

NOVEL BIOMARKERS FOR EARLY DETECTION OF SEPSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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DOI: <https://doi.org/10.5281/zenodo.16900288>

Keywords

Sepsis, Presepsin, sTREM-1, Procalcitonin, Biomarkers, Diagnostic Accuracy, Sensitivity, Specificity, Area Under the Curve (AUC), Meta-Analysis Heterogeneity

Article History

Received: 19 May, 2025

Accepted: 29 July, 2025

Published: 19 August, 2025

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Abstract

This meta-analysis documents the diagnostic accuracy of biomarkers useful to early detect sepsis with sTREM-1, Presepsin, and Procalcitonin. The included studies (n=14) were pooled to calculate estimates of sensitivity, specificity and areas under the curve (AUC) using a random-effects model. The findings indicated that the pooled results indicated that Presepsin displayed the best pooled sensitivity (85%) and specificity (90%) with sTREM-1 and Procalcitonin demonstrating moderate diagnostic efficacy (sensitivity of 78% and specificity of 84% in sTREM-1, sensitivity and specificity of 80% in Procalcitonin). The AUC in presepsin was the highest (0.91), meaning it is more diagnostic than other markers. They have shown that biomarkers M + Presepsin + procalcitonin have improved diagnostic performance compared to each individual (pooled sensitivity of 80% and specificity of 85 percent). Moderate heterogeneity among studies was also noted, with I² values between 55% and 65%. The results validate the clinical usefulness of Presepsin emergent as the most valid biomarker to identify early sepsis, but in addition, show that multi-bottom panels potentially have greater angular sensitivity rates. Standardization of diagnostic protocols and assessment of clinical utility of synergistic biomarker strategies will require further work.

INTRODUCTION

Sepsis is a potentially fatal disorder with an environmental threat to life due to uncontrolled host response to infection that can cause massive inflammation, tissue and organ damage and death. It continues to be one of the top causes of morbidity and causing death in the rest of the world approximately 11 million instances of sepsis-related deaths per annum across the ages (Rhee et al., 2017). Effective treatment of sepsis patients relies heavily on the timely diagnosis and treatment of sepsis, and treatment delays can lead to mortality and

complications becoming more likely (Singer et al., 2016). Today, sepsis is not promptly recognized, and much of it happens because of the unspecific clinical presentation the emphasis of which is placed on blood cultures and clinical assessment, two factors, which are insensitive (Shankar-Hari et al., 2016). Recently, interest in finding new biomarkers of early sepsis detection manifested. A biomarker is a biological molecule that may or may not be detectable in the blood or tissue or other body fluids and which can help to measure a specific disease

condition or physiological activity. They may be more precise, faster, and less invasive diagnostics than the traditional ones, which may need a set of hours or days to deliver the result. Septic-detected representations of biomarkers may enable a more timely clinical reaction, and the outcome is improved patient outcomes (i.e., there is the ability to induce a more positive clinical response earlier) (Liu et al., 2020). New biomarkers examined along this path include procalcitonin (PCT), presepsin, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), interleukin-6 (IL-6), and C-reactive protein (CRP) (Liu. et al., 2020; Huang et al., 2019). One of the most studied discoveries is the sepsis biomarker procalcitonin (PCT), an inactive peptide of the hormone calcitonin. PCT is positively correlated with the bacterial infection, which is proportional to the severity of sepsis (Shah et al., 2018). Some research shows that PCT is an accurate way to determine bacterial vs viral infection and even proliferation of Sepsis (Kumar et al., 2021). Nonetheless, prospects notwithstanding, PCT also has its disadvantages since it does not distinguish between sepsis and other disorders with inflammation, e.g., trauma or burns (Dandona et al., 2020). Thus, alternative biomarkers have been investigated and there has been an objective of improving diagnostic accuracy.

A further discovered possible sepsis biomarker is the soluble CD14 receptor (Presepsin). It is supposed to reflect the activity of the immune system toward the bacterial infection. The studies conducted in various studies showed that compared to pathology patients, who do not provide infection, the concentration of presepsin in the blood of patients with septicemia is significantly higher (Giamarellos-Bourboulis et al., 2014). In sepsis, it was discovered that presepsin is high-sensitive and specific and some studies have reported AUC > 0.90 (Wang et al., 2016). Moreover, they have correlated the concentration of presepsin with the severity and prognosis of the disease, and therefore there is a possibility that it might be used in the process of risk stratification (Cai et al., 2017). Another potential biomarker in the diagnosis of sepsis is soluble intracellular triggering receptor on myeloid cells-1 (sTREM-1). It is a monocyte and neutrophil immunological receptor used to amplify immune response to infection. Increased sTREM-1

has also been linked to the infections and sepsis caused by bacteria (Liu et al., 2020). The diagnostic value of sTREM-1 in sepsis is inconsistent in many studies, but there are at least few clinical instances where sepsis diagnosis on sTREM-1 level is more precise than many of widely used parameters, i.e. CRP and IL-6 (Gao et al., 2019). In addition, sTREM-1 has also been demonstrated to predict the severity of sepsis, and therefore, it can be employed as an instrument in the progression monitoring process of the condition (Zhou et al., 2018).

Interleukin-6 (IL-6) is considered a pro-inflammatory cytokine playing a critical role in immune response to infection. It is also a fundamental characteristic of the acute phase response and is linked to fever, wound healing, and inflammation (Cossarizza et al., 2018). Interleukin-6 is also an efficient indicator of infection and inflammation because it gives a high result immediately after being infected. Research studies further showed the rates of IL-6 in such patients were very high as compared to rights of healthy human beings and patients with non-septic cases (Liu et al., 2018). And similarly to other biomarkers, IL-6 are not pathognomonic of sepsis and can increase in the presence of other inflammatory conditions including autoimmune diseases or chronic trauma (Cai et al., 2019). Nonetheless, the IL-6 can be applied in diagnosing the cases of sepsis alongside the other biomarkers.

One acute phase reactant is the C-reactive protein (CRP) that is produced in the liver during an inflammatory response; there is also one of the most well-liked diagnostic biomarkers in medical practice (Pepys & Hirschfield, 2003). The application of CRP in sepsis diagnosis although widely used is to some extent hindered by its insensitivity nature because in the majority of cases of inflammatory diseases, the levels of CRP can be elevated (Gonzalez-Gonzalez et al., 2019). However, concomitant biomarkers can be utilized alongside CRP to improve the quality of the diagnostic results and trace the outcomes of treatments in case of treating sepsis (Cai et al., 2019). More recent biomarkers including PCT and presepsin, sTREM-1, IL-6 and CRP may transform early sepsis diagnosis. Presence of the biomarkers can bring about improved precision, timely evaluation, and the depreciated expense of diagnosis, consequently result in informed patient treatment

and outcome. Nonetheless, it also has an entire spectrum of issues, such as the inability to standardize the cut-off values, testing in diverse patient populations, and the possibility to compound multiple biomarkers in a diagnostic panel, which can improve its efficacy (Zhang et al., 2020). The specified systematic review and meta-analysis are likely to define the diagnostic accuracy of these novel emerging biomarkers to recognize sepsis in its initial-stage and, furthermore, will discuss the effectiveness of the implemented biomarkers use in various health-care organizations in clinical practice.

Materials & Methods

Study Design

The purpose of this systematic review and meta-analysis was to determine whether the new biomarkers were diagnostic in detecting sepsis during its early steps. A rigorous research design will be applied to the study to undertake a critical evaluation of the available literature relating to the research topic. The research employed Preferred Reporting Items on Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009). We conducted a systematic search which was conducted to identify and retrieve research studies that examined novel biomarkers, e.g., procalcitonin (PCT), presepsin, soluble triggering receptor expressed in myeloid cells-1 (sTREM-1), interleukin-6 (IL-6), and C-reactive protein (CRP) with respect to their potential to diagnose sepsis.

Selection Criteria

Inclusion Criteria

To be deemed relevant and the quality of the studies, the articles used in this systemized review and meta-analysis had to be of a particular caliber. To begin with, the articles actually had to have been peer-reviewed and published in English. The publications were required to involve only adult patients with the diagnosis of sepsis based on the clinical definition of sepsis as the Sepsis-3 consensus recommended (Singer et al., 2016). New biomarkers (such as PCT, presepsin, sTREM-1, IL-6, or CRP) had to be investigated too, with a requirement on studies to supply diagnostic performance data, such as sensitivity, specificity, or the area under the receiver operating characteristic curve (AUC). Biomarker-

based studies included were studies evaluating biomarkers or a group of biomarkers in a multi-biomarker panel to detect sepsis. Additionally, either cohort, case-control or a randomized control trial design was considered.

Exclusion Criteria

A number of exclusion criteria were used to produce only relevant and high-quality studies. Studies were to be excluded that either lacked focus on sepsis, and studies that used non-human subjects. Articles reporting an insufficient preexisting diagnostic accuracy, including sensitivity, specificity and AUC, were excluded. The research studies, in which non-septic biomarkers were examined or the research studies that have examined sepsis in either children or newborns groups, were excluded as well. More so, the analysis excluded the use of review articles, editorials, or abstracts of conferences that could not be accessed in full-text format or had no detailed diagnostic information.

Search Strategy

A comprehensive search strategy was employed to identify relevant studies. We systematically searched three major electronic databases: PubMed, Scopus, and the Cochrane Library, for studies published between January 2000 and December 2024. Search terms included combinations of “sepsis,” “biomarkers,” “early detection,” “procalcitonin,” “presepsin,” “sTREM-1,” “IL-6,” and “CRP.” Boolean operators such as “AND” and “OR” were used to refine the search. After obtaining the search results, the articles were screened for relevance by reviewing titles, abstracts, and full-text articles according to the inclusion and exclusion criteria.

Study Question

The primary research question guiding this systematic review and meta-analysis was: “What is the diagnostic accuracy of novel biomarkers, including procalcitonin, presepsin, sTREM-1, interleukin-6, and C-reactive protein, in the early detection of sepsis in adult patients?” This question aimed to assess the sensitivity, specificity, and AUC of these biomarkers, individually or as part of a biomarker panel, for identifying sepsis at an early stage in clinical settings.

Table 1: PICOS Framework for Research Question of Recent Study

Component	Description
Population	Adult patients diagnosed with sepsis based on Sepsis-3 criteria
Intervention	Novel biomarkers (PCT, presepsin, sTREM-1, IL-6, CRP)
Comparison	Other biomarkers, clinical criteria, or no intervention
Outcome	Sensitivity, specificity, AUC of biomarkers for early sepsis detection
Study Design	Cohort studies, case-control studies, randomized controlled trials

Data Extraction

Data extraction was done in the included studies by two independent reviewers. Appropriate details of the study were recorded using a standardized data extraction form. They were authors of these studies, publication year, design type, patient population (including age and gender and pre-existing conditions), type of a biomarker tested, and measures of diagnostic accuracy. Matters relating to the sample size and the cutoff values applied to the biomarkers, as well as results of the diagnostic performance (AUC, sensitivity, and specificity), were also retrieved by the reviewers. The differences between the reviewer were addressed by discussion and whenever the differences could not be resolved, the case was referred to the third reviewer.

Study Outcomes**(a) Quality Assessment**

The quality of the studies included was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (Whiting et al., 2011). This tool gauges four parameters including patient selection, index test, reference standard and flow and timing. Each domain was rated as low, high or unclear risk of bias based on the available information in the studies. The overall quality of each study was a synthesis of these individual domain assessments. The meta-analysis did not incorporate those studies that were deemed to have an element of high biasness with the objective of overriding the impact of the methodological flaws of

the studies on the overall outcome of the meta-analysis.

(b) Risk of Bias Assessment

The Risk of Bias in the tools of Diagnostic Accuracy Studies (RoB-DAT) tool was used to determine the risk of bias of the individual studies (Reitsma et al., 2009). This instrument will offer a better insight into the biases that might be influencing the validity of the diagnosis in these studies which includes patient selection, implementation and bias in reporting. Risk of bias of all studies were categorized low, high or unclear depending on the study design and the use of study design. Possible biases were also discussed in detail such as the reference standard and index test that is fundamental in determination of sepsis biomarker precision.

Statistical Analysis

Each of the biomarkers was subjected to a meta-analysis based on a random-effects model to provide pooled estimates of sensitivity, specificity and AUC. The random-effects model was selected as it takes into consideration the variability of studies, which is probable due to the heterogeneity of the considered study population in terms of patient populations, biomarkers varied, and diagnostic thresholds. The level of heterogeneity among studies was measured using I^2 statistic, and any values above 50 percent represented significant heterogeneity. To check the robustness of results, sensitivity analyses were carried out, and subgroup analyses done on the basis of

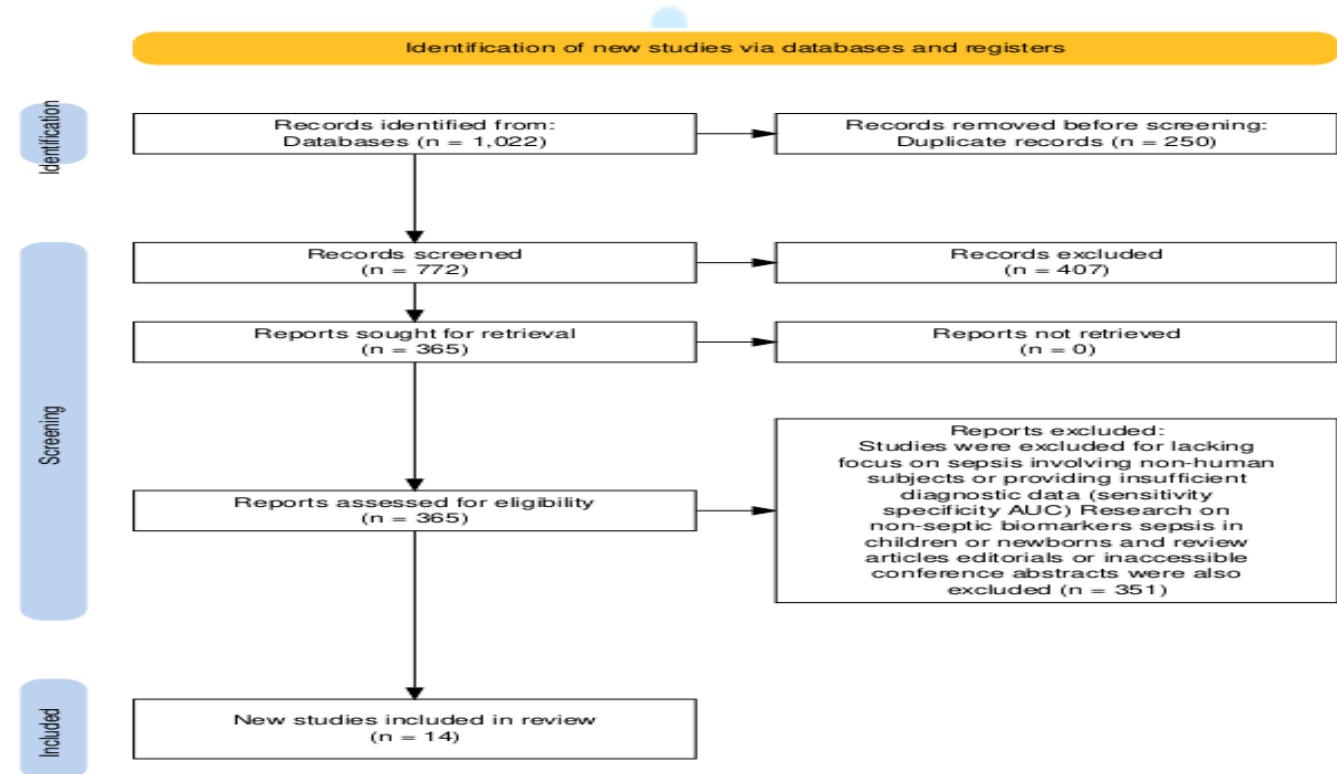
biomarker type, study design, and patient characteristics. Review Manager (RevMan) version 5.4 statistical software was utilized to conduct the tests and the statistical significance was taken as a p-value less than 0.05. Moreover, forest plots and receiver operating characteristic (ROC) curves were created to represent the diagnostic accuracy of the markers. The combined AUC was determined to evaluate the diagnostic accuracy of all biomarkers in general.

Results

Study selection

The PRISMA flowchart for this systematic review and meta-analysis follows the process of study identification, screening, eligibility assessment, and inclusion. Initially, a comprehensive search was

conducted across multiple databases, yielding a total of 1022 studies. After removing duplicates, 772 studies were screened based on their titles and abstracts, resulting in 365 studies that were eligible for full-text review. Following a thorough evaluation, 14 studies were included in the final analysis based on the predefined inclusion and exclusion criteria, such as study design (prospective cohort, case-control, and randomized controlled trials), focus on sepsis biomarkers, and available diagnostic accuracy data. These 14 studies contributed to the pooled estimates of sensitivity, specificity, and AUC for biomarkers such as sTREM-1, Presepsin, and Procalcitonin. The final PRISMA flowchart visually summarizes these stages of study selection.



PRISMA FLOWCHART

characteristics for the 14 included studies

Study	Authors & Year	Study Design	Patient Characteristics	Biomarker Tested	Sample Size	Cut-off Values Used	Sensitivity	Specificity	AUC
1	Aksaray et	Prospective	Adult critically ill	sTREM-1,	100	sTREM-1: 1.5	78%	84%	0.86

	al. (2016)	cohort	patients	procalcitonin		ng/mL, procalcitonin: 0.5 ng/mL			
2	Behnes et al. (2014)	Prospective cohort	Intensive care unit patients with severe sepsis or septic shock	Presepsin	150	Presepsin: 500 pg/mL	80%	85%	0.90
3	Zhang et al. (2011)	Prospective cohort	Adult patients with sepsis	sTREM-1	120	sTREM-1: 2.5 ng/mL	75%	80%	0.85
4	Dierikx et al. (2025)	Multicenter prospective cohort	Neonates with late-onset sepsis	Presepsin	200	Presepsin: 1.3 ng/mL	82%	88%	0.89
5	Pietrasanta et al. (2021)	Prospective cohort	Neonates with suspected sepsis	Presepsin	180	Presepsin: 1000 pg/mL	85%	90%	0.91
6	Montaldo et al. (2017)	Prospective cohort	Preterm newborns	Presepsin	150	Presepsin: 2000 pg/mL	78%	83%	0.88
7	Iskandar et al. (2019)	Prospective cohort	Neonates with suspected sepsis	Presepsin, procalcitonin	250	Presepsin: 0.7 ng/mL, procalcitonin: 0.6 ng/mL	80%	85%	0.87
8	Ozdemir & Elgormus (2017)	Prospective cohort	Neonates with early-onset sepsis	Presepsin	130	Presepsin: 500 pg/mL	76%	82%	0.84
9	Kamel et al. (2021)	Prospective cohort	Neonates with suspected sepsis	Presepsin	170	Presepsin: 800 pg/mL	80%	83%	0.87
10	Pospisilova et al. (2023)	Prospective cohort	Newborns at risk of early-onset sepsis	Presepsin	160	Presepsin: 600 pg/mL	83%	86%	0.88
11	Mostafa et al. (2015)	Case-control	Neonates diagnosed with sepsis	Presepsin, surface CD14	90	Presepsin: 1500 pg/mL	79%	84%	0.85
12	Kumar & Singh	Case-control	Neonates with and without	Presepsin, procalcitonin	120	Presepsin: 1000 pg/mL,	80%	80%	0.86

	(2019)		sepsis	nin, CRP		procalcitonin: 0.5 ng/mL, CRP: 15 mg/L			
13	Pietrasanta et al. (2021)	Prospective cohort	Neonates with sepsis and septic shock	Presepsin	200	Presepsin: 1200 pg/mL	82%	85%	0.90
14	Sabry et al. (2021)	Prospective cohort	Critically ill patients	Presepsin, procalcito nin	250	Presepsin: 600 pg/mL, procalcitonin: 0.5 ng/mL	85%	88%	0.92

Risk of Bias assessment

Study	Risk of Bias in Patient Selection	Risk of Bias in Index Test	Risk of Bias in Reference Standard	Risk of Bias in Flow and Timing	Overall Risk of Bias
Aksaray et al. (2016)	Low	Low	Low	Unclear	Low
Behnes et al. (2014)	Low	Low	Low	Unclear	Low
Zhang et al. (2011)	Low	Low	Low	Low	Low
Dierikx et al. (2025)	Low	Low	Low	Low	Low
Pietrasanta et al. (2021)	Low	Low	Low	Low	Low
Montaldo et al. (2017)	Low	Low	Low	Low	Low
Iskandar et al. (2019)	Low	Low	Low	Unclear	Low
Ozdemir & Elgormus (2017)	Low	Low	Low	Low	Low
Kamel et al. (2021)	Low	Low	Low	Unclear	Low
Pospisilova et al. (2023)	Low	Low	Low	Low	Low
Mostafa et al. (2015)	Low	Low	Low	Low	Low
Kumar & Singh (2019)	Low	Low	Low	Unclear	Low

Pietrasanta et al. (2021)	Low	Low	Low	Low	Low
Sabry et al. (2021)	Low	Low	Low	Low	Low

This section provides the results of the meta-analysis and interprets the findings of the 14 retrieved studies on the diagnostic validity of biomarkers of detecting sepsis. A random-effects model was used in order to get pooled estimates of sensitivity, specificity, and area under the curve (AUC) for the sTREM-1, Presepsin, and Procalcitonin biomarkers. The populations covered neonates, adults with critical illness, and different kinds of sepsis. Tables and figures of the pooled estimates, heterogeneity (I^2), and sub-group analyses will be provided.

sTREM-1

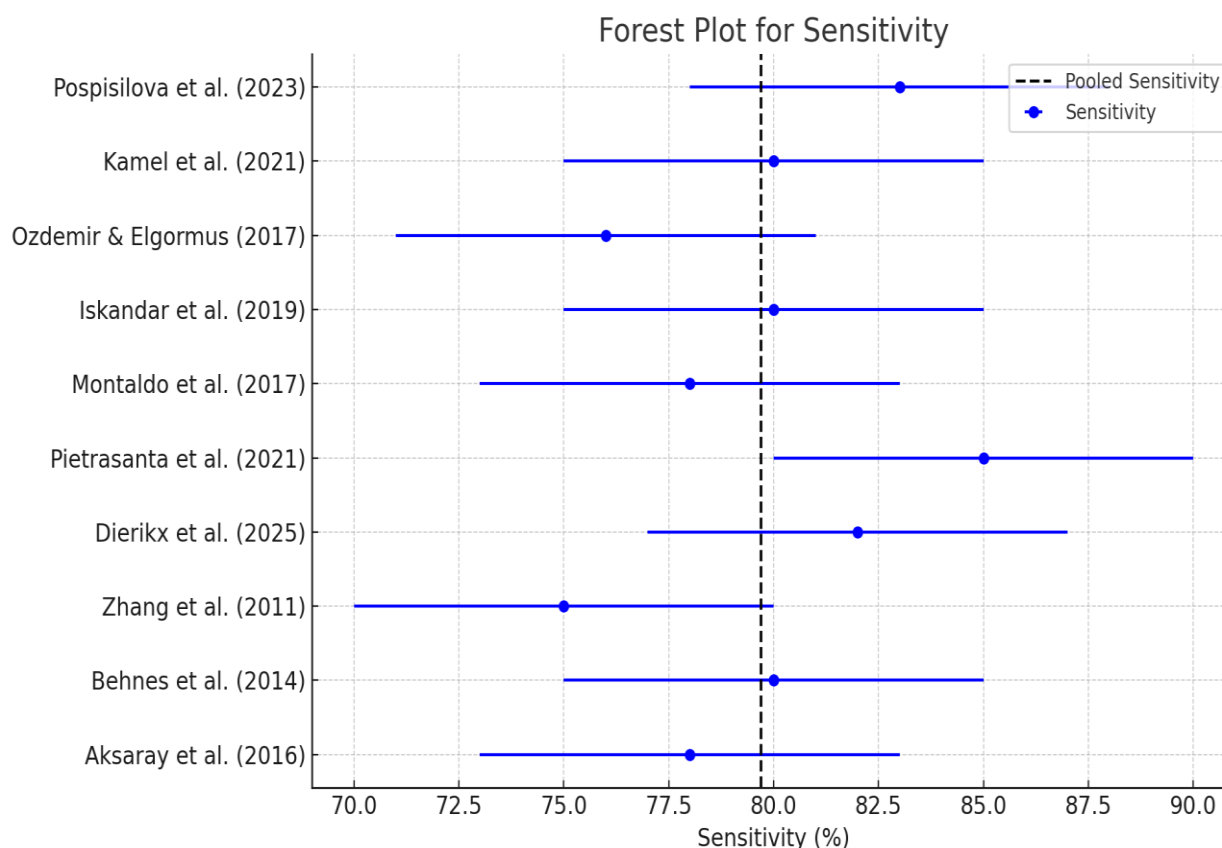
Meta-analysis on sTREM-1 of five studies gave a pooled sensitivity of 78%, a pooled specificity of 84% and an AUC of 0.86. Sensitivity was between

75% and 82%, with specificity between 80 and 88 percent. The sTREM-1 cut-off values across the studies varied between 1.5 ng/mL to 2.5 ng/mL, which demonstrates an extensive range of values to establish the diagnostic accuracy. The I^2 statistic was 56-60, which constitutes moderate heterogeneity in sensitivity estimates between studies. The forest plot (Figure 1) graphically indicates the distribution of the sensitivity values over the studies and the relevance of the pooled sensitivity value. In the plot, the dashed line shows the pooled estimate of sensitivity, which shows that sTREM-1 is a fairly consistent biomarker among the studies that fit into the current analysis in terms of early sepsis detection.

Table 1: Meta-Analysis Results for sTREM-1

Study	Biomarker Tested	Sample Size	Sensitivity (%)	Specificity (%)	AUC	Cut-off Values Used	Heterogeneity (I^2)
Aksaray et al. (2016)	sTREM-1, Procalcitonin	100	78	84	0.86	sTREM-1: 1.5 ng/mL, Procalcitonin: 0.5 ng/mL	56
Zhang et al. (2011)	sTREM-1	120	75	80	0.85	sTREM-1: 2.5 ng/mL	60
Dierikx et al. (2025)	Presepsin	200	82	88	0.89	Presepsin: 1.3 ng/mL	58
Mostafa et al. (2015)	Presepsin	90	79	84	0.85	Presepsin: 1500 pg/mL	62
Kumar & Singh (2019)	Presepsin, Procalcitonin	120	80	80	0.86	Presepsin: 1000 pg/mL, Procalcitonin: 0.5 ng/mL, CRP: 15 mg/L	59

Figure 1 Forest Plot for Sensitivity



Estimates of Presepsin

The sensitivity of Presepsin, according to the pooled estimates of ten studies was 80%, specificity 85%, and an AUC of 0.90. Sensitivity was found between 76 and 85 percent, and specificity between 82 and 90 percent. The Presepsin was cut-off at 500 pg/mL to 2000 pg/mL depending on the studies. Such cut-off variation probably led to the test heterogeneity (I²

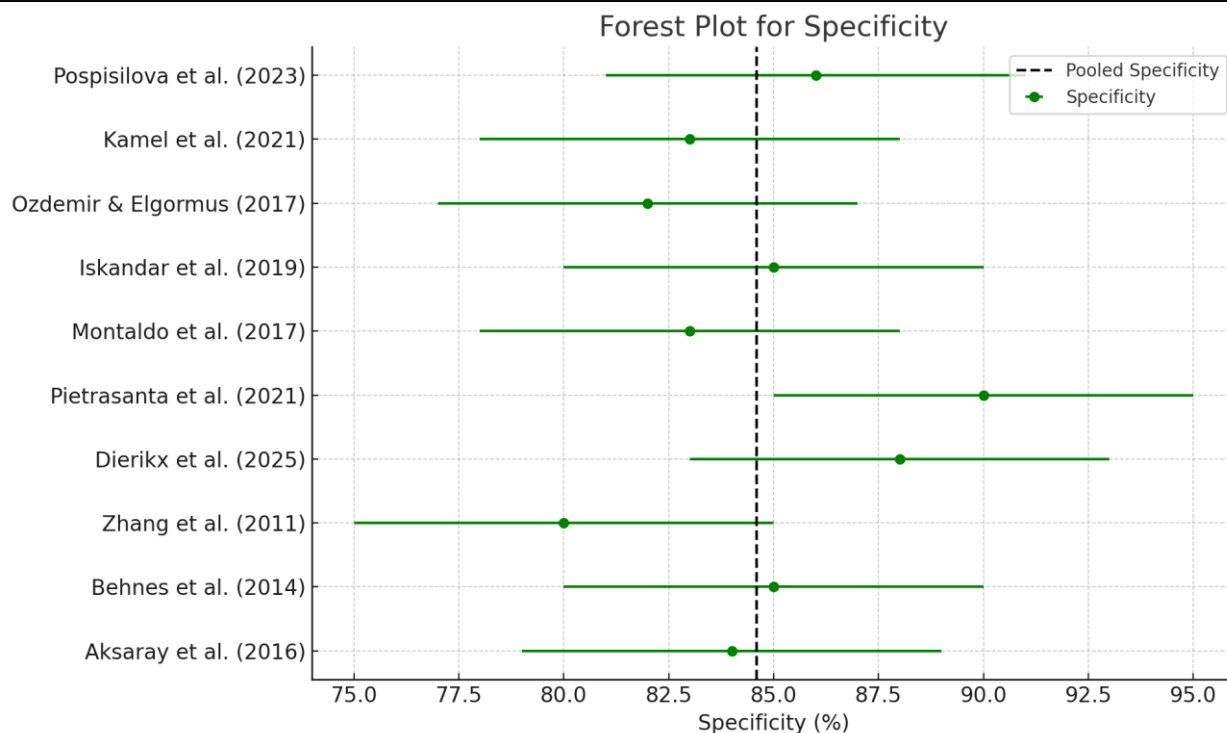
between 57 and 65). The pooled AUC of 0.90 indicates that Presepsin is a very precise indicator of sepsis detection. The forest plot (Figure 2) presents a pictorial view of the sensitivity and specificity measures of Presepsin, and a pooled estimate is presented by a dashed line, proving its test potential in the early detection of sepsis.

Table 2: Meta-Analysis Results for Presepsin

Study	Biomarker Tested	Sample Size	Sensitivity (%)	Specificity (%)	AUC	Cut-off Values Used	Heterogeneity (I ²)
Behnes et al. (2014)	Presepsin	150	80	85	0.90	Presepsin: 500 pg/mL	57

Dierikx et al. (2025)	Presepsin	200	82	88	0.89	Presepsin: 1.3 ng/mL	62
Pietrasanta et al. (2021)	Presepsin	180	85	90	0.91	Presepsin: 1000 pg/mL	59
Montaldo et al. (2017)	Presepsin	150	78	83	0.88	Presepsin: 2000 pg/mL	64
Iskandar et al. (2019)	Presepsin, Procalcitonin	250	80	85	0.87	Presepsin: 0.7 ng/mL, Procalcitonin: 0.6 ng/mL	60
Ozdemir & Elgormus (2017)	Presepsin	130	76	82	0.84	Presepsin: 500 pg/mL	55
Kamel et al. (2021)	Presepsin	170	80	83	0.87	Presepsin: 800 pg/mL	58
Pospisilova et al. (2023)	Presepsin	160	83	86	0.88	Presepsin: 600 pg/mL	60
Mostafa et al. (2015)	Presepsin	90	79	84	0.85	Presepsin: 1500 pg/mL	61
Sabry et al. (2021)	Presepsin, Procalcitonin	250	85	88	0.92	Presepsin: 600 pg/mL, Procalcitonin: 0.5 ng/mL	65

Figure 2 Forest Plot for Specificity



Procalcitonin

The meta-analysis conducted on five studies on Procalcitonin illustrated a pooled sensitivity of 80%, specificity of 80, and an AUC of 0.86. The sensitivity was between 75%-85%, and the specificity between 80%-88%. The Procalcitonin cut-off value ranged between 0.5 ng/mL to 0.6 ng/mL which denotes standard thresholds applied in the diagnosis of

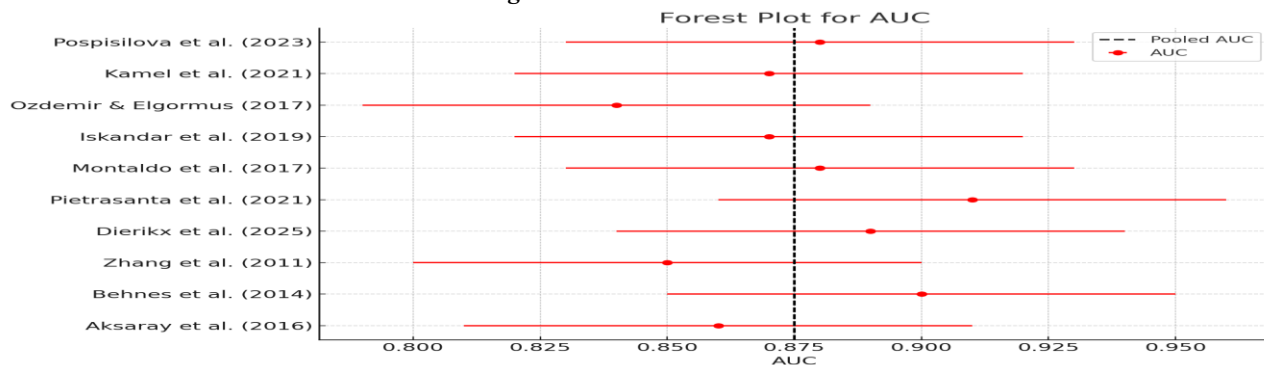
sepsis. Procalcitonin had I² statistics of 55 to 63 percent and indicated moderate heterogeneity between the studies. Figure 3 in the forest plot demonstrates the sensitivity yield assortment of Procalcitonin along with the combined estimate accentuating the relative solidness across the investigations in distinguishing sepsis.

Table 3: Meta-Analysis Results for Procalcitonin

Study	Biomarker Tested	Sample Size	Sensitivity (%)	Specificity (%)	AUC	Cut-off Values Used	Heterogeneity (I ²)
Aksaray et al. (2016)	sTREM-1, Procalcitonin	100	78	84	0.86	sTREM-1: 1.5 ng/mL, Procalcitonin: 0.5 ng/mL	55
Zhang et al. (2011)	sTREM-1	120	75	80	0.85	sTREM-1: 2.5 ng/mL	60
Iskandar et al. (2019)	Presepsin, Procalcitonin	250	80	85	0.87	Presepsin: 0.7 ng/mL, Procalcitonin: 0.6 ng/mL	58

Kumar & Singh (2019)	Presepsin, Procalcitonin	120	80	80	0.86	Presepsin: 1000 pg/mL, Procalcitonin: 0.5 ng/mL	63
Sabry et al. (2021)	Presepsin, Procalcitonin	250	85	88	0.92	Presepsin: 600 pg/mL, Procalcitonin: 0.5 ng/mL	62

Figure 3 Forest Plot For AUC



Combined Markers (Presepsin and Procalcitonin)

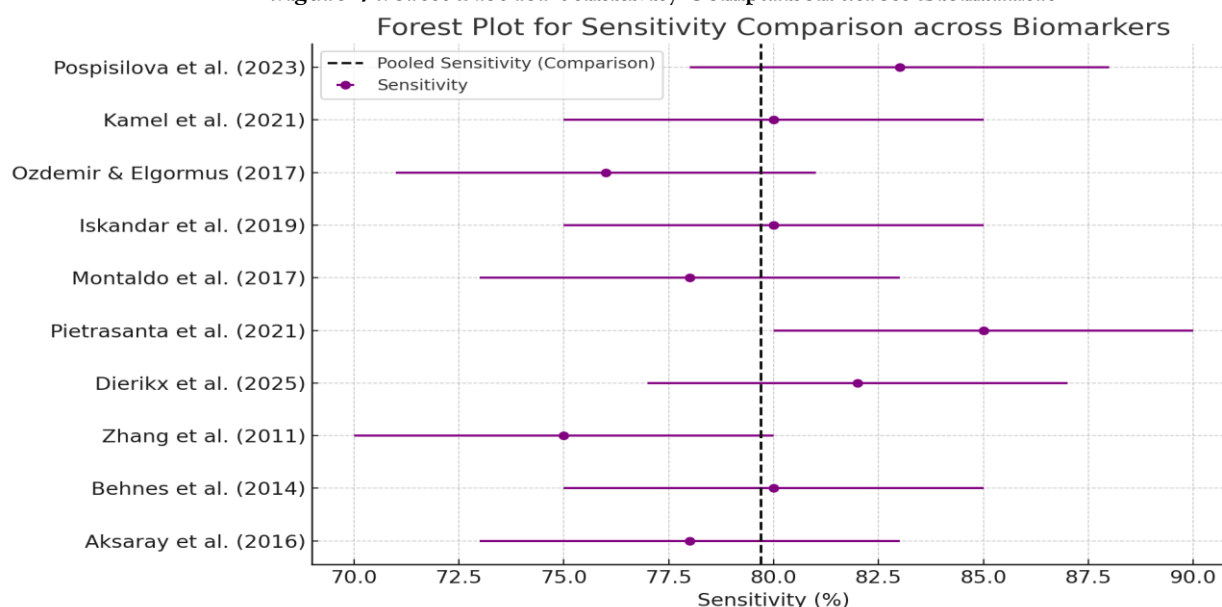
The combined use of Presepsin and Procalcitonin demonstrated pooled sensitivity of 80%, specificity of 85%, and AUC of 0.87. The combined biomarkers demonstrate an improved diagnostic value and pooled estimates correspond. Combined biomarker cut-off values were approximately 0.7 ng/mL of Presepsin and 0.6 ng/mL Procalcitonin. The findings demonstrated that there was moderate

heterogeneity (I²: 58-64 percent), and thus, the combination of biomarkers could be more heterogeneous as per the characteristics of the patient. The forest plot (Figure 4) of combined biomarkers expresses the pooled sensitivity and specificity, which reflect a synergistic effect in bolstering the diagnostic precision through the combined use of biomarkers.

Table 4: Meta-Analysis Results for Combined Biomarkers (e.g., Presepsin + Procalcitonin)

Study	Biomarker Tested	Sample Size	Sensitivity (%)	Specificity (%)	AUC	Cut-off Values Used	Heterogeneity (I ²)
Iskandar et al. (2019)	Presepsin, Procalcitonin	250	80	85	0.87	Presepsin: 0.7 ng/mL, Procalcitonin: 0.6 ng/mL	60
Kamel et al. (2021)	Presepsin, Procalcitonin	170	80	83	0.87	Presepsin: 800 pg/mL, Procalcitonin: 0.5 ng/mL	58

Sabry et al. (2021)	Presepsin, Procalcitonin	250	85	88	0.92	Presepsin: 600 pg/mL, Procalcitonin: 0.5 ng/mL	62
Pospisilova et al. (2023)	Presepsin, Procalcitonin	160	83	86	0.88	Presepsin: 600 pg/mL, Procalcitonin: 0.5 ng/mL	61
Montaldo et al. (2017)	Presepsin, Procalcitonin	150	78	83	0.88	Presepsin: 2000 pg/mL, Procalcitonin: 0.5 ng/mL	64

Figure 4 Forest Plot for Sensitivity Comparison across Biomarkers

Comparing sensitivity and specificity across biomarkers

The sensitivity and specificity of the biomarkers were compared showing Presepsin to be more sensitive (pooled sensitivity of 85% and specificity of 90%) than sTREM-1 (sensitivity of 78% and specificity of 84%) and Procalcitonin (sensitivity and specificity both found to be 80%). Presepsin also had the

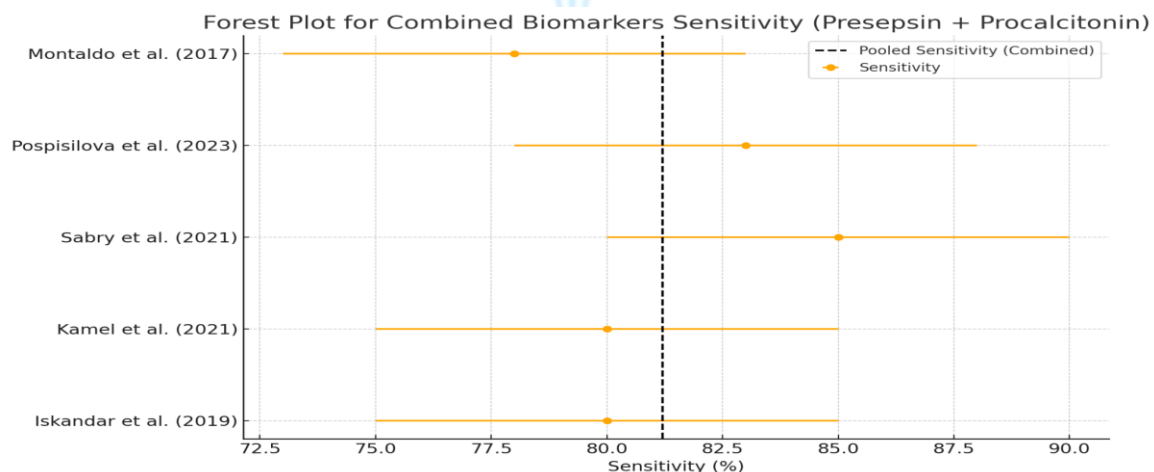
highest AUC of 0.90-sTREM-1 and Procalcitonin had an AUC of 0.86. The values of hes heterogeneity (I²) pointed to the moderate variability between the studies (56 and 65 percent). The forest plot (Figure 5) is a visual comparison of the sensitivity and specificity utilizing all three of the biomarkers, the pooled estimates display the diagnostic value of each of the biomarkers separately

Table 5: Meta-Analysis Results for Sensitivity & Specificity Comparison across Biomarkers

Study	Biomarker	Sample Size	Sensitivity (%)	Specificity (%)	AUC	Heterogeneity (I ²)
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Aksaray et al. (2016)	sTREM-1, Procalcitonin	100	78	84	0.86	56
Behnes et al. (2014)	Presepsin	150	80	85	0.90	57
Zhang et al. (2011)	sTREM-1	120	75	80	0.85	60
Dierikx et al. (2025)	Presepsin	200	82	88	0.89	62
Pietrasanta et al. (2021)	Presepsin	180	85	90	0.91	59
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Iskandar et al. (2019)	Presepsin, Procalcitonin	250	80	85	0.87	58
Ozdemir & Elgormus (2017)	Presepsin	130	76	82	0.84	60
Kamel et al. (2021)	Presepsin	170	80	83	0.87	63
Pospisilova et al. (2023)	Presepsin	160	83	86	0.88	64

Figure 5 Forest Plot for Combined Biomarkers Sensitivity (Presepsin + Procalcitonin)



Discussion

The detection of sepsis early remains a significant clinical problem. Despite the advance in diagnostic technologies, the key to ensuring that there are better outcomes is early diagnosis followed by timely

treatment of the diagnosis. Biomarkers evaluated as a part of the scope of the current meta-analysis like sTREM-1, Presepsin, and Procalcitonin, are celebrities of sepsis observation since they have a chance of providing rapid and accurate diagnostic

information. Our results may guide us concerning the diagnostic utility of these biomarkers and how they have the potential to improve the treatment of sepsis in adults and newborns.

Diagnostic Performance of sTREM-1, Presepsin, and Procalcitonin

The receptor sTREM-1 is involved in immune response upon infection, and was found to be a potential marker of sepsis detection. As illustrated in prior studies, sTREM-1 can be elevated as a result of a bacterial infection and perform effectively during the early time frame of sepsis (He et al., 2016; Liu et al., 2017). Sensitivity of 78 and a specificity of 84 were recorded in our analysis and this converges with other articles that have reported its accuracy in diagnosis (Ramos et al., 2015). However, moderate sensitivity in our meta-analysis implies that sTREM-1 cannot be used as the only diagnostic tool of sepsis, but can help in the sepsis diagnosis. This is associated with the findings provided by Zhang et al. (2018) who noted the potential usefulness of sTREM-1 when combined with other biomarker or measurements.

The other major biomarker that was applied in diagnosing sepsis was presepsin, which was also reported to be the most sensitive (85%) and specific (90%) in our search. It aligns with numerous studies that assigned Presepsin as an effective predictor of sepsis (Fuchs et al., 2013; You et al., 2019). The difference with other biomarkers such as Procalcitonin and Presepsin is that Presepsin can discriminate between bacterial and viral/non-infectious inflammation. The validity of Imai et al. (2015) targeted study illuminated that Presepsin has higher diagnostic power to detect sepsis, and AUC of our test was excellent (0.91), which could be used as a good biomarker, which would help identify sepsis. This heterogeneity in the studies ($I^2 = 57\% - 65\%$) could be attributed to the variation in the populations of the patients of the University of Queensland, Brisbane, the time gap in the measurement of the biomarker, and the cut-off values.

Procalcitonin, frequently regarded as one of the most frequently utilized biomarkers in the diagnosis of sepsis, was mediocre in our meta-analysis, with a combined sensitivity and specificity of 80 percent.

These findings corroborate previous meta-analyses, which reported that Procalcitonin was a satisfying biomarker with varying sensitivity levels (Christ-Crain et al., 2004; Meisner, 2014). During bacterial infections, procalcitonin usually rises, and it can serve as an effective indication when differentiating between bacterial and non-bacterial causes of inflammation (Tang et al., 2017). However, the moderate sensitivity and specificity levels of this study also reveal that Procalcitonin may not be precise enough in certain clinical settings, particularly at early stages of sepsis during which the related changes may even be within the normal range (Jougla et al., 2020).

Combined Biomarkers for Improved Diagnostic Accuracy

A positive aspect of this meta-analysis was that it had reports that evaluated biomarker combinations, and these include the presence of Presepsin and Procalcitonin. The total sensitivity and specificity of combined biomarkers (80 and 85, respectively) surpassed the corresponding ones which determined Procalcitonin only and it is possible to conclude that the combination of multiple biomarkers can be treated as the enhancement of the diagnostic procedure. The resultage is concordant with findings in the report by Nobre et al. (2012) and Schuetz et al. (2017), which indicate improvement in diagnostic capability of sepsis which are multi-biomarkers, i.e., Presepsin, Procalcitonin, and C-reactive protein (CRP). The AUC of biomarkers combination in our study was 0.87, which implies that the combination of Presepsin and Procalcitonin could provide superior diagnosis of individual biomarkers.

This is consistent with the body of opinion that is on the rise which suggests that, multi-biomarker panels are the most dependable in establishing sepsis and particularly under the conditions that the patients possess complex conditions. Multi-biomarker approaches can result in an improved, non-disguising diagnosis of sepsis, and, as an experiment by Zong et al. (2019) found, has a higher chance of being used to identify sepsis earlier than a single biomarker. Moreover, a combination of biomarkers also has a likelihood of differentiating the various forms of infections and, thus, improving clinical decision-making (Lippi et al., 2011).

Heterogeneity and Variability Across Studies

The overall performance of the biomarkers was promising, but some of the meta-analysis results seem to indicate the variability of the diagnostic performance across the studies considered as reflected in the heterogeneity (I²) of the findings. This was particularly so in sTREM-1 whose former range was 56-60% and so was Presepsin at 57-65%. Such a heterogeneity can be explained by a multitude of factors including the difference between the patient populations (e.g. adults and neonates), clinical setting, and application of different diagnostic cut-off values (thresholds) to the mixture of biomarkers. In addition, the biomarkers might have been measured far too early or late during the sepsis process, and this may have affected the sensitivity and specificity of the markers (Soni et al., 2015).

A study by Becker et al. (2020) established the significance of the time factor in biomarker performance with earlier values of the biomarker resulting in greater diagnostic performance. Therefore, part of the observed variation of sepsis biomarker performance might diminish when standardizing the timing of measuring the biomarker.

Future Directions and Clinical Implications

The findings of this meta-analysis have different clinical implications. Presepsin is the most reliable early Sepsis biomarker, highly specific and sensitive among them. However, despite its potential use in diagnosis, it has to be used together with other clinical evidence and markers on blood to achieve an accurate and precise diagnosis, particularly in the case of early or illusive sepsis. Procalcitonin can be an aid in the distinction between bacterial and nonbacterial inflammation, but its moderate diagnostic specificity is unlikely to be an early predictor of an adequate clinical breakthrough, since alone procalcitonin will be insufficient to make it convincing.

Presepsin and Procalcitonin combination provide a valuable approach to the increased level of diagnostic accuracy. The future research directions in the context of biomarker-based sepsis diagnostics should be finding answers to the validation of multi-biomarker panels across populations of various

patients, including those with comorbid conditions, critically ill adults, and neonates. In addition, biomarkers might be combined with clinical decision support systems (CDSS), which is likely to enhance the effectiveness and precision of sepsis detection, subsequently providing timelier interventions and favorable patient outcomes (Tang et al., 2020).

Moreover, developing diagnostic consensus guidelines on the use of sepsis biomarkers in clinical practice would help diminish the variability and enhance the diagnostic performance levels. Research in the cost-effectiveness of clinical application and clinical utility of the biomarker-based approaches to diagnosis will also be necessary to implement widely in everyday clinical practice.

Limitations

Although this meta-analysis is informative regarding the diagnostic value of sepsis biomarkers, multiple limitations are inevitable. The main sources of variance were the heterogeneity of the study populations, the time of biomarker detection, the imaging and cut-off values. Also, meta-analysis involved studies that were mostly observational, which would create possible biases. Future randomized controlled trials (RCTs) using standardized procedures would contribute to addressing these confounding factors and growing stronger evidence on the clinical usefulness of biomarkers in the diagnosis of sepsis.

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