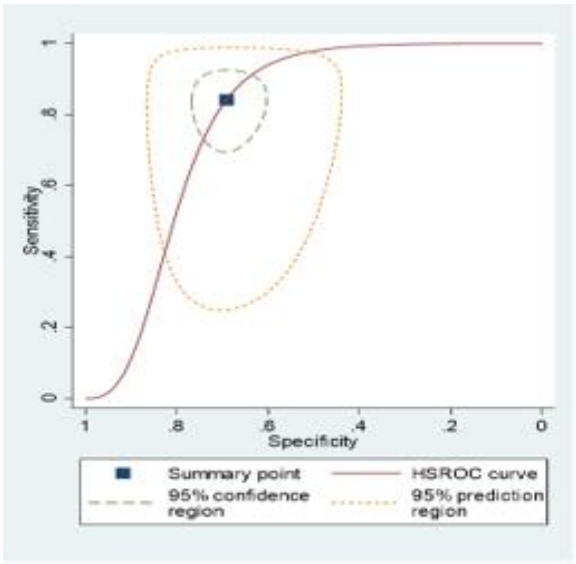


presepsin CRP

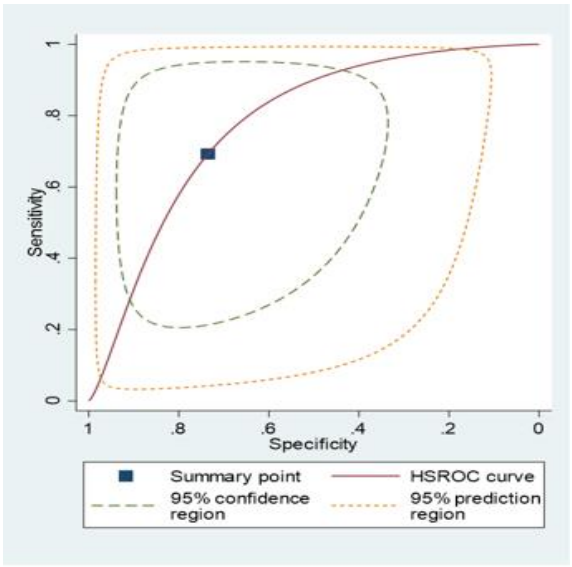


procalcitonin

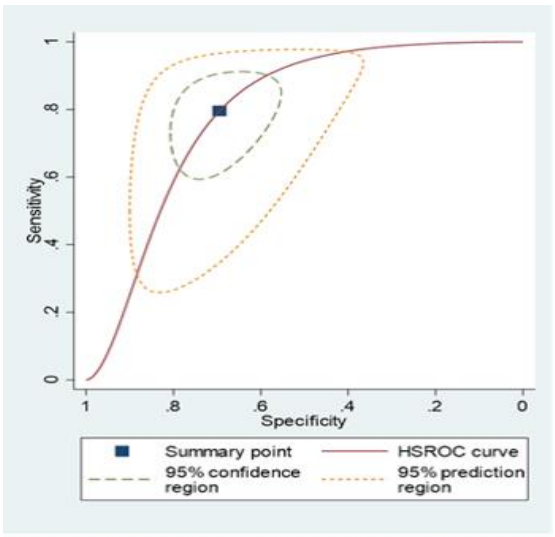
Figure 3: SROC curve of presepsin, procalcitonin and CRP.



HSROC curve of presepsin



HSROC curve of CRP



HSROC curve of Procalcitonin

Figure 4: HSROC curve of presepsin, CRP and Procalcitonin.

Figure 3, 4 show SROC & HSROC curve of presepsin, procalcitonin and CRP. Which show that AUC of presepsin, procalcitonin and CRP was 0.89, which was greater than the results of PCT and CRP which was 0.81, 0.79 respectively.

Discussion

Sepsis and septic shock are some of the most common conditions handled in the Emergency Department (ED) and ICU, and, despite modern antibiotic therapy in conjunction with cardiovascular and respiratory support, mortality rates remain between 30% and 60% (9, 10).Early recognition of these conditions, the speed and appropriateness of therapy in the initial hours after presentation are likely to influence the outcomes of septic patients (11, 12). Today, alert and earliest timing of diagnosis and treatment is still recommended as the best method of choice to prevent sepsis and septic shock. No single new effective medical therapy or decisive diagnostic tool has been found over the last decades (13).

Additionally, the increasing number of patients surviving sepsis or septic shock is endangered by an adverse long-term prognosis and therefore these patients need to be increasingly focused upon. A broad range of clinical and laboratory parameters are specifically combined and define the diagnostic standard of severe sepsis and septic shock (14).

Biomarkers can be defined as any objective, reproducible characteristics by which (patho) physiologic processes can be identified and measured. Within the field of sepsis, one can differentiate between diagnostic, prognostic, and therapeutic biomarkers. Diagnostic biomarkers differentiate between infectious and non-infectious disease or help identify specific pathogens. Prognostic biomarkers are useful for assessing the risk of poor outcomes in septic patients and can help us stratify patients by their risk profiles (15).

Although non-specific for the diagnosis of sepsis, CRP and procalcitonin (PCT) are often used to detect inflammation because of their high sensitivity. CRP is an acute-phase reactant protein synthesized by the liver, primarily induced by IL-6 (16), whereas PCT is a precursor for the calcitonin hormone, normally made in the thyroid gland. When compared to CRP, PCT levels increase faster after stimulation, reach their peak faster, and also decline faster after resolution of infection. These are desirable characteristics for a biomarker, especially in the ER, as they describe the current state of a patient more accurately (17).

Among various molecules, presepsin appears to be a promising biomarker, as it has been reported to be involved in the early stages of the septic process. When monocytes are activated by an infectious agent, the soluble CD14 subtype, presepsin, is released into the plasma. Subsequently, presepsin levels continue to increase in the early stages of sepsis (18, 19).

The main finding of our meta-analysis that presepsin is associated with very good diagnostic value in diagnosis of sepsis and septic shock as the area under the SROC curve was 0.89, which was greater than the results of PCT and CRP which was 0.81, 0.79 respectively. The pooled sensitivity and specificity of presepsin were 0.84 & .073 respectively. On the other side sensitivity & specificity of procalcitonin (0.80 and 0.69 respectively) and of CRP (0.69 and 0.68 respectively), which exhibit the highest sensitivity among the proposed biomarkers in differentiating sepsis form other non-infectious SIRS.

The rescue principles indicate that the infection foci of patients with sepsis should be detected within 6 hours, followed by antibiotic treatment within 1 hour after the diagnosis of sepsis (20). Generally, PCT increases 4 hours after infection, slowly reaching a plateau at 8–24 hours and peaking one day after infection. Compared with PCT, presepsin increases at 2 hours post-infection in the cecal ligation and puncture (CLP) sepsis model and peaks at 3 hours. Presepsin can be detected in the early stage of infection using rapid dosage methods based on chemi-luminescence enzyme immunoassay, which are available and permit automated measurements in 1.5 hours (19).

Also, like hood ratios and diagnostic odds ratio are of importance for clinician in exhibiting sepsis, according to our meta-analysis The PLR and NLR of presepsin were 2.7 (95 % CI: 2.2, 3.3) and 0.22 (95 %

CI: 0.14, 0.37), respectively and of procalcitonin were 2.6 (95 % CI: 2, 3.2) and 0.29 (95 % CI: 0.19, 0.44), respectively and of CRP were 2.6 (95 % CI: 1.4, 4.6) and 0.41 (95 % CI: 0.21, 0.81), respectively. The DOR of presepsin, procalcitonin and CRP was 11.8 (95 % CI: 6.3, 22.2), 8.8 (95 % CI: 5.1, 15.2), 6.2 (95 % CI: 2, 18.8) respectively. Which means that presepsin is associated with higher sensitivity, specificty, PLR, AUC and lower NLR than procalcitonin and CRP, and that is interpreted as presepsin is more accurate biomarker of sepsis than procalcitonin and CRP.

Several limitations should be considered when interpreting the findings of this meta-analysis. First, despite the extensive literature search, the number of included studies was small; however, the number of patients enrolled was satisfactory (n = 2679), thereby decreasing error. Second, falsely elevated values of presepsin or PCT and CRP are observed in conditions of chronic renal failure or a history of resuscitation and trauma. Thus, future research should be designed in consideration of how comorbidities may influence their levels to confirm an optimal cutoff point for clinical use. Third, due to the small number of eligible studies and the lack of necessary data reported in the original publications, we could not specifically analyze patients with different conditions (e.g., different severities of sepsis or different sites of infection) to distinguish the sepsis, nor could we determine the therapeutic decisions in the individual patient. Forth, some studies only confirm septicemia by positive blood cultures, microscopy, or polymerase chain reaction, whereas others also consider a comprehensive assessment of the patient chart and assessment of clinical, radiological, and laboratory data.

Conclusion

This study demonstrated that presepsin is a reliable biomarker for sepsis because of its higher sensitivity and Specificity than procalcitonin and CRP.

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