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Invited Review Article

Use of infection biomarkers in the emergency department

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Abstract:

The use of infection biomarkers in the emergency department is discussed in terms of their possible contributions to diagnostic-prognostic uncertainties, appropriate antibiotic treatments, and triage and follow-up planning. Procalcitonin (PCT), C-reactive protein (CRP), proadrenomedullin (proADM), and presepsin are among the most discussed infection biomarkers for use in the emergency department. Due to the variable sensitivity results and cutoff values, there are insufficient data to recommend the widespread use of CRP and procalcitonin (PCT) for the diagnosis and prognosis of infection in the emergency department. However, these biomarkers can be used for appropriate antibiotic use in selected infection groups, such as community-acquired pneumonia, especially to reduce unnecessary antibiotic prescribing. With its prognostic superiority over other biomarkers and its contribution to prognostic score systems in community-acquired pneumonia (CAP), proADM can be used to predict hospitalization, preferably within the scope of clinical studies. Although presepsin has been shown to have some advantages over other biomarkers to rule out sepsis, there are insufficient data for its clinical use in the emergency department.

Keywords:

Biomarkers, C-reactive protein, emergency, proadrenomedullin, presepsin, procalcitonin

Introduction

Biomarkers are laboratory tools that need to be integrated into clinical algorithms for disease identification, classification, and completion of basic medical processes.^[1] In emergency departments, biomarkers can be used to reduce diagnostic uncertainties, make correct treatment decisions, and appropriate triage.^[1] This clinical impact varies due to the inability to select appropriate tests, lack of understanding of the methodological limitation, and misinterpretation of test results.^[1,2] Therefore, biomarkers should be integrated into clinical algorithms by knowing the advantages and limitations of the tests and should not be used as a way to escape clinical evaluation.^[1]

Infections are one of the most common diagnoses in the emergency department.^[3] Emergency departments are important areas of acute medical care which have a pivotal role in the diagnosis of infection, follow-up planning, and initiation of antibiotic therapy.^[4] In this review, we aimed to identify appropriate biomarkers as helpful tools in the diagnostic and prognostic approach to infection as well as to discuss the advantages and limitations of these biomarkers. Another purpose of this review is to evaluate the possible impact on antibiotic prescribing in the emergency department.

Many biomarkers can be used as a part of the diagnostic and prognostic approach to infections, especially sepsis. These biomarkers are acute phase proteins (C-reactive protein [CRP] and hsCRP), complement proteins, cytokines, and

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chemokines (interleukin [IL] 6, IL 10, tumor necrosis factor [TNF] alpha, etc.), endothelial cells and BBB markers (sICAM 1, E selectin, etc.), gut permeability markers, membrane receptors, cell proteins, and metabolites (CD 4, CD 68, presepsin, TREM 1, etc.), peptide precursor of the hormone and hormones (MR proADM, PCT, etc.), neutrophil cells, and related biomarkers (lactate, etc.), soluble receptors (suPAR, etc.), and lipoproteins (LDL C, etc.).^[5] Some of these biomarkers, many of which were evaluated for research purposes, were selected according to the criteria of finding at least one randomized controlled trial in the emergency department or evaluating data from emergency department studies through meta-analysis. In this review, PCT, CRP, proADM, and presepsin biomarkers are included due to the availability of high-evidence intervention studies or the systematic analysis of literature data.

Procalcitonin

PCT was discovered as a calcitonin prohormone produced by the C-cells of the thyroid gland and converted to the active hormone by proteolytic enzymes inside the cell.^[4] In 1993, high PCT levels were detected in bacterial infections, and the relationship of PCT with bacterial endotoxins and cytokines such as TNF-alpha and IL-6 was demonstrated.^[4] After administration of bacterial endotoxin to healthy volunteers, increased PCT levels were detected in serum samples 4 h later, remained stable between 8 and 24 h, and regressed after 24 h.^[2,6] Despite its increase in serious bacterial infections and especially in sepsis, its diagnostic value continues to be discussed due to its variable course in nonsevere infections and noninfectious conditions.^[4] In addition to bacterial infections, nonspecific elevations in PCT were also detected in noninfectious conditions such as severe trauma, surgery, cardiac shock, and malignancies (medullary thyroid cancer of neuroendocrine cell origin, small cell lung cancer, and carcinoid tumors).^[7,8] Besides its diagnostic value for infection, the role of PCT in predicting infection outcomes and its use for initiating antibiotic therapy is still discussed.^[4]

Diagnostic use of procalcitonin

The diagnostic value of PCT is most commonly discussed for sepsis. The sepsis diagnostic approach is important because of the high incidence estimated to be 640–1600 per 100,000 population in Turkey, the high mortality rate ranging from 20% to 45%, and the relationship between early treatment and mortality.^[9,10] The most difficult part of the diagnostic approach to sepsis is to prove the presence or absence of infection.^[11] In a meta-analysis of 39 studies conducted between 2000 and 2018 in emergency and intensive care patients

using different sepsis diagnostic criteria, the diagnostic sensitivity and specificity of PCT for the diagnosis of sepsis were 0.82 (95% confidence interval [CI]: 0.78–0.85) and 0.78 (95% CI: 0.74–0.82), respectively.^[12] With a pretest probability of 50%, the posttest probabilities for positive and negative PCT values are 79% and 19%, respectively.^[12] This meta-analysis result supported the diagnostic contribution of PCT for sepsis but showed that PCT-based evaluation alone could lead to diagnostic error in one-fifth of the patients.^[12] Different diagnostic criteria for sepsis, different PCT cut-off levels and confounding factors may affect the sensitivity of PCT in the diagnosis of sepsis.^[12] Therefore, current sepsis guidelines do not recommend the use of PCT in the diagnosis of sepsis.^[11]

PCT is also used in predicting bacterial infections other than sepsis in emergency departments. In a randomized controlled trial, the sensitivities of PCT ≥ 0.5 mg/L for confirmed and confirmed/suspected bacterial infections were 0.52 (95% CI: 0.45–0.60) and 0.43 (95% CI: 0.38–0.48), respectively.^[13] In more specified infection groups, the diagnostic sensitivity of PCT may increase. In a meta-analysis including emergency populations, the sensitivity of low PCT values (<0.5 ng/mL) was 0.76 (0.69–0.82) for bacteremia.^[14] Similarly, negative PCT levels (<0.5 ng/mL) were found to exclude catheter-related bloodstream infection with an error probability of 11%.^[15] However, PCT levels may change depending on the source of infection and infectious agents, limiting the use of PCT to exclude bacterial infections.^[16]

The diagnostic efficacy of PCT was also evaluated in infections other than sepsis and bacteremia. In CAP patients, PCT median values in viral, atypical, and typical bacterial pneumonia were 0.09 ng/mL (interquartile range [IQR], <0.05 –0.54 ng/mL), 0.20 ng/mL (IQR, <0.05 –0.87 ng/mL), and 2.5 ng/mL (IQR, 0.29–12.2 ng/mL), respectively.^[17] In the same study, the sensitivity and specificity of PCT with a threshold level of 0.1 ng/mL for typical and atypical pneumonia were 80.9% (95% CI: 75.3%–85.7%) and 51.6% (95% CI: 46.6%–56.5%), respectively. However, when the cutoff level was taken as 0.5 ng/mL, the sensitivity was found to be 58.5% (51.9–64.8).^[17] In a published meta-analysis, the sensitivity of PCT at a cutoff level of 0.5 μ g/L to exclude bacterial etiology in pneumonia was low (0.55, 95% CI: 0.37–0.71; $I^2 = 95.5\%$). In the published meta-analysis, the sensitivity of PCT to exclude bacterial etiology in pneumonia at the 0.5 μ g/L thresholds was low (0.55, 95% CI: 0.37–0.71; $I^2 = 95.5\%$), and it was not recommended to be used in the decision of antibiotic treatment in CAP.^[18] In meningitis patients, the sensitivity and negative likelihood ratio of serum PCT in differentiating bacterial meningitis from aseptic

meningitis were 0.90 (0.84–0.94) and 0.13 (0.07–0.23), respectively. Therefore, it can be used to exclude bacterial meningitis, especially in patients with negative microscopic (Gram stain) examination and pleocytosis in cerebrospinal fluid (CSF).^[19] In another meta-analysis, the posttest probability values of negative serum and CSF PCT to rule out bacterial meningitis were 0.03 and 0.12, respectively (pretest probability: 0.36).^[20] However, the small case series of the studies included in the meta-analyses and the variability of the diagnostic criteria limit the impact of the results on clinical practice. In addition, there is no intervention study evaluating the clinical effects of PCT detected before the microbiological results on clinical practice and antibiotic use.

Prognostic use of PCT

The incidence of mortality increased from 1% to 15% in parallel with PCT values in patients in emergency departments, and this relationship was also present in different age, gender, and diagnosis subgroups. However, the relationship between PCT and mortality could not be explained due to the heterogeneity of the subgroups (cardiovascular, metabolic, cancer, infection, etc.) included in the study and the observational nature of the study.^[21] The prognostic role of PCT in specific diagnostic groups was also evaluated by meta-analyses. High PCT level was associated with an increased risk of mortality (RR: 4.38, 95% CI: 2.98–6.43) in patients with CAP. Because of the low sensitivity of 0.5 ng/mL breakpoints for PCT in excluding mortality in CAP, the use of a 0.1 ng/mL cutoff value was recommended.^[22] While there was a significant difference in PCT values between the groups with and without mortality in sepsis patients, there was no difference in the emergency service subgroup.^[23] In some clinical studies, a reduction of >80% in sequential PCT measurements instead of a single PCT measurement was associated with survival. However, sequential PCT follow-up cannot be applied in emergency departments due to the variability of the follow-up time of the patients.^[24] In these results, PCT measurement is associated with mortality and poor prognosis, but it is unclear what this will have a modifying effect on patient management in emergency departments.

The effect of procalcitonin on antibiotic use

Recently, the potential impact of PCT on antibiotic use has been discussed, rather than its diagnostic and prognostic uses. Initiation of antibiotics under PCT guidance (if PCT \geq 0.5 mg/L, it was recommended to start antibiotic therapy) in patients presenting to the emergency department with fever did not reduce antibiotic use compared to the control group (77% vs. 73%, $P = 0.28$).^[13] In this study, clinicians preferred to make decisions with clinical evaluation rather than PCT. In the study, the sensitivity of PCT for confirmed bacterial infections was

0.52 (95% CI: 0.45–0.60) and the specificity was 0.73 (95% CI: 0.68–0.78), which also supported the accuracy of this approach.^[13] In contrast, PCT guided antibiotic use had low mortality (8.6% vs. 10%, OR: 0.83, 95% CI: 0.70–0.99, $P = 0.037$), short antibiotic duration (5.7, vs. 8.1 days, 95% CI: -2.71 to 2.15, $P < 0.001$), and low antibiotic related adverse events (16.3% vs. 22.1% OR: 0.68, 95% CI: 0.57–0.82, $P < 0.001$).^[25] The use of PCT in patients with a chronic obstructive pulmonary disease (COPD) attack reduced the frequency of antibiotic prescribing (RR: 0.56 [0.43–0.73]) and shortened the duration of antibiotic exposure (mean difference: -3.83, 95% CI [-4.32–3.35]) without affecting clinical outcomes.^[26] Although the national COPD exacerbation management guideline does not recommend the routine use of PCT, it has been stated that PCT-guided treatment can shorten the duration of antibiotic use and reduce the rate of re-admissions.^[27] However, contrary to these results, PCT did not affect antibiotic initiation in a randomized controlled trial in patients with lower respiratory tract infection (34.1% vs. 38.7%, -4.6 [-12.2–3], noninferiority margin: 4.5). This was associated with a limited PCT effect due to possible parallelism between low PCT and clinical findings.^[28] The use of PCT in sepsis cases also shortened the total duration of antibiotic therapy -1.28 days (95% CI: -1.95 to -0.6, $I^2 = 86\%$). However, the impact of studies involving hospitalized patients on the antibiotic approach in emergency departments was unclear.^[29]

Procalcitonin: Advantages and limitations

In the emergency department, the sensitivity of PCT in excluding the diagnosis and poor prognosis of infections is highly variable. In the emergency department, as part of clinical algorithms, PCT can be used as a biomarker to rule out infection, with varying susceptibility depending on patient characteristics, cutoff levels, and source of infection. However, the use of PCT alone is not reliable for excluding bacterial infections and for the decision to start antibiotics in emergency departments. Clinical studies beyond observational analyzes are needed, especially for optimal cutoff levels. Since the frequency of antibiotic initiation can be reduced with PCT, PCT can be integrated into antibiotic stewardship programs.

Author's opinion about procalcitonin use in the emergency department

Due to variable susceptibility results and uncertain cutoff values, the routine use of PCT alone in the emergency department is unreliable for excluding bacterial infections and deciding to start antibiotics and is not recommended by the authors. However, PCT-guided therapy can reduce antibiotic prescription and shorten the duration of antibiotic use in some special clinical conditions, such as respiratory tract infections, and COPD.

C-reactive protein

CRP was discovered in 1930 when a precipitate of polysaccharide-C was noticed in the serum of patients infected with *Streptococcus pneumoniae*.^[30] This reaction occurred as an early chemical response to inflammatory conditions and was nonspecific for pneumococci.^[30] CRP is released by stimulation of cytokines (IL-1, IL-6, and TNF), rises within 6-8 hours after stimulation, reaches peak levels in approximately 48 h, and has a half-life of approximately 20–24 h.^[4] Due to its high sensitivity to inflammatory conditions, the use of CRP has become increasingly common, but its low specificity has limited its diagnostic use for infection.^[4] The diagnostic and prognostic values of CRP for different conditions in the emergency departments have been evaluated by clinical studies.

Diagnostic use of C-reactive protein

The diagnostic use of CRP as an inflammation marker for infection in the emergency department is limited due to its low specificity and cutoff uncertainty. Serum CRP levels may increase in association with acute inflammatory conditions other than infection, such as trauma, postsurgery, malignancy, autoimmune diseases, and cardiovascular diseases.^[4] CRP levels are uncertain to distinguish between these inflammatory conditions and infection. In the meta-analysis, the sensitivity and specificity of CRP for the diagnosis of sepsis were 0.80 (95% CI: 0.63–0.90) and 0.61 (95% CI: 0.50–0.72), respectively. The cutoff values of CRP used in the studies included in the meta-analysis ranged from 12 to 90 mg/L, indicating the uncertainty about the optimal cutoff value of CRP.^[31] There was a similar uncertainty in the CAP studies. When CRP cutoff levels were increased from >10 mg/L to 100 mg/L for the diagnosis of CAP, sensitivities of CRP reduced from 0.90 (0.52–0.99) to 0.58 (0.39–0.74).^[32]

A CRP value >50 mg/L had a positive likelihood ratio for predicting bacteremia of 1.36 (1.11–1.68), and its additional contribution to predicting the probability of bacteremia was only 5%. The negative likelihood ratio of 0.20 (0.03–1.38) at the same cutoff value indicates that CRP can be used to exclude bacteremia.^[33] In some patients with proven Gram-negative bacteremia, CRP values remained below <30 mg/L with other factors such as the source of bacteremia, advanced age, male gender, and symptom duration.^[34] However, when the second CRP measurement was made in these patients, the CRP values increased approximately 5 times.^[34] In some similar studies, it was stated that CRP single measurement values were not sufficient to define bacterial infection and the change in CRP level was beneficial.^[35] With the results, the researchers stated that the second measurement for CRP may be beneficial,

but there is still no study evaluating the effect of sequential CRP kinetic follow-up on clinical outcomes. The use of CRP to distinguish between bacterial and viral infections is important because of its possible effect on antibiotic treatments. In a meta-analysis, the sensitivities of CRP in excluding bacterial infections from noninfectious conditions and viral infections were found to be 0.75 (0.62–0.84) and 0.86 (0.65–0.95), respectively.^[36] However, the meta-analysis includes studies using different subpopulations, different clinical diagnoses, and different optimal cutoff values.^[36] In more recent studies, in a retrospective study in emergency departments, no significant difference was found in CRP levels between viral and bacterial infections (63.84 [0–526.7] vs. 65.12 [0–526.7], $P > 0.05$).^[37]

Prognostic use of C-reactive protein

The prognostic role of CRP has been evaluated in different infections such as sepsis, pneumonia, and urinary tract infections. There was a correlation between CRP level and the prevalence of radiological involvement in CAP (pneumococcal and nonpneumococcal).^[38] In prospective studies, the risk of mortality in CAPs increased in correlation with CRP levels (for CRP 10–99 mg/L OR: 3.756 (2.320, 6.080), for CRP >200 mg/L, OR: 23.348 (13.304, 40.975), $P < 0.001$).^[39,40] There are clinical studies that reach different results in urinary system infections. CRP did not help predict treatment failure in febrile urinary tract infections.^[41] In contrast, in elderly patients discharged with a diagnosis of UTI, a CRP >30 mg/L increased the risk of re-admission and re-hospitalization at 2.4 (OR 2.436; 95% CI: 1.017–3.9; $P = 0.024$) and 3.2 (OR 3.224; 95% CI: 1.235–8.419; $P = 0.017$), respectively.^[42] The Bayesian model created by Cochon *et al.* showed that the contribution of CRP use to mortality prediction was between 5.7% and 18.1% in the evaluation based on the MEDS score in sepsis cases.^[43] However, there were different subgroups in the studies included in the model (neonatal-adult, intensive care-postsurgery, etc.), and the optimal cutoff values varied between 6 and 100 mg/L.^[36] Optimal cutoff value uncertainties limit the use of CRP in the prognostic as well as the diagnostic approach in emergency departments. CRP levels change with age, gender, antibiotic use, steroid use, comorbidities (DM and renal and hepatic insufficiency), and duration of symptoms, making it difficult to determine optimal cutoff values.^[44,45] Another situation that limits the prognostic use of biomarkers, including CRP, in emergency departments is what to recommend if the risk is identified. Current evidence-based guidelines do not recommend changes in early clinical follow-up and treatment approaches with biomarkers, including CRP.^[11,46,47]

The effect of C-reactive protein on antibiotic use

The effect of CRP on antibiotic initiation and antibiotic treatment processes is evaluated, and normal CRP values generally reduce the frequency of antibiotic prescribing in emergency departments.^[48] This effect is generally present in patients with upper-lower respiratory tract infections and fever in primary health-care delivery. In patients with fever, CRP values of <40 mg/L decreased the frequency of antibiotic prescribing, without changing clinical outcomes, compared with the control group (39% vs. 34%, aOR: 0.80, 95% CI: 0.65–0.98). However, if the CRP value is >40 mg/L, the frequency of antibiotic prescription increases significantly compared to the control group (78% vs. 48%, $P < 0.0001$).^[49] Therefore, the difference in the cutoff values will lead to a change in the effect of CRP on the initiation of antibiotics. Published meta-analysis showed that the use of point-of-care CRP in respiratory tract infections resulted in a 13.2% decrease in antibiotic use and a 3.5% increase in re-consultation. When both results were evaluated, the use of point-of-care CRP in upper and lower respiratory tract infections led to antibiotic-free treatment with a net benefit in one of 11 patients.^[50] In a recently published randomized controlled trial, it was shown that the frequency of starting antibiotics decreased with CRP-guided antimicrobial therapy in COPD patients without changing the outcome.^[51,52] Furthermore, a published national evidence-based guideline evaluating the management of COPD patients stated that the use of CRP to guide antibiotic therapy in outpatients presenting to the emergency department with a COPD exacerbation could result in a significant reduction in antibiotic therapy.^[27]

C-reactive protein: Advantages and limitations

The use of CRP in the emergency department in the exclusion of bacterial infections is limited due to uncertainties about the limit values. Although the use of CRP in patients diagnosed with infection provides a prognostic prediction, new studies are needed to determine its effect on clinical outcomes and optimal cutoff values. In patients with lower-upper respiratory tract infections and COPD, point-of-care use of CRP can be used to reduce antibiotic use without increasing the risk. For this purpose, CRP can be integrated into targeted antibiotic stewardship programs.

Author's opinion about C-reactive protein use in the emergency department

The routine use of CRP for the exclusion of bacterial infections in the emergency department is not recommended by the authors due to uncertainties regarding the cutoff values. However, the authors recommend the use of CRP in patients with lower-upper respiratory tract infections and COPD to reduce the use of antibiotics without increasing the risk.

Proadrenomedullin

Adrenomedullin is a calcitonin derivative polypeptide whose secretion is increased in pathological conditions such as cardiovascular diseases, renal diseases, sepsis, and malignancy in association with hypoxia, inflammatory cytokines, and bacterial toxins. However, its measurement in plasma is difficult due to the unstable nature of adrenomedullin, its high receptor binding, and its short half-life. Proadrenomedullin (proADM), a stable precursor peptide, is detected in plasma and is generally evaluated for its prognostic role in bacterial infections.^[1] The prognostic role of ProADM is most frequently evaluated in CAP, sepsis, and UTI infections. High proADM in CAPs increased the risk of mortality (pooled RR was 6.16 (95% CI: 4.71–8.06) and had a diagnostic sensitivity of 0.74 (95% CI: 0.67–0.79) to exclude mortality.^[53] In this meta-analysis, the breakpoints of proADM ranged from 0.75 to 4.89 nmol/L.^[53] In another meta-analysis, adding proADM to the CURB-65 score resulted in an 8% (95% CI: 2%–14%) increase in distinguishing early mortality.^[54] Similarly, in sepsis cases, proADM had a more accurate prognostic value (early and late mortality) when compared with prognostic score systems (SOFA, SAPS II, and APACHE II) score and other biomarkers (CRP, PCT, and lactate). Despite the decrease in PCT levels in sepsis patients, high proADM values is associated with mortality. (HR [95%CI]: 19.1 [8.0–45.9] and 43.1 [10.1–184.0]).^[55] The possible impact of the prognostic role of proADM on the emergency department approach is the identification of patients requiring hospitalization. The randomized controlled trial results of Castillo *et al.* showed that in addition to clinical evaluation, the use of proADM with a cutoff value of 0.87 nmol/L could reduce the frequency of hospitalization by 17% (40.6% vs. 57.6%, $P = 0.024$). Despite the decrease in hospitalization, the frequency of re-admissions within 28 days increased partially in the proADM arm (11.1% vs. 9.5%, the difference of 1.6% [95% CI: –12.2%–15.4%]).^[56] A similar study was conducted for community-acquired UTI infections, and the sensitivity of proADM was 0.86 (0.79–0.92) to exclude complicated UTI infections with a cutoff value of 0.80 nmol/L. In this study, MR-proADM (0.80 nmol/L cutoff point) based triage was compared with other triage approaches reduced hospitalization rates from 72-90% to 66% and readmission rates from 11-28% to 2%.^[57]

Proadrenomedullin: Advantages and limitations

ProADM can be used to predict hospitalization, especially in pneumonia cases, with its prognostic superiority compared to other biomarkers (CRP and PCT) and its contribution to prognostic score systems.

Author's opinion about proadrenomedullin use in the emergency department

The authors consider that ProADM can be used to predict hospitalization with other scoring systems, especially in cases of pneumonia.

Presepsin

CD-14 is a lipopolysaccharide (LPS) receptor expressed in macrophages, monocytes, and dendritic cells. It transmits the LPS signal from bacteria via Toll-like receptor-4, triggers the release of pro-inflammatory cytokines, and activates a systematic inflammatory response. Presepsin is one of the soluble forms of CD-14 and can be easily measured biochemically in serum, rises within 2 h after infection, and reaches its peak within 3 h; therefore, it is used as an early diagnostic and prognostic biomarker.^[58-60] Presepsin was most frequently evaluated as a diagnostic biomarker in sepsis. The diagnostic sensitivity and specificity of presepsin in the diagnosis of sepsis were 0.94 (95% CI: 0.74–0.99) and 0.71 (95% CI: 0.35–0.92), respectively, and were superior to CRP and PCT in excluding sepsis.^[58] Presepsin cutoff values for sepsis, septic shock, and 30-day mortality prediction were 582 pg/mL ($P < 0.001$), 1285 pg/mL ($P < 0.001$), and 821 pg/mL ($P = 0.005$), respectively.^[60] In a small case-control study of sepsis patients, presepsin levels were higher in the group that did not survive the early (<1 day) and follow-up measures (up to 7 days), in contrast to PCT.^[61] However, in the meta-analysis, there was no significant difference in presepsin levels between the survivor and nonsurvivor groups (mean difference: 0.92 [95% CI: 0.62–1.22]) in the random-effects model ($I^2 = 79\%$, $P < 0.01$).^[62] However, the small and retrospective studies included in the meta-analysis, including heterogeneous groups, and the high selection and publication bias reduce the acceptability of the results.

Presepsin levels were also elevated in bacteremia cases, but its role in predicting bacteremia could not be demonstrated due to the small sample size of the study (OR: 8.84; 95% CI: 0.95–81.79; $P = 0.02$).^[63] Presepsin was also more sensitive than PCT and CRP in predicting disease severity (determined by PSI and CURB-65) in pneumonia cases. However, it is unclear what its additional contribution would be to the PSI or CURB-65 scoring systems currently used in the prognostic approach to pneumonia.^[64]

Presepsin: Advantages and limitations

Although presepsin has been shown to have some advantages over other biomarkers to rule out sepsis, there are insufficient data for its clinical use in the emergency department.

Author's opinion about presepsin use in the emergency department

The authors do not recommend routine clinical use of presepsin in the emergency department due to a lack of evidence.

Conclusion

Studies on biomarkers in the emergency department and their meta-analyses mostly include diagnostic and prognostic reporting. The lack of intervention studies complicates the clinical use of biomarkers. The use of any single biomarker alone as a diagnostic and prognostic decision-maker could not be recommended by the available literature. Confusing factors that can directly affect the levels of biomarkers and are not often taken into account in studies and significantly varying optimal threshold values prevent universal general recommendations. Acceptable diagnostic sensitivity results of biomarkers can be used by local clinical algorithms to exclude serious infections. The use of some biomarkers such as proADM in triage evaluations should be supported by well-planned prospective studies targeting homogeneous patient groups. One of the strongest aspects of the evaluated biomarkers is their potential impact on antibiotic use. However, this will be possible by identifying specific patient and diagnostic groups and adding biomarkers to antibiotic stewardship programs.

Author contributions (CRediT)

HSO and ES: Conceptualization, review, writing, and editing (equal).

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