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Review

Presepsin: A promising biomarker for the detection of bacterial infections

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ABSTRACT

Appropriate recognition of bacterial infections in health care setting is the basis for effective treatment and control of infectious diseases. The positivity rate of traditional methods is low and is influenced by quality and quantity of specimens, patient antibiotic administration, severity of infection, and laboratory sufficiency. Currently, there are novel non-culture-based techniques that are being accomplished to improve the identification of infections. Several immunologic biomarkers have been assessed to develop the best indicator of infections. Presepsin is an immunologic biomarker which has been demonstrated as new, emerging, early indicator for the detection of different infections. The biological function of presepsin is not well known. However, it is believed that it may be a regulatory molecule of the adaptive immune system and also a stimulator of monocyte phagocytosis. The early increased levels of presepsin during the sepsis and other bacterial infections have made it an attractive indicator for laboratory testing. Several studies have investigated the capacity of presepsin for use in clinical settings. The aim of the present study was review the clinical application of presepsin in diagnosis and prediction of infections. To achieve this objective, the documents on diagnostic and clinical assessment were evaluated in PubMed and Scopus databases regarding the use of presepsin as indicators of infections.

1. Introduction

Infections are demonstrated by signs and symptoms that overlapped with other acute disorders in certain cases. The identification of bacterial infections from other diseases is clinically critical, but often also very challenging. This incomplete understanding may lead to unnecessary antibiotic therapy, which is a principle cause of antibiotic resistance [1–3]. Traditional techniques for the detection of infections such as culture-based approaches, biochemical methods, and antibody-based detection and molecular techniques often need sophisticated equipment and highly proficient operators; therefore, their analysis cost is very high [4,5]. Consequently, there is a continuous requirement for the simple, reliable, manageable, fast, sensitive, and cost-effective point-of-care analyses [5]. Recently, several immunologic biomarkers have been assessed in order to develop the best indicator of infections [6–8]. Soluble CD14 subtype (sCD14-ST), known as presepsin, is a biomarker which has been demonstrated as a new, emerging, early indicator for the detection of different infections [7,9]. Presepsin is elevates in response to bacterial infections and is decreased after healing or efficient treatment [6,10]. The aim of the present study was to review the clinical application of presepsin in diagnosis and prognosis of infections. To achieve this objective, the papers on diagnostic, prognostic and clinical assessment were evaluated in PubMed and Scopus databases regarding the use of presepsin as indicators of infections.

2. Presepsin

Survival from infections can be influenced by the capacity of the host immune system in identified microbial pathogens and triggering an immediate and effective response [11,12]. This mechanism is divided into an innate and an adaptive system [13,14]. In contrast to adaptive systems, innate mechanisms depend on an immediately response, an effective pathway and mediators such as antimicrobial peptides, alternative complement systems, and phagocytosis. The activation of innate immunity responses need the recognition of the pathogens by different receptors at the cellular surface of immune effector cells particularly monocytes/macrophages [13,15,16]. These receptors are innately pre-determined, and they identify a wide range of antigens known as pathogen-associated molecular patterns (PAMPs) on the surface of most microbial pathogens [17]. After recognition, effector cells are stimulated in a direct pathway without any preceding

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multiplication. Therefore, innate immune system provides an instant and protective response to invasive pathogens [17,18]. CD14 is a member of Toll-like receptor (TLR), that has the ability to identify several groups of ligands of both Gram positive and Gram negative pathogens, such as lipids, peptidoglycan and other surface patterns [19,20]. The best studied ligand is lipopolysaccharide (LPS) of Gram negative bacteria. To be potentially recognized, LPS needs the association of Lipoprotein Binding Protein (LBP) which presents LPS to CD14. CD14 is a coreceptor which is constitutively expressed at the surface of monocyte/macrophage [21,22]. CD14 plays an important role in the presentation of LPS to TLR and actively contributes to intracellular signals and promotes the expression of genes responsible for the immune response such as cytokines production by effector cells [23,24]. The complex CD14-LPS-LBP stimulates signals [25,26]. Soluble subtypes of CD14 are released and are detectable in the general circulation [27,28]. CD14 has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). The sCD14 is found in plasma, and is produced by mCD14 fall-off or cell secretion. sCD14 is cleaved by cathepsin D and other proteases in plasma or in the phagolysosome and the N-terminal fragments of 13 kDa constitutes sCD14 subtype (sCD14-ST) which has been named presepsin. The complex of CD14-LPS-LBP is submitted to an enzymatic processing that needs cathepsin D. Presepsin is released in the general circulation by proteolysis and exocytosis (Fig. 1). Whereas the biological function of presepsin is not well described, it is demonstrated that it has lost its capacity to bind LPS. However, presepsin has been reported as a regulatory molecule. [26,29]. Plasma levels of presepsin can be considered as an indicator of activated innate immune effector cells in response to invasive pathogens. The secretion of presepsin has been reported as a stimulus of monocytes phagocytosis [26,30]. Therefore, recognition of presepsin is predictable even in healthy non-infective individuals. The concept for presepsin proposes that its levels should be measureable in non-infective individuals, increase the early steps of bacterial infections, and its levels should be dependent on the intensity of the innate immune induction [26].

3. Measurement of presepsin

An presepsin assay kit using antibody and a special sandwich technique is useful for qualitative and quantitative measurement of presepsin with appropriate sensitivity and specificity [31]. Firstly, a traditional two-step sandwich enzyme-linked immunosorbent assay (ELISA) was used for the detection of presepsin by the recombinant CD14 (S286C) as standard within 4 h. This assay was not appropriate and lacked the speed and accuracy that is essential for routine presepsin assessments in intensive care units (ICU) [32]. A few years later, a one-step ELISA assay developed and was evaluated using recombinant presepsin and two new antipresepsin antibodies: F1106-13-3 monoclonal antibody as capture antibody and S68 polyclonal antibody as the recognition antibody. As a result, the total analysis time was reduced from 4 h to 1.5 h, and the dynamic range of the one-step ELISA assay was changed to 0.05–3.00 ng/mL (compared to 3–150 ng/mL with the two-step assay) [32]. A novel, highly-sensitive, fully automated PATHFAST presepsin measurement system, based on the chemiluminescent enzyme immunoassay (CLEIA) principle, has been developed to analyzing the entire blood samples that provides its result within 17 min. This approach is applicable for use in the Emergency Department (ED), ICU, and the surgical wards. No interference of presepsin has been detected with other analytes such as bilirubin, hemoglobin, lipids, triglyceride, or rheumatoid factors [33]. Determination of a normal range is essential for the development of a biomarker as a diagnostic tool. [26]. An effective breakpoint for diagnosis procedure at the 95th percentile value has been suggested for most of the traditional biomarkers. This value can be detected with enough statistical confidence (> 95% CI) only if the studied population is > 300 volunteers. This detection should be established for the clinical use of presepsin in infections diagnosis [26]. Presepsin levels have been demonstrated to be remarkably elevated in patients with a bacterial infection when compared to non-infective patients according to the site or blood culture. It has higher levels in patients with Gram-negative bacterial infections than patients with Gram-positive infections. In addition, patients with abdominal or urinary tract infections had higher baseline presepsin levels than patients with lung infections [38].

4. Sepsis diagnosis and prognosis by presepsin

According to the results of several multicenter prospective studies, presepsin levels are significantly higher in patients with systemic bacterial infections than in those with nonbacterial infections [28,39–41]. The cutoff value of 600 ng/L has been reported for the discrimination of

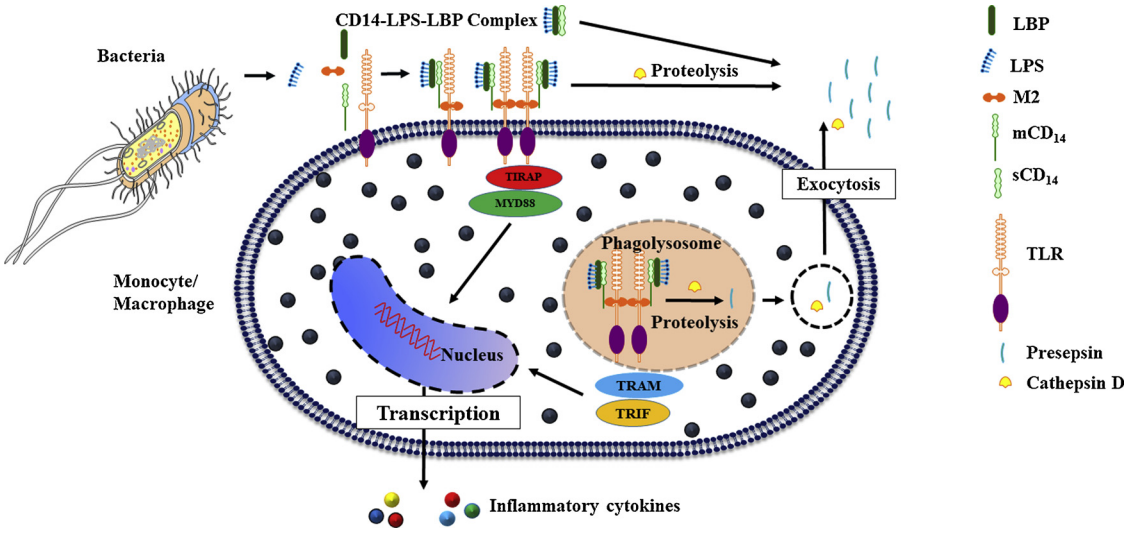

Fig. 1. The mechanism of presepsin production. LBP: Lipoprotein Binding Protein, LPS: lipopolysaccharide, TLR: Toll-like receptor. CD14 exists in two forms, membrane CD14 (mCD14) and soluble CD14 (sCD14). Soluble CD14-subtype (sCD14-ST), or Presepsin, is produced by circulating plasma proteases effect on sCD14. The molecular complex CD14-LPS-LBP is internalized into a phagolysosome. CD14-LPS-LBP is exposed to an enzymatic processing that needs cathepsin D. CD14 proteolysis and internalization processes release a small soluble peptid fragment. The product of CD14 cleavage has been named soluble CD14subtype (sCD14-ST) or presepsin that is released in the general circulation by proteolysis and exocytosis.

bacterial and nonbacterial sepsis by presepsin with the sensitivity and specificity of 87.8% and 81.4%, respectively [39]. At the cutoff value of 670 ng/L for presepsin, sensitivity and specificity has been reported as 70.3% and 81.3%, respectively while at a cutoff value of 864 ng/L, sensitivity and specificity were 71.4% and 63.8% [42]. Using a cutoff of 600 ng/L, presepsin levels are not significantly different between patients with Gram-positive and Gram-negative bacterial infections and also between the blood culture-positive and -negative groups [39]. However, at a concentration at baseline of 946 ng/L, higher levels of presepsin have been reported in patients with Gram-negative bacterial infections, than in patients with Gram-positive infections [38]. The presepsin values (mean ± standard deviation) have been reported for the healthy, SIRS, and sepsis group as 258.7 ± 92.53 ng/L, 430.0 ± 141.33 ng/L, 1508.3 ± 866.6 ng/L, respectively [42]. The presepsin levels are significantly higher in sepsis patients than in SIRS cases [42]. According to the results of the meta-analysis, presepsin has found to have a higher sensitivity and specificity in the diagnosis of sepsis and may be a helpful and valuable biomarker in early diagnosis of sepsis [43]. However, presepsin showed a moderate diagnostic accuracy in differentiating sepsis from non-sepsis which prevented it from being recommended as a definitive test for diagnosing sepsis in isolation, but the results should be interpreted cautiously [44]. Change in presepsin levels may be an appropriate indicator for monitoring antibiotic therapy that improve the prognosis and increase the survival rate in severe sepsis or septic shock cases. Presepsin levels tended to reduce on day 7, in patients with positive blood cultures and appropriate antibiotic therapy. However, it elevated in those with positive blood cultures and inappropriate antibiotic therapy [38,45]. Most of the inappropriate empirical antibiotic therapy was related to infections caused by multidrug-resistant bacteria [46]. Elevated presepsin levels on day 1 may be associated with acute kidney injury and renal replacement, a longer ICU stay, longer mechanical ventilation and time for discontinuation of vasopressor or inotropic agents, as well as a longer duration, a lower degree of resolution of the primary infection and subsequent mortality in ICU [38,47]. Table 1 is the overview of different performance efficiency of presepsin as indicator in different types of infections.

5. Presepsin for the detection of Pneumonia

Bacterial pathogens are the common cause of CAP; thus, early and accurate identification of etiology is critical for appropriate treatment of CAP. [48,49]. The accuracy of presepsin assessment has been reported in the diagnosis of CAP (Table 1). In an observational prospective study, presepsin assay with a cutoff at 588 ng/L shows sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 81%, 80%, 94% and 52%, respectively in diagnosis of CAP [50]. Presepsin levels have been reported in pulmonary tuberculosis to be higher than the healthy control individual (218.0 [146.0, 368.0] ng/L versos 128.0 [101.5, 176.5] ng/L) and lower than bacterial community acquired pneumonia (128.0 [101.5, 176.5] ng/L versos 532.0 [364.0, 852.3] ng/L). Compared with both Gram positive and Gram negative bacteria, *Mycobacterium tuberculosis* induces a limited increase in presepsin levels. At the cut-off value of 401 ng/L, presepsin demonstrated sensitivity, specificity, PPV and NPV of 70.8%, 83.5%, 89.4% and 59.3% in the discrimination between active pulmonary tuberculosis and bacterial CAP. Presepsin combined with CURB-65 score (confusion, serum urea > 7 mmol/l, respiratory rate ≥ 30/min, systolic blood pressure < 90 mm Hg and/or diastolic blood pressure ≤ 60 mm Hg, and age ≥ 65 y) remarkably improved the discrimination capacity between active pulmonary tuberculosis and bacterial CAP, that is essential for early identification and the determination of the appropriate initial therapy [48]. Plasma presepsin concentration has been demonstrated to be significantly higher in severe CAP than in CAP cases (689.0 [395.5–1225.5] pg/mL vs 400.0 [231.5–691.5] pg/mL). The median Presepsin level has been reported more in the non-survivors than survivors in CAP and severe CAP patients at the 28-day follow-up (699.0 [373.0–1250.0] pg/mLvs 410.5

Table 1
Different performance efficiency of presepsin as indicator in different type of infections.

Infection	Cutoff (ng/L)	Sen (%)	Spe (%)	PPV (%)	NPV (%)	Setting	Study Population	Ref
Sepsis	907	69.7	83.3	88.5	60.0	ICU	76	[91]
Sepsis	686	46.5	91.3	ND	ND	ED	223	[65]
	207	95.5	21.7	ND	ND			
Sepsis	670	70.3	81.3%	ND	ND	ICU	247	[92]
	864	71.4	63.8%	ND	ND			
Sepsis	729	81.1	63.0	30.0	94.4	ED	226	[66]
Sepsis	600	85.96	72.09%	ND	ND	CCU	21	[90]
Sepsis	600	78.95	61.90	ND	ND	ED	106	[36]
Sepsis	542	77.3	76.4	72.3	80.7	Burn	37	[37]
Sepsis	430	87.7	82.2	88.9	80.4	ED	118	[45]
Sepsis	466	90	55	82	71	ICU	100	[50]
CAP	401	70.8	83.5	89.4	59.3	ED	408	[48]
CAP	588	81	80	94	52	ICU	58	[50]
Sever CAP	498.5	63.4	64.4	51.5	74.7	ED	214	[49]
ARDS	468.5	72.6	57.8	88.4	32.4	ED	125	[49]
DIC	591.5	64.0	65.5	25.6	90.8	ED	89	[49]
Meningitis	625	84.2	82.1	86.5	79.3	S,ICU	18	
Systemic Infections	221.5	92.31	77.7	70	94	RA	151	[52]
	300	73.08	88.8	76	84			
	400	46.15	97.7	92	75			
	500	34.62	100	100	73			
Pyelonephritis	200	0.92	0.51	93	49	ED	312	[85]
	300	78	83	97	36			
	320	76	87	98	35			
	340	74	94	99	35			
	350	71	94	99	33			
SSI	702	72	66	ND	ND	Cardiac Surgery	51	[93]

AbbreviationARDS: Acute Respiratory Distress SyndromeCAP: Community-acquired pneumoniaCCU: Cardiac Care UnitDIC: disseminated intravascular coagulationED: Emergency DepartmentICU: intensive care unitND: none definedNPV: negative predictive valueRA: rheumatoid arthritisPPV: positive predictive valueS: surgerySen: sensitivitySpe: specificitySSI: surgical site infection.

[242.3–697.0] pg/mL). CAP patients with plasma presepsin levels higher than a cutoff of 556.0 pg/mL have shown significantly lower survival rates, compared to patients with levels lower than this cutoff (50.0% vs 76.6%) [49]. The highest sensitivity (54%) and highest specificity (81%) of presepsin levels, in tracheal aspirate for diagnosing early onset neonatal pneumonia, have been reported to have a cutoff of 511 ng/L and 768.5 ng/L, respectively. Therefore, additional studies, primarily on a larger population, are needed to confirm or discard the claims considering the use of this marker [51].

6. Presepsin for the detection of other infections

Direct Cerebral Spinal Fluid (CSF) assessment gives data of bacterial meningitis in only 50–80% of cases [40]. It is well known that other techniques applied for identification, such as Polymerase Chain Reaction (PCR), immunological, and biochemical methods have their own restrictions. presepsin in CSF has been reported as an applicable diagnostic biomarker in the detection of meningitides and in the case of meningitis and ventriculitis in children with a cutoff of 625 pg/ml which indicated an 84.2% and 82.1% of sensitivity and specificity, respectively (compared to 77.4% sensitivity and 77.3% specificity for leukocytes in CSF) [6].

Although early identification of infections in rheumatoid arthritis patients is remarkably essential for the treatment, it can be a problematic assignment. For many cases, a physical assessment may not provide a deterministic diagnosis. A higher concentration of presepsin has been reported in the non-infected group of rheumatoid arthritis, compared to in the healthy control group (25). Presepsin may be valuable in the identification of infections in rheumatoid arthritis patients other biomarkers [52]. In rheumatoid arthritis cases, presepsin is a promising novel marker for the diagnosis of bacterial infections regardless of rheumatoid arthritis disease activity [53]. Different sensitivity and specificity for presepsin has been reported in the detection of infection in rheumatoid arthritis patients. The highest levels of sensitivity (92.31%) and specificity (100%) were observed in cutoff values of 221.5 ng/L and 500 ng/L, respectively [52]. In another study, presepsin levels for bacterial infection in rheumatoid arthritis patients had a cutoff value of 278 ng/L, and sensitivity and specificity were reported as 79.2% and 80.6%, respectively [53]. Surgical Site Infections (SSIs) can increase the costs and duration of hospitalization. Moreover, SSIs can cause a higher risk of morbidity and lower life quality in surgical patients [54,55]. Patients who develop major infections after cardiac operations show a five-fold increase in presepsin. In all patients, the presepsin levels on post-surgery day 0, post-surgery day 1 and post-surgery day 2 have been reported as significantly more elevated than the baseline (176 [123–275] ng/L) with the levels of 220 (166–445), 328 (210–581) and 310 (202–368) ng/L, respectively [56]. The presepsin level of 300 ng/L, one week after surgery, has been suggested to be used as a novel indicator for suspected SSIs [57]. Further prospective studies with larger and more diverse populations are needed to validate the presepsin level for detection of SSIs.

7. Presepsin for ICU and ED patients

Sepsis is a common reason of mortality during major processes of ICU and ED [36]. The important issue associated with sepsis in ICU n and ED is an appropriate identification of etiology [58,59]. Presepsin has been reported by several studies as an appropriate indicator for the detection of likely infections in cases that required ICU and ED (Table 1). The sensitivity and specificity of presepsin for the prediction of infection in the ICU sepsis patients have been reported as 84.6% and 62.5%, respectively and are significantly associated with APACHE II score value (*p-value* = 0.016) [62]. At a cutoff value of 466.5 ng/L sensitivity and specificity of presepsin, to severe sepsis and septic shock diagnosis in ICU patients, were 90% and 55%, respectively, with a PPV of 82% and NPV of 57% [50]. At a cutoff value of 101.6 ng/L, sensitivity, specificity, PPV and NPV of presepsin to diagnosis in the first 24 h from ICU admission allowing a better management of septic patients (diagnostic and prognostic) both in severe sepsis and septic shock were reported as 81.9%, 96.5%, 82.4% and 96.3%, respectively [63]. Liu et al reported plasma presepsin levels to be a promising indicator for diagnosing sepsis and predicting severity of sepsis, septic shock and 28-day mortality in septic patients in the ED. According to their study, a cutoff of 449 ng/L, presepsin predicting severity sepsis with sensitivity of 82.4%, specificity of 72.4%, PPV of 71.3%, NPV of 83.2% with the predictive accuracy of 77.0%. At a presepsin cutoff of 550 ng/L, septic shock has been predictable with the sensitivity, specificity, PVV and NPV of 85.7%, 63.6%, 28.5% and 96.3%, respectively and the predictive accuracy of 66.8%. Presepsin also has been demonstrated as an indicator of 28-day mortality by these researchers at the cutoff of 556 ng/L with the sensitivity of 62.2%, specificity of 66.8%, PPV of 48.3%, NPV of 78.0% and the predictive accuracy of 65.3% [40]. A single-center, prospective observational study reported the differentiation between SIRS and sepsis at presentation in the ED with a high discriminatory power, sensitivity of 61% and specificity of 100% at a presepsin cutoff of 581 ng/L [64]. The performance of presepsin, for identify of infection, is depended on the considered cutoff. In the cutoff 273 ng/L, the performance of presepsin was reported with sensitivity of 95.5%, specificity of 21.7% for diagnosis of infection in the ED, however using the cutoff of 686 ng/L in the same study these values were reported as 46.5% and 91.3%, respectively. The sensitivity of 97.1% and 67.1% and specificity of 16.9% and 80.8% for the diagnosis of sepsis in the ED were reported by using of 312 ng/L and 849 ng/L, respectively [65]. In the cutoff of 729 ng/L the sensitivity, specificity, PPV and NVP of 81.1%, 63%, 30% and 94.4%, respectively were reported for the diagnosis of SIRS in the ED [66]. Different value reported by different studies may be due to the heterogeneity established in the included studies, with possible sources such as the study strategy (prospective or not), clinical setting (emergency department, ICU), type of patients, reference for sepsis criteria and even the type of sample (plasma, serum or whole blood) for the measurement of presepsin. An advantage of the determination of presepsin is also its power to predict the severity of bacterial infections. In addition, the measurement of presepsin can be performed by an easy process that takes less than 17 min in ICU and ED [62].

8. Presepsin: the marker of pediatric bacterial infection

Rapid identification and treatment of pediatric bacterial infections are important in treatment choices and outcomes, and proves to be a challenge even for highly experienced pediatricians [8,67]. The application of presepsin has been investigated for diagnosis of several severe infections of children such as late-onset sepsis (LOS) in preterm newborns, early-onset sepsis (EOS), meningitides and pneumonia in preterm newborns, pediatric oncology patients, critically ill children and febrile neutropenic pediatric patients with hematological malignancies [6,41,68–77]. The performance efficiency of presepsin in pediatric bacterial infections, which are reported by different studies, were summarized in Table 2. Mean presepsin levels of 649 ng/L have been reported in healthy term neonates and 720 ng/L in preterm neonates without clinical signs or symptoms of infection [28]. The reference levels of presepsin in neonates without symptoms of infection have been observed to be considerably higher than those shown in healthy adults. The triggering of the innate immune system happens after birth due to the transition from the generally sterile intra-uterine condition to an environment that is rich in foreign antigens could partly describe the higher concentrations of presepsin reported in normal neonates compared to healthy adults. After birth, the skin and gut of neonates are quickly colonized with bacterial flora, which is a continuous motivation for the innate immune system. In addition, it is recognized that TLR role and reactivity are well established in neonates. When compared to healthy adults, preterm and full-term neonates express considerably

Table 2
The performance efficiency of presepsin in the diagnosis of pediatric bacterial infections.

Infection	Gestational Age (week)	Postnatal Age	Population	Cutoff (ng/L)	Sen (%)	Spe (%)	PPV (%)	NPV (%)	Setting	Ref
LOS	32≤	4 - 30 days	82	800.5	67	100	100	74	ICU	[41]
EOS	< 34	1 day	70	453	66	84	82	65	ICU	[80]
LOS	32≤	4 to 60 days	40	885	94	100	100	95	ICU	[79]
EOS	< 39	first 72 hours	69	539	80	75	91	59	ICU	[76]
sepsis	–	1.5 – 18.9 years	55	299	84	58	37	93	Oncology	[73]
sepsis	< 35	ND	65	548	100	81.2	ND	ND	ICU	[75]
sepsis	< 37	8 day	51	706.5	85.7	68.8	85.7	68.8	Perinatology	[68]
sepsis	–	3 to 15 years	60	951	93.8	100	ND	ND	Oncology	[71]
				1014	100	85.7	ND	ND		

AbbreviationEOS: early- onset sepsis, ICU: intensive care unit, LOS: late- onset sepsis, ND: none defined, NPV: negative predictive value, PPV: positive predictive value, Sen: sensitivity, Spe: specificity.

Table 3
The performance efficiency of presepsin in comparison to other biomarkers.

Biomarker	Cutoff*	Sen (%)	Spe (%)	PPV (%)	NPV (%)	AUC	Infections	Study population	Setting	Main finding	ref
Presepsin	686	46.5	91.3	ND	ND	0.775	Sepsis	223	ED	PCT: the highest diagnostic accuracy for infection	[65]
	237	95.5	21.7	ND	ND					PCT and presepsin: similar performance to identifying sepsis	
CRP	60	80.5	65.2	ND	ND	0.588					
	20	94	30.4	ND	ND						
PCT	0.22	77.5	95.7	ND	ND	0.815					
	0.19	83.5	87.0	ND	ND						
Presepsin	729	81.1	63.0	30.0	94.4	0.750	SIRS	225	ED	Presepsin: similar diagnostic accuracy to PCT	[66]
CRP	105	62.2	51.9	20.2	87.5	0.602					
PCT	0.45	81.1	63.0	30.0	94.4	0.787					
Presepsin	542	77.3	76.4	72.3	80.7	0.834	Sepsis	37	Burn	Presepsin: similar diagnostic efficiencies to PCT, both were superior to CRP	[37]
CRP	65	91.6	58.2	62.1	90.2	0.819					
PCT	0.759	75.7	78.6	73.6	80.3	0.847					
Presepsin	600	78.95	61.90	ND	ND	0.701	Sepsis	106	ED	PCT: a better diagnostic accuracy than presepsin.	[36]
PCT	0.18	95%	75.90	ND	ND	0.875					
Presepsin	2455	76.5	53.7	ND	ND	0.684	Sepsis	157	ICU	Presepsin, galectin-3, and sST2: better than PCT for the prediction	[47]
PCT	0.16	100.0	10.57	ND	ND	0.513			ED	of 30-day mortality	
Galectin-3	28.4	91.2	56.9	ND	ND	0.776				Galectin-3: the strongest risk predictor of 30-day mortality	
sST_2	215.2	73.5	57.7	ND	ND	0.673					
Presepsin	957.5	94.7	85.7	90.0	92.3	0.891	Sepsis	76	ICU	Presepsin: similar diagnostic accuracy to PCT, significantly better	[91]
CRP	97.0	47.4	64.3	64.3	47.4	0.445				than CRP	
PCT	2.60	8.9	100.0	100.0	77.8	0.932					
Presepsin	299	0.84	58	37	93	0.489	Sepsis	33	PO	Presepsin: slightly better for prediction of clinical signs of sepsis	[73]
CRP	49.4	50	71	35	82	0.570					
PCT	0.68	67	80	50	89	0.798					
IL-6	106	81	61	42	90	0.674					
Presepsin	466	90	55	82	71	0.748	Sepsis	144	ICU	Presepsin: not superior to that of PCT	[50]
PCT	0.5	80	59	82	57	0.808					
Presepsin	588	81	80	94	52	0.858	Pneumonia				
PCT	0.5	69	80	93	40	0.793					
Presepsin	706.5	85.7	68.8	85.7	68.8	0.804	Sepsis	51	Pediatric	Presepsin seems to provide better early diagnostic	[68]
PCT	161.3	68.6	62.5	80	47.6	0.667					

AbbreviationAUC: Area under the curve, CRP: C-reactive protein, ED: Emergency Department, ICU: intensive care unit, IL-6: interleukin-6, ND: none defined, NPV: negative predictive value, PCT: procalcitonin, PO: pediatric oncology, PPV: positive predictive value, Sen: sensitivity, Spe: specificity, sST_2: soluble suppression of tumorigenicity- 2.

* ng/L for Presepsin and IL-6, ng/mL for sST2 and galectin-3, mg/L for CRP, μg/L for PCT.

higher levels of TLR_4 on peripheral blood monocytes, both at baseline and following LPS prompt. Considerably higher CD14 expression at baseline and following LPS induction have been demonstrated in full-term neonates compared to healthy adults [28,78].

Different performance efficiency of presepsin reported at different cutoff values in the pediatric settings (Table 2). At the cutoff of 885 ng/L, presepsin demonstrated a sensitivity of 94% and specificity of 100%, for the detection of LOS in preterm newborns [79]. At a cut-off value of 800.5 ng/L, presepsin showed 67% sensitivity and 100% specificity in the detection of LOS in preterm infants and gradually reduced during treatment [41]. Diagnostic values of presepsin in the detection of EOS have been reported. Presepsin levels in the EOS are higher than the healthy control group. At a cutoff of 539 ng/L, the sensitivity and specificity of presepsin has been reported as 80% and 75%, respectively [76]. At a cut-off of 788 ng/L, the sensitivity of 93% and specificity of 100% were recorded for presepsin in the diagnosis of early-onset sepsis in preterm newborns [80]. In contract to PCT, presepsin is not affected by gestational age in healthy infants [28,76,79]. The better sensitivity and NPV have been reported for presepsin, in comparison to CRP and PCT in diagnosing neonatal sepsis [70].

9. Presepsin compared to other immunologic biomarkers for diagnosis and prognosis of infections

In this comparative evaluation the diagnostic and prognostic efficiency of presepsin and other biomarkers has been investigated in different groups of patients. Controversial results of presepsin efficiency, compared to other biomarkers of sepsis, have been reported. Presepsin

with a cutoff of 2455 ng/L has been reported to be better than PCT, in the prediction of 30-day mortality of sepsis (AUC of 0.684 versus 0.513), and to be higher in non-survivors than in survivors [47]. At the cutoff of 413 ng/L presepsin has been shown to be higher in AUC than in PCT (0.705 versus 0.630) and lower than CRP (0.705 versus 0.734) in the detection of bacterial infections for patients admitted to hospital ICU [62]. AUC-ROC% values for diagnosis of burn sepsis have been reported to be 83.4% for presepsin, 84.7% for PCT, 81.9% for CRP and 50.8% for WBC. For burn sepsis patients, significantly changed presepsin, CRP and WBC, but not PCT, levels were reported on the first day of sepsis compared to previous days [37]. Neonatal sepsis, when compared to PCT, presepsin has been shown to be a better early diagnostic efficiency for faster therapeutic decision making and possible positive impact on the outcome [68]. Other multicenter prospective studies reported a higher diagnostic accuracy of PCT than presepsin (AUCs of 0.875 for PCT and 0.701 for presepsin) for sepsis in the ED. Mean presepsin levels were considerably more elevated in non -survivor septic patients (60-day mortality) than in survivors. However, a significant relationship has not been observed between PCT and survival [36]. The role of the immunologic biomarkers in monitoring infection is examined by the analysis of serial measurements, which was performed at admission time (T_0) and at different times after admission with twenty-four hour intervals (T_1 and T_2). Presepsin levels were reported to be considerably higher at T_0 than at T_1 and T_2, but PCT levels were higher at T_2. The performance efficiency of presepsin in comparison to other immunologic biomarkers, which were reported by different studies, was summarized in Table 3. Presepsin levels are increased prior to PCT and CRP. [8,36,81]. According to the results of the meta-analysis, presepsin has been shown to be an appropriate marker for the diagnosis of sepsis in PCT or CRP. As the only diagnostic approach, presepsin is not appropriate to rule out or confirm sepsis, and its diagnostic value should be considered with the other sepsis characterizations [10,82,83]. Presepsin in combination with IL-6 has been shown to increase sensitivity in comparison to only using presepsin in the detection of sepsis in pediatric hemato-oncological patients. Presepsin in combination with PCT and CRP have not shown better accuracy than only presepsin in the detection of sepsis in these patients [73]. The combination of presepsin with PCT, Galectin-3, and soluble suppression of tumorigenicity- 2 (sST2) has been reported to increase AUC more than the sole use of presepsin for the prediction of mortality in sepsis [47]. A higher specificity of presepsin and PCT have been reported for the detection of sepsis, septic shock and pneumonia in combination, when compared to only PCT or presepsin [50].

10. Limitation of presepsin assessment

Some pathophysiological conditions may influence its concentration, such as: age (neonates and elderly individuals), renal dysfunction, bacteremia, and hemophagocytic syndrome (HPS) [30,84–86]. Further investigations are required to define the effect of steroid usage on presepsin levels. Presepsin elevated levels, under certain conditions such as burn, may be associated with false positive signs of infection and may lead to inappropriate treatments [56,87]. It appears that the kidney has an essential function in the metabolism and/or excretion of presepsin [88]. Presepsin concentrations were significantly higher in individuals under hemodialysis. In individuals who were not under hemodialysis, presepsin concentrations may be elevated as the glomerular filtration rates reduce. Therefore, the assessment of presepsin concentrations in patients with chronic kidney syndromes needs future study, and a different cutoff value is required for detecting sepsis in such patients [89]. Presepsin also is influenced by translocation of the gut microbial flora, and also some aspects of its formation *in vivo* are indefinite. Animal experiments seem to propose that phagocytosis, in response to bacterial colonization/infection, may play a major role [90]. Presepsin has limited efficacy to identify the possible bacterial or viral etiology of infections. Thus, culture based methods continue to be the gold standard of infection detection and immunologic biomarkers should be used in addition to culture [76]. Further investigations are required to define the effect of steroid usage on presepsin levels.

11. Conclusion

An advantage of the assessment of presepsin is its capacity to predict the severity of a bacterial infection. In addition, the measurement of presepsin can be done by an easy procedure that takes less than 17 min. To increase the accuracy, presepsin could be used in combination with other markers and standard methods of infection diagnosis. The different performance efficiency values may be due to the heterogeneity established in the included studies, with possible sources such as the study strategy (prospective or not), clinical setting (ED, ICU), type of patients (adults or neonate), reference for sepsis criteria and even the type of sample (plasma, serum or whole blood) for measurement of presepsin. Further prospective studies with larger and more diverse populations are required to establish the cut of presepsin for the diagnosis and prognosis of infections. The knowledge of conditions, that influence the levels of presepsin, can reduce the false positive rate of infection diagnosis and inappropriate treatments. Future studies are necessary, for the identification of these conditions and the determination of cutoff values for the detection of different types of infections in different groups of patients would also be effective in the clinical application of this biomarker.

Conflict of interest

There is no conflict of interest.

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