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Review

# Presepsin as a diagnostic marker of sepsis in children and adolescents: a short critical update

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**Abstract.** *Background and aim:* Sepsis is a potentially fatal condition which has an incidence of 1.2 million pediatric cases worldwide per year. New biomarkers have been proposed in the assessment of the risk of sepsis progression and in the identification of patients with the worst outcome. This review aims to assess the diagnostic value of presepsin, a promising new biomarker, in pediatric sepsis, with particular attention to its usefulness in the emergency department setting. *Methods:* We performed a literature review in the last 10 years looking for presepsin related studies and reports concerning the pediatric population aged from 0 months to 18 years. We mainly focused on randomized placebo-control studies, followed by case-control studies, observational (both retrospective or prospective), and finally systematic reviews and meta-analysis. The article selection process was carried out independently by three reviewers. *Results:* A total of 63 records were identified in the literature, 49 were excluded according to the exclusion criteria. The highest presepsin sensitivity value was 100%, with a high cut-off (800.5 pg/mL). The highest sensitivity-specificity ratio was 94% vs 100%, with a similar considered presepsin cut-off (855 ng/L). As regards the presepsin cut-offs reported in the various studies, several authors agree on a critical threshold of about 650 ng/L to guarantee a sensitivity> 90%. The analyzed studies show a wide variability for patients' age and presepsin risk cut-offs. *Conclusions:* Presepsin seems to be a new useful marker for early diagnosis of sepsis, even in a pediatric emergency setting. Being a new marker of sepsis, more studies are required to better understand its potential. (www.actabiomedica.it)

**Key words:** Children, Pediatric Emergency Department, Presepsin, Sepsis, Sepsis biomarkers

## Introduction

Sepsis is an acute, rapidly evolving disease defined as a potentially fatal organ dysfunction caused by an aberrant or dysregulated response to infection. It is the leading cause of death or morbidity in the pediatric population and is estimated that 1.2 million children worldwide are affected by it each year (1).

Given its high mortality rate if not recognized and treated adequately, a rapid start of adequate antibiotic and supportive therapy is critical to significantly improve patient prognosis.

Sepsis in children is usually diagnosed based on the presence of a systemic inflammatory response syndrome (SIRS) in response to a suspected or proven infection. Infection is confirmed when the blood culture/stain/PCR results are positive for a specific pathogen. Sepsis is suspected based on clinical, radiological, or laboratory findings. The positivity of blood cultures remains the gold standard for determining the presence of microorganisms in the circulation, but the percentage of false negatives is high and it takes several days to obtain the results (2).

The presence of a standardized, sensitive, specific and effective assessment tool for the early identification

of septic patients would certainly favor the decision-making process and the subsequent correct management of the patient. Currently, the main biomarker used in the septic patient is procalcitonin (PCT), whose circulating levels, especially if extremely high, are used to guide the choice of an antibiotic treatment. However, PCT levels do not always correlate linearly with the risk of organ dysfunction: a US study of 500,000 patients showed that the highest number of deaths from sepsis occurred in patients with low or decreasing levels of PCT and, hence, apparently with less severe sepsis.

Therefore, new biochemical markers have recently been proposed in the assessment of the risk of sepsis progression and in the identification of patients with the worst outcomes; among these, a growing interest has been directed to presepsin (P-SEP) (3).

Since in sepsis the P-SEP plasma levels increase before those of PCT and since the current methods available allow measurement of P-SEP plasma levels within 17 min, P-SEP could represent a sepsis biomarker particularly suited for the emergency department and critical care (4,5).

The aim of this review is to assess the diagnostic value of P-SEP in pediatric sepsis, with particular attention to the usefulness of P-SEP in the emergency department.

## Methods and results

We performed a literature search of the last 10 years to find presepsin related studies and reports; the following electronic databases were systematically searched: PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL).

The research strings were:

- Presepsin AND sepsis
- Presepsin AND pediatric.
- Presepsin AND emergency department
- Presepsin AND critical care
- Presepsin AND ICU

Search was limited to pediatric studies on pediatric population from 0 month to 18 years old.

English language restriction was applied while geographical restrictions were not.

We mainly focused on randomized placebo-control studies, followed by case-control studies, observational (both retrospective or prospective), and finally systematic reviews and meta-analysis.

The article selection process was carried out independently by three reviewers (LC, SF and GM).

All relevant reviewed articles were further analyzed for additional references not considered in the initial search.

A study was considered eligible for the analysis if the following criteria were met: (1) population sample was represented by children from 0 to 18 years old; (2) sepsis was considered as outcome; (3) serum concentrations of P-SEP were obtained as part of the initial patient evaluation.

Exclusion criteria were: (1) non-diagnostic studies; (2) non-original studies (e.g. literature reviews, case reports, comments, duplicate studies); (3) studies with insufficient data about P-SEP diagnostic accuracy (sensitivity and/or specificity); (4) population sample represented by adults over 18 years old.

Review or commentary papers without novel data were excluded, whereas their contents were used for interpretation of collected information.

All papers not clearly concerning presepsin were equally excluded.

The following domains were considered to assess trial quality: random sequence generation (selection bias), similarity of patients at baseline regarding the most important prognostic indicators (homogeneity bias), allocation concealment (selection bias), blinding of personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), avoidance of cointerventions (co-intervention bias), description of drop out (drop out bias).

A total of 63 records were identified through the literature review. Among them, 49 were excluded according to the exclusion criteria, based on the titles, the abstracts, and the type of study.

The main characteristics of the selected studies are resumed in Table 1.

**Table 1.** Main features of the included studies.

| First author and year of publication | Study design | Total Cases (n.)/ Sepsis (n.) | Patients | Outcome Measured | Values P-SEP T0 sepsis group | Values P-SEP TO non-sepsis group | AUC* | Cutoff P-SEP | Specificity (%) | Sensitivity (%) | Main results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Poggi et al. 2015 (6) | Prospective single-center | 21/19 | Preterm neonates | LOS | 1295 (977–1500) ng/L | 562 ng/L, (337–726) | 0.972 | 855 ng/L | 100 | 94 | P-SEP is an accurate biomarker for the diagnosis of possible LOS providing useful information for monitoring the response to therapeutic interventions. |
| Topcuoglu et al. 2016 (7) | Clinical Trial | 82/42 | Preterm neonates | LOS | 1024 pg/mL, (295–8202) | 530 pg/mL, (190–782), | 0.864 | 800.5 pg/mL | 67 | 100 | P-SEP is a reliable biomarker for late onset sepsis and treatment response in preterm infants. Not demonstrate the efficacy of presepsin for the detection of disease severity or prognosis. |
| Plesko et al. 2016 (8) | Prospective longitudinal observational study | 69/16 | 0 to 18.9 years haemato-oncological patients | Bacterial infectious complications | / | / | 0.489 | 299 ng/L | 58 | 84 | P-SEP was characterized by poor specificity and positive predictive value for predicting bacteraemia, and by better sensitivity and specificity for predicting clinical signs of sepsis. |
| Baraka et al. 2018 (9) | Case–control study | 90/18 | Children aged 2-15 years with hematological malignancies and febrile neutropenia | Bacteremia and clinically proved infection | 2390 (1128–4137) pg/mL | 178.5 (76.1–319) pg/mL | 0.996 | ≥ 951 pg/mL | 100 | 93.8 | P-SEP levels are related to the severity of sepsis and can be used to predict the prognosis. |

(Continued)

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Bellos et al. 2018 (10) | Meta-analysis | 783/391 | Full term and preterm neonates | Neonatal sepsis | / | / | 0.975 | ≤ 650-≥ 850 pg/mL | 91 | 91 | P-SEP presents high diagnostic efficacy in neonatal sepsis |
| El Gendy et al. 2018 (11) | Prospective observational study | 160/80 | Critically ill children | Sepsis | 5.27 (0.013–27.9) ng/mL | 0.78 (0.25 – 2.1) pg/mL | 0.480 | / | 53.1 | 46.9 | P-SEP has a potential role for sepsis diagnosis |
| Parri et al. 2019 (12) | Review | 636/636 | Full term and preterm neonates | Neonatal sepsis | / | / | 0.968 | < 600 ng/L | 93 | 81 | Diagnostic accuracy of P-SEP resulted high in detecting neonatal sepsis. |
| Yoon et al. 2019 (13) | Systematic review | 308/308 | Children and adolescents with sepsis | overall diagnostic accuracy of presepsin and compare it to those for C-reactive protein and procalcitonin | 650 pg/mL | | 0.925 | <650 pg/mL | 0.71 | 0.94 | P-SEP has higher sensitivity and diagnostic accuracy, but lower specificity than PCT or CRP. |
| Sakyi et al. 2020 (14) | Case-control study | 90/60 | 0-6 years | Pediatric sepsis | 25.46 (19.2–66.2) µg/L Laboratory confirmed sepsis: 69.54 (24.0–132.7) Clinically confirmed sepsis: 22.76 (18.4–28.2) | 18.09 (13.8–20.9) µg/L | 0.75 | 28.05 µg/L | 76 | 71 | CRP, PCT, and P-SEP are independent predictors of paediatric sepsis due to their high prognostic values. |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Agnello et al. 2020 (15) | Prospective observational study | 26/26 | Oncologic patients with neutropenia | Bacteriemia and fever of unknown origin | 378 (442-314) pg/mL | | 0.58 | / | / | / | P-SEP displays poor clinical usefulness for Febrile Neutropenia in oncologic children. |
| Hassuna et al. 2021 (16) | Prospective case control comparative study | 132/58 | Children with signs of acute and severe inflammation | Sepsis versus SIRS | 440 (80-650) pg/mL | 40 (20-313) pg/mL | 0.751 | 100 pg/mL | 83 | 67 | P-SEP has a potential role as biomarkers in differentiating between sepsis and SIRS in critically ill children. |
| Arikan et al. 2021 (17) | Prospective, case-control study | 79/39 | Febrile neutropenia in hematological malignant neoplasms | Bacteriemia/ sepsis | 750 pg/mL | / | 0.74 | / | 64 | 85 | Presepsin could be used in combination with other biomarkers to detect bacteremia. |
| Khera et al. 2022 (18) | Prospective cohort study | 54/36 | 1 month-18 years | Sepsis | 609.77 ± 417.30 pg/mL | 865.8 ± 661.7 | 0.73 | 721 pg/mL | 58.3 | 77.8 | Elevated presepsin levels may indicate greater severity of sepsis, particularly in those with shock. |
| Poggi et al. 2022 (19) | Systematic review and meta-analysis | 828/368 | Full term and preterm neonates | Neonatal Early onset sepsis | / | / | 0.76-0.99 | 200 to 1066 pg/mL | 69 | 79 | Presepsin was an accurate biomarker of EOS. |

**AUC:** Area under receiver operating characteristic curve; **P-SEP**: Presepsin; **LOS:** late onset sepsis.

*The old sepsis markers*

## CRP and PCT

C reactive protein (CRP) is an acute phase plasma protein synthesized by the liver. CRP levels increase 6 hours after stimulation by interleukin 6 (IL-6) and its half-life is 20-24 hours. It has a high sensitivity but low specificity for bacterial infections. Furthermore, the evolution of sepsis does not correlate with changes in plasma CRP.

Procalcitonin is normally synthesized by thyroid cells. During inflammatory processes, various tissues and immune cells acquire the ability to produce PCT. This biomarker increases within 4 hours of the onset of the innate immune response, and peaks within 6-8 hours. Although its role as a biomarker in septic patients has been established, PCT has several limitations: it transiently increases in patients with non-septic conditions and systemic inflammatory response syndrome (e.g. in trauma, surgery, heart attack, exercise). However, it can be used as an index of progression of septic shock and multi-organ failure.

*New sepsis marker*

## P-SEP and sepsis

Presepsin (or sCD14) is a free fragment of the membrane glycoprotein CD14 in monocytes and macrophages. It acts as a receptor for lipopolysaccharides (LPSs) on the outer wall of Gram negative bacteria and for lipopolysaccharide binding proteins (LBPs). After contact with infectious agents, CD14 activates an intracellular signaling pathway mediated by Toll-like receptor 4 (TLR4), initiating the inflammatory response against the microorganism.

P-SEP arises from cleavage of CD14 by plasma proteases during the inflammatory response.

In healthy subjects, P-SEP is present in low concentrations in serum, but increases in response to bacterial infections, based on the degree of severity of the infection.

Recent studies confirm that P-SEP can be a useful biomarker in the diagnosis of sepsis, to define its severity and predict clinical outcome. Stated that serum P-SEP concentrations progressively decrease during antibiotic treatment, this biomarker may also play a role in monitoring response to therapy.

P-SEP blood levels increase in 2 hours and peak in 3 hours and have a halftime of 8 hours, earlier than CPR and PCT.

It has a high sensitivity and good specificity and can be quickly measured in the emergency room (in about 15 minutes) using chemiluminescence enzyme immunoassay (PATHFAST presepsin assay).

Serum P-SEP could play a role in different pediatric scenarios.

*Neonatal sepsis*

Sepsis is one of the main clinical challenges in the management of term and preterm neonates. It is a life-threatening event in which early diagnosis is crucial. Having a sepsis marker that rises early could have decisive effects on clinical outcomes in terms of therapy and survival. For this reason, P-SEP, in consideration of its kinetic characteristics, has long been studied in this field.

In 2015, Poggi et al. (6), led a monocentric prospective study on 21 preterm neonates, 19 of them with sepsis, identifying a P-SEP cut off- for sepsis of 855 pg/mL, with 100% specificity and 94% sensitivity. They demonstrated for the first time in a cohort of preterm newborns that P-SEP could be an accurate biomarker for the diagnosis of possible late onset sepsis (LOS) and may also provide useful information to monitor the response to therapeutic interventions.

As for full term neonates, Parri et al. (12) conducted a review in 2019 including 636 neonates with sepsis and analyzing the role of P-SEP in identifying neonatal sepsis. What emerged is that P-SEP, with a cut off of 600 ng/mL, has a high diagnostic accuracy in detecting neonatal sepsis, with a sensitivity of 81% and a specificity of 93%. Despite this, they didn't recommend it as a single diagnostic test, but as a helpful and valuable biomarker in neonates with suspected sepsis.

Studies on the role of presepsin in neonatal sepsis have shown that its serum values are not significantly influenced by perinatal variables related to non-infectious conditions.

In a recent systematic review conducted in 2022, Poggi et al. (19) aimed to assess presepsin accuracy in the diagnosis of early-onset sepsis (EOS) in full term and preterm neonates. With a sensitivity of 79% and a specificity of 69%, presepsin was evaluated as an accurate biomarker of EOS.

*Pediatric sepsis*

Pediatric sepsis is defined as an infection causing a dysregulated host response leading to organ dysfunction with a high morbidity and mortality rate in children. Its recognition in the emergency department (ED) can be challenging, considering the high prevalence of common infections, poor specificity of clinical features, and the capacity of children to compensate until advanced stages of shock. On the other hand, sepsis outcomes are strongly dependent on the timeliness of recognition and treatment. Thus, an early sepsis biomarker could be helpful to improve outcome in this patient population.

Considering P-SEP characteristics, many studies focused on its capacity of early sepsis diagnosis.

In 2018 Fady M. El Gendy (11) conducted a case control study on 160 children, 80 critically ill and 80 healthy controls matched for age and sex. P-SEP resulted significantly elevated among septic children compared with controls, suggesting a potential role for sepsis diagnosis. No P-SEP cut-off was described.

Yoon et al. (13), in 2019, reviewed the overall diagnostic accuracy of P-SEP and compared it to C-reactive protein (CRP) and procalcitonin (PCT) in pediatric sepsis. They enrolled 308 patients aged between 1 month old and 18 years. Patient population was heterogeneous, also including hematological malignancy (HM) and Catheter-related bloodstream infection (CRBSI). The diagnostic sensitivity and specificity of P-SEP, using a sepsis-cut off of 650 pg/ml, were respectively 0.94 and 0.71. Presepsin showed higher sensitivity and accuracy but relatively lower specificity for the diagnosis of pediatric sepsis compared to either PCT or CRP.

Sakyi et al. (14) in 2020 for the first time evaluated the individual and combined diagnostic accuracy of procalcitonin (PCT), presepsin (sCD14-ST) and high sensitive C-reactive protein (hs-CRP) using a Bioscore model. Bioscore combination of these biomarkers was significantly associated with increased odds for sepsis.

In 2021 Hassuna et al. (16) conducted a prospective case control comparative study including 58 children diagnosed with sepsis, 24 with systemic inflammatory response syndrome without infection (SIRS), and 50 healthy children as controls. P-SEP, with a cut-off of 320pg/ml, showed higher levels in children with sepsis compared to SIRS and healthy ones. They concluded that P-SEP might be a potential ad useful biomarker in differentiating sepsis and SIRS in critically ill children, but, considering the small number of analyzed samples, more studies are needed to clarify P-SEP role.

Khera D. et al. (18) in 2022 enrolled all consecutive admissions aged 1 month to 18 years with a diagnosis of sepsis and compared the presepsin, procalcitonin, and C-reactive protein (CRP) levels on admission (day 1) and 72 hours later (day 4) with the clinical outcomes. The mean presepsin values in blood culture-proven sepsis patients at admission and 72 hours later were 609.77 ± 417.30 and 839 ± 748.07, respectively. The procalcitonin and presepsin levels at 72 hours in sepsis patients with shock were significantly elevated (38.2 ± 45.55 and 1129.1 ± 1133.80, respectively) as compared to those without shock (10.7 ± 25.42 and 472.5 ± 507.81, respectively), $p$ <0.05. They evaluated that elevated presepsin levels may indicate greater severity of sepsis, particularly in those with shock. However, it lacks diagnostic ability early in the disease and has limited prognostic potential in predicting mortality.

*P-SEP in oncologic pediatric patients*

Bacterial infection is the most common complication in pediatric oncological patients during cancer treatment. Documented mortality associated with pediatric febrile neutropenia is 2%. The potential for early diagnosis of bacteraemia through serum biomarkers has been the subject to extensive research

In 2016, Plesko et al. (8) enrolled, in a prospective longitudinal observational study, 69 children aged 0 to 18.9 years, with a primary diagnosis of a haematological malignancy (HEM), who were admitted to the inpatient paediatric oncology service. The primary

inclusion criterion was the presence of fever, hypothermia, chills, or other signs of possible sepsis. Patients with febrile episodes thought to be an adverse effect of chemotherapy, patients who did not have blood cultures drawn and patients with proven non-bacterial infection, were excluded. Of the 22 positive blood cultures, only seven patients developed sepsis. P-SEP, with a cut-off level for mild sepsis of 338 – 950 ng/l, and for severe sepsis and septic shock >950 ng/l, predicted 12 cases of positive blood culture and 13 cases of documented sepsis (of 16 total cases), demonstrating to have a good sensitivity (83% and 84%) in predicting bacteremia and septic status in oncological patients.

Baraka et al. (9) in 2018 evaluated the role of P-SEP in the diagnosis of bacterial infections in children with HEM during episodes of febrile neutropenia and the correlation between P-SEP levels and other diagnostic biomarkers (PCT and CRP) of infection. They enrolled sixty pediatric patients with different HEM (acute lymphoblastic leukemia 36, acute myeloid leukemia 12, non-Hodgkin lymphoma 10, and Hodgkin disease 2) and thirty age and sex-matched healthy children serving as control. Patients' P-SEP level showed a significant elevation in the HEM group when compared to the control group, with an strong increase in the positive blood culture patients compared to those with negative cultures. In addition, sensitivity, AUC, and specificity of P-SEP were better than that of PCT and CRP in the prediction of bacterial infections in these patients.

Arikan K. et al. (17) in 2021 investigated the value of presepsin and proadrenomedullin (proADM) as new markers for febrile neutropenia, by comparing them with conventional markers. With a sensibility of 85% and a specificity of 64% (AUC 0.74), they concluded that Presepsin could be used in combination with other biomarkers to detect bacteremia.

Moreover, Agnello et al. (15) in 2020, conducted a prospective observational study, evaluating 37 febrile neutropenia (FN) episodes in 26 children receiving chemotherapy due to cancer. Patients were classified into a bacteremia (B) group and fever of unknown origin (FUO) group, according to blood culture and clinical findings. P-SEP levels were evaluated at admission (T0), after 24/48h (T1) and at discharge (T2). What emerged is that circulating P-SEP levels were increased on admission and decreased during the following days, thanks to antibiotic therapy. They also demostrated that P-SEP levels at T0 were significant predictors of length of stay but not of the duration of fever.

## Discussion

P-SEP (or sCD14) is a free fragment of the membrane glycoprotein CD14 in monocytes and macrophages and arises from cleavage of CD14 by plasma proteases during the inflammatory response. It is a new sepsis marker with excellent blood kinetic characteristics.

Given the fact that sepsis is one of the most challenging life-threatening events in children, with a prognosis that improves in an inversely proportional way to the time of diagnosis and the start of appropriate therapy, a new marker with an earlier peak seems to be revolutionary (2).

P-SEP could have numerous possible implications in pediatric settings.

Starting from the first moments of life, neonates, considering their immature immune systems, have a high sepsis-risk. Clinically, newborn sepsis has many possible manifestations, some of which are difficult and challenging. First of all, the septic newborn may not present with fever, which is one of the main signs of sepsis in older child.

A lot of RCT, reviews and metanalysis studied the role of P-SEP in early sepsis diagnosis, also in comparison with the well known and most used markers, i.e. CRP and PCT.

As demonstrated by Parri et al in a large review done in 2019, P-SEP, with his high specificity and sensitivity, has an important role in early diagnosis of neonatal sepsis. (12).

One important P-SEP characteristic, which distinguishes it from PCR, is that its serum values are not significantly influenced by perinatal variables related to non-infectious conditions. This increases its sensitivity and specificity, as well as its reliability in the diagnosis of sepsis, making it an important marker. Furthermore, P-SEP has shown good accuracy in diagnosing both neonatal EOS and LOS, even if the data are still limited (2).

P-SEP shows both a valuable diagnostic accuracy as an early biomarker of sepsis in term and preterm

neonates, when compared with current standard of care analytes. Another advantage resides in the small volume (50 μL) required for P-SEP measurement. And in the rapid measurement times. Furthermore, the cost per sample is comparable between P-SEP and standard of care biomarkers (20).

Even in the pediatric age, sepsis recognition in the ED can be challenging, (21,22) and early diagnosis and treatment are critical.

An important review was done by Yoon et al. (13) in 2019, investigating on the overall diagnostic accuracy of P-SEP overall and in comparison to CRP and PCT. What emerged is that P-SEP showed higher sensitivity and accuracy but relatively lower specificity for the diagnosis of pediatric sepsis than either PCT or CRP (9,10). Furthermore, in 2021, Hassuna et al, (16), highlighted that P-SEP could possibly have a role in distinguishing sepsis from SIRS, with important therapuetical repercussions.

P-SEP may have a role also in pediatric oncological patients. As known, febrile neutropenia is one of the most frequent events during chemotherapy treatment. Not all of these episodes are linked to a bacterial infection and sepsis, and P-SEP may help in identifying them. In 2016 Plesko et al. (8) demonstrated that P-SEP can help in distinguishing and recognizing febrile episodes due to bacteremia and septic status, with a sensitivity of 84%.

Baraka et al. (9), in 2018, compared P-SEP characteristics with CRP and PCT. Sensitivity, AUC, and specificity of P-SEP were found to be better than that of PCT and CRP in predicting bacterial infections, in a population of children aged 2-15 years with hematological malignancies and febrile neutropenia.

In 2020, Agnello et al. (15) studied serum levels of P-SEP during antimicrobial therapy in oncologic patients admitted for febrile neutropenia. P-SEP levels were evaluated at admission (T0), after 24/48h (T1) and at discharge (T2). Its circulating levels were increased at admission and decreased during the hospital stay, configuring it as a possible predictor of length of stay but not of the duration of fever.

The analysis performed by Topcuoglu et al. (7) showed the highest P-SEP sensitivity value (100%), despite the reported cut-off being one of the highest proposed by the studies analyzed in this review. However, it should be noted that this study was conducted exclusively on premature infants and its data are not currently confirmed by the other available pediatric studies on P-SEP. The study characterized, instead, by the highest sensitivity-specificity ratio (94% vs 100%, respectively) is that of Poggi et al. (6), who shares with Topcuoglu et al. (7) study population and objectives, with an overlapping cut-off value.

In regards to the P-SEP cut-offs reported in the various studies, several authors agree on a critical threshold of about 650 ng/L to guarantee a sensitivity> 90%. However, there is a wide variability of suggested cut-offs, with wide variation in different ages. The unclear cut-off value is a disadvantage in P-SEP use as it does not allow to clearly distinguishing a negative value from a positive one. Moreover, no data are available for adolescent age, which is a critical one as it straddles the pediatric age to adulthood. It is necessary to perform further studies in order to establish more defined ranges.

## Conclusions

P-SEP seems to be a new useful marker for early diagnosis of sepsis, from the newborn, to the older child and the oncologic patient. It is particularly useful in a pediatric setting given it presents with an early plasma peak and requires a small amount of blood for its dosage,.

Furthermore, P-SEP is a promising biomarker to initially diagnose and stratify risk in sepsis, and a potential marker to distinguish gram-positive and gram-negative bacterial infection, but as far as we know it cannot predict mortality risk.

In the emergency department, P-SEP appears to be a promising sepsis marker, due to an earlier increase in plasma levels when compared to PCT, thus allowing an early recognition and a rapid start of therapy in the ED. Being a new marker of sepsis, more studies are required to better understand its potential.

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