REVIEW ARTICLE

Measurement of Pancreatic Stone Protein for Diagnosis of Sepsis in ICU Compared with C-reactive Protein and Procalcitonin: A Systematic Review

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Abstract

Background: Sepsis remains a significant challenge in the intensive care unit (ICU), with prompt diagnosis and management being critical to improve patient outcomes. Biomarkers have emerged as valuable tools in identifying and predicting sepsis outcomes, with procalcitonin (PCT), pancreatic stone protein (PSP), and C-reactive protein (CRP) being three promising candidates. This systematic review is aimed to analyze and contrast the diagnostic accuracy of PCT, PSP, and CRP for sepsis in the ICU.

Materials and methods: Literature was reviewed to examine the different diagnostic performances of the three biomarkers. The PubMed Central, PubMed, ScienceDirect, OxfordAcademic, SpringerLink, and Cochrane Database were searched in July 2023. The data regarding the area under curve–receiver operating characteristics (AUC–ROC) of the biomarkers were extracted. The Newcastle–Ottawa Quality Assessment Scale for Cohort Studies was used for evaluating included studies.

Results: Three studies (n = 858) that examined the three biomarkers in adult patients admitted to the ICU were included. The biomarker PSP, along with the other two compared biomarkers, performs well and is proven reliable in diagnosing sepsis in adult patients hospitalized in the ICU.

Conclusion: PSP, along with PCT and CRP, has shown reliability as a marker in diagnosing sepsis. This systemic review only emphasizes the accuracy of the three biomarkers in question.

Keywords: C-reactive protein, Diagnosis, Intensive care, Pancreatic stone protein, Procalcitonin, Sepsis.

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Introduction

Sepsis is a serious, life-threatening medical condition characterized by an uncontrolled host response to infection, leading to dysfunction in multiple organs.[1] Sepsis and septic shock remain a global health problem and are associated with high morbidity and mortality.[2] Sepsis affects >30 million people worldwide every year and is the biggest killer in children (about 5 million every year).[1,3] Sepsis is the primary reason for hospital readmission,[4] reduced quality of life, and increased morbidity and mortality.[1] When dealing with acute infections, general practitioners (GPs) usually take the lead in evaluating patients and deciding whether they need immediate hospital care or can be treated safely at home.[5,6] Early diagnosis and management of sepsis are key to improving patient outcomes but remain challenging.[1]

There are three biomarkers that aid in diagnosing sepsis—C-reactive protein (CRP), pancreatic stone protein (PSP), and procalcitonin (PCT).[5] CRP is a well-known marker of inflammation, widely utilized to assist in diagnosing infections, while PCT has undergone extensive evaluation over the last 2 decades as a marker of bacterial infection.[5,6] Despite their common use in sepsis diagnosis, both CRP and PCT have shown less than optimal performance as biomarkers in various conditions.[6,7]

The PSP is a type of lectin protein that activates polymorphonuclear cells and exhibits proinflammatory activity in laboratory settings.[8] It is a newly identified biomarker for infections that has been thoroughly evaluated in various patient groups and clinical settings, including emergency rooms and intensive care units (ICU).[9] In a study of critically ill adults, PSP outperformed PCT and other sepsis biomarkers in accurately identifying sepsis,[2] and it was also found to be a predictor of ICU mortality, unlike PCT and CRP.[10] Additionally, point-of-care CRP and PCT are not possible; however, PSP can be measured within 5 minutes using a single drop of blood, allowing simple and frequent biomarker assessments instead of a single measurement when sepsis is suspected.[11] PSP is not only being utilized for diagnosis but also for severity assessment and outcome prediction. Nevertheless, the establishment of a clinically significant threshold level for PSP remains unresolved.[5]

Our objective was to conduct an individual patient-level systematic review of existing data to assess how PSP performs in comparison to PCT and CRP for sepsis diagnosis in the ICU.

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Materials and Methods

Search Strategy and Selection Criteria

A comprehensive search was conducted following the PRISMA individual patient data guidelines, using the following search strategy. Databases including PubMed Central, PubMed, ScienceDirect, OxfordAcademic, SpringerLink, and Cochrane Database were searched for the original human cohort on PSP published in English before March 2019. The focus was on studies evaluating the performance of PSP in the early detection of infection in the ICU. We used "sepsis," "procalcitonin," "pancreatic stone protein," "PSP," "C-reactive protein," "CRP," "intensive care," and "ICU" as keywords. A total of 175 studies were collected, which were then independently examined for duplicates by each reviewer. Subsequently, each reviewer independently screened 129 of these studies and assessed them for inclusion and exclusion criteria. The inclusion criteria for this study encompassed cohort studies that employed PSP, PCT, and CRP to establish sepsis diagnoses in adult patients who had not previously received a sepsis diagnosis in the ICU. Reviewers excluded pediatric cohort/trials, study protocols, and guidelines. The third reviewer manually extracted area under curve–receiver operating characteristics (AUC–ROC) data, which represents the accuracy of sepsis diagnosis, from the relevant studies for further comparison in our research.

It became evident that the resulting pool of eligible studies was insufficient in terms of quantity to warrant a comprehensive meta-analysis. Given the limited number of studies meeting our stringent criteria, it is prudent to acknowledge that conducting a meta-analysis would be impractical and potentially yield inconclusive results. Therefore, we proceed with this study in a systematic review without meta-analysis or the implementation of Synthesis Without Meta-analysis (SWiM) manner using a proper available guideline provided by the SWiM Project Team (swim.sphsu.gla.ac.uk). The primary outcome was the sepsis diagnosis in the patient's assessed PSP, PCT, and CRP levels. The Newcastle–Ottawa Quality Assessment Scale for Cohort Studies was used for evaluating included studies. The third reviewer evaluated independently the three domains of the quality assessment process—selection, comparability, and outcome (Fig. 1).

Results

Study Selection

A total of three studies were identified after excluding duplicates, pediatric studies, review, and guideline studies/study protocol (Fig. 1). The final three studies were selected and met the eligibility and included 858 participants. The three studies that were included in this systematic review examined the use of biomarkers for sepsis. In this review, we examined whether the three specific biomarkers (PSP, PCT, and CRP) have any differences regarding sepsis diagnosis in the ICU. The complete study information is addressed and can be viewed in Table 1.

The Newcastle–Ottawa Quality Assessment Tools for Cohort Studies were used to assess the quality of each study that was included. Among all cohort studies, Pugin et al. scored the best, and Parlato et al. scored the lowest. All studies examined in Table 2 are qualified as good with no bias in data selection, good comparability of cohort groups, and assessment of the outcome.

Characteristics of Included Studies and Participants

The characteristics of the three studies used in this systematic review are summarized in Table 3. The clinical sepsis diagnosis establishment process was different among the three studies (due to the variability in clinical presentation of patients included), yet the biomarker tests within all the studies were examined similarly. Although eligibility criteria in these studies were not homogenous, the patient population in those studies can be categorized as presenting with infection or no infection prior to sepsis.

Discussion

Prompt sepsis diagnosis is important due to its precarious disease progression. In the ICU setting, sepsis contributes to 30% of mortality globally, and increased complications are seen in 50% of the cases.[3] Hence, the question of choosing the most useful

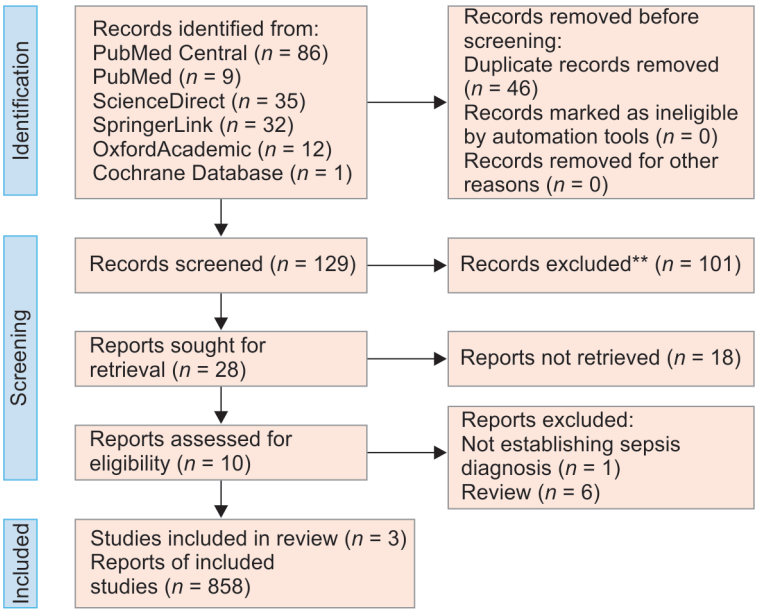

Fig. 1: Diagram of eligible studies

Table 1: Study characteristics

Author, (year)	*Study design*	*Period of data collection*	*Country*	*Clinical condition*	*Participant number (n)*	*Patients' age, median*	*Male gender, %*	*Female gender, %*	*ICU LOS (days)**
Pugin et al.	Multicenter, prospective blind cohort	June 2018 to March 2019	France; Switzerland; Italy; and United Kingdom	Unselected ICU patients	243	65	63	37	9
Loots et al.	Prospective blind cohort	June 2018 to March 2020	Netherlands	Sepsis within 72 hours in ICU	336	79	60	40	4.7
Parlato et al.	Multicenter, prospective blind cohort	December 2011 to April 2013	Paris, France	ICU patients with sepsis or nonseptic systemic inflammatory response syndrome (SIRS)	279	65	63	37	–

ICU LOS, intensive care unit length of stay (in days) *median

Table 2: Quality assessment for kinds of literature using Newcastle–Ottawa Quality Assessment Scale for Cohort Studies

	Selection[a]					*Outcome*[c]			
Author, (year)	*Representativeness of the exposed cohort*	*Selection of the nonexposed cohort*	*Ascertainment of exposure*	*Incident disease*	*Comparibility*[b]	*Assessment of the outcome*	*Length of follow-up*	*Adequacy of follow-up*	*Total number of stars*
Pugin et al. (2021)	A*	A*	A*	A*	A**	A*	A*	B*	9
Loots et al. (2022)	A*	A*	A*	B	A**	A*	A*	A*	8
Parlato et al. (2018)	A*	A*	A*	B	A**	A*	A*	D	7

[a]Selection: (1) Representativeness of the exposed cohort: A. truly representative; B. somewhat representative; C. selected group; D. no description of the derivation of the cohort. (2) Selection of the non-exposed cohort: A. drawn from the same community as the exposed cohort; B. drawn from a different source; C. no description of the derivation of the non-exposed cohort. (3) Ascertainment of exposure: A. secure record; B. structured interview; C. written self-report; D. no description. (4) Absence of outcome in the beginning of study: A. yes; B. no.
[b]Comparability: To ensure that the cohorts are comparable based on their design or analysis methods: A. study controls for co-morbidities; B. study controls for any additional factor (e.g., age and severity of illness); C. not done.
[c]Outcome: (1) Outcome assessment: A. independent blind assessment; B. record linkage; C. self-report; D. no description. (2) Was follow-up long enough for outcomes to occur? A. yes, (i.e., in-hospital or up to 30 days); B. no. (3) Adequacy of follow-up of cohorts: A. complete follow-up and all subjects accounted for; B. subjects lost to follow-up was unlikely to introduce bias, C. follow-up rate 90% or lower with no description of those lost; D. no statement

Table 3: Characteristics of included studies with compared variables

Author, (year)	*Study purpose*	*Infection (n)*	*No infection (n)*	*Population characteristics*	*Measurement*	*SOFA score**	*AUC–ROC data*			*Study summary*
							PSP	*PCT*	*CRP*	
Pugin et al. (2021)	Evaluation of Serial PSP and PCT levels for early sepsis detection	53	190	ICU patients without prior infection and no sepsis diagnosis	Accuracy (AUC–ROC) for sepsis vs no sepsis group	6 (5,9) $p < 0.05$	0.75 (95% CI = 0.67–0.82)	0.75 (95% CI = 0.68–0.82)	0.77 (95% CI = 0.69–0.84)	Similar diagnostic accuracy across PSP, PCT, and CRP
Loots et al. (2022)	Comparison of sepsis-related biomarkers to clinical diagnostic model for sepsis diagnosis	141	195	ICU patients critically ill and experiencing fever, confusion, decline in health, or severe infection		–	0.57 (95% CI = 0.49–0.63)	0.71 (95% CI = 0.65–0.76)	0.60 (95% CI = 0.54–0.66)	No added diagnostic value in biomarkers compared to diagnostic model (based on clinical and patient's symptoms)
Parlato et al. (2018)	Evaluation of sepsis-related biomarkers to differentiate sepsis diagnosis with nonseptic SIRS	188	91	ICU patients with hypo- and hyperthermia and at least another SIRS criterion considered for antimicrobial therapy		9 (8,10) $p > 0.05$	0.63 (95% CI = 0.54–0.71)	0.55 (95% CI = 0.47–0.62)	0.73 (95% CI = 0.65–0.81)	CRP performs the best among tested biomarkers

AUC–ROC, area under curve–receiver operating curves; SOFA, sequential organ failure assessment. *Median (Q1, Q3)

tools to diagnose sepsis is key. An ROC curve plays a central role in this diagnostic process. It serves as an analytical tool presented graphically, employed for assessing the performance of binary diagnostic classification methods. To apply this method, diagnostic test outcomes, often expressed as continuous or ordinal variables, must be categorized into distinct binary categories, typically indicating the presence or absence of a disease.[12] The AUC, widely utilized to assess the accuracy of diagnostic tests, offers an effective combined measure of sensitivity and specificity, conveying the inherent validity of these tests.[12,13] The ROC curve links data points by utilizing specificity (false positive rate) on the X-axis and sensitivity (true positive rate) on the y-axis, encompassing all cutoff values derived from the test outcomes.[12] When the standards for classifying a positive result become more stringent, the curve exhibits a trend of shifting downward and toward the left (more specific in nature), reflecting this increased stringency in the diagnostic criteria. Conversely, when a lenient standard is employed, the point on the curve shifts upward and toward the right (more sensitive in nature).[12]

For a meaningful diagnostic technique, AUC should exceed 0.5 and typically surpass 0.7 for fair acceptability.[12,13] When comparing multiple diagnostic tests, the ROC curve with the highest AUC is deemed superior in diagnostic performance.[12] It is often accompanied by a 95% confidence interval (CI) due to the influence of statistical errors on the data, providing a range of potential values around the actual AUC value.[12]

In our systematic review, we focused on comparing biomarkers for diagnosis of sepsis, in particular PCT and PSP. We found that, generally, the three biomarkers have a positive correlation between sepsis diagnosis and positive test results observed by the value of AUC–ROC obtained for each of the included studies. This proves the usefulness of said biomarkers in the interest of establishing sepsis diagnosis.

The use of CRP as a biomarker to help diagnose and treat sepsis better has been documented in studies.[14] Regular use of CRP is found to be successful in improving antibiotic therapy in critically ill patients by decreasing treatment duration.[15] However, based on prior studies, CRP's accuracy was not found to be consistent throughout.[14,16] It may have been because of CRP's nature as an acute response protein; hence, when exposed to a diverse unique situation of testing, it was found hard to endure.[16] An alternative biomarker offering a more stable nature related to an actual septic event within circulation has been in dire need to be proposed.

Studies have already shown the specificity and sensitivity among the most used biomarkers in patients with suspected or confirmed sepsis diagnosis. The bespoken biomarkers analyzed (PCT vs PSP vs CRP) each have a unique use case. One study analyzed the differences in diagnostic value for a total of eight biomarkers (CRP, lactate, PCT, high sensitivity troponin I, N-terminal pro-b-type natriuretic peptide, creatinine, urea, and PSP).[17] The previous author conducted the study by comparing the sensitivity and specificity between biomarkers using the ROC curve and calculating the C statistic (area under the ROC curve) after obtaining the sensitivity and specificity number for different cutoffs.[17]

Based on supplementary files attached by Loots et al.,[17] the cutoff values for PCT, CRP, and PSP were as follows—PCT >0.25 ng/mL (sensitivity of 51% and specificity of 79%), CRP >100 mg/L (sensitivity of 40% and specificity of 72%) and PSP <100 ng/mL (sensitivity of 71% and specificity of 37%). From the ROC curves, it was also shown that PCT line graphs were positioned above the reference curve and PSP's curve with CRP's curve in the middle in the same study.[17]

Although PSP was issued as having an inferior stance than PCT to establish a sepsis diagnosis, another study exhibited a novel use of measuring PSP when used sequentially.[10] The higher sensitivity rates of PSP were taken advantage of to predict a sepsis event.[10] Pugin et al.[10] conducted a cohort study design with unselected critically ill patients without an initial history of sepsis diagnosis in the ICU. They observed the patient as the disease progressed and investigated the clinical and diagnostic test results (including biomarkers) until the sepsis diagnosis was established. However, it has to be addressed that in this study, sepsis diagnosis was not the same as the sepsis event.[10] The researchers suspected that sepsis events occur before a sepsis diagnosis can be established; therefore, the researchers formed an independent committee (composed of three ICU experts) to retrospectively review the case. Then furthermore, it was validated whether the patient had experienced a septic event while staying in the ICU.[10]

They also studied the median time interval from the septic event to the clinical diagnosis of sepsis. It was noted that PSP values were elevated 5 days ($p = 0.003$) prior to the clinical diagnosis of sepsis, PCT levels were elevated 3 days ($p = 0.025$) prior to the clinical onset of sepsis,[10] and CRP levels were elevated 2 days prior sepsis diagnosis ($p = 0.009$). This study has several limitations that should be acknowledged to provide a comprehensive understanding of its findings. Firstly, the study solely focuses on evaluating diagnostic accuracy using the AUC–ROC. While AUC–ROC is a valuable metric for assessing the performance of diagnostic tests, it should be noted that it represents a single perspective in the evaluation process. Further well-designed studies are needed in this regard to confirm the findings of the above study.

Conclusion

Sepsis remains a major challenge in the ICU, requiring prompt diagnosis and appropriate management to improve patient outcomes. PCT and PSP are two biomarkers that have shown promise in the diagnosis and prognostication of sepsis. While the three biomarkers have demonstrated high sensitivity and specificity in several studies, their clinical utility may depend on various factors, such as patient population, disease severity, and comorbidities. PSP and PCT offer benefits that are unique in certain aspects and may be useful not only to diagnose but also to improve patient care among individuals with or suspected sepsis. However, future research should focus on optimizing the use of these biomarkers to improve the accuracy of sepsis diagnosis and risk stratification in the ICU, ultimately leading to better patient outcomes.

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