Chapter

Presepsin as a Diagnostic and Prognostic Biomarker in Sepsis

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Abstract

Sepsis is defined as a life-threatening condition with organ failure, caused by an inadequate response of the host to the infection. It is a public health and economic problem worldwide. Early and accurate diagnosis of sepsis and timely inclusion of appropriate therapy are important for the outcome of the treatment of patients with sepsis. Sepsis biomarkers may provide information to achieve an early diagnosis, and predict prognosis and therapeutic response. Today, the literature lists more than 250 different biomarkers related to sepsis. However, stronger clinical evidence of clinical usefulness has emerged only for a few biomarkers from many published studies and meta-analyses. Among them, presepsin (sCD14-ST) appears to be one of the most promising biomarkers of sepsis in daily clinical practice. This chapter highlights the utility of presepsin as a diagnostic and prognostic biomarker of sepsis both in adult and pediatric patients.

Keywords: biomarker, diagnosis, infections, presepsin, prognosis, sepsis

1. Introduction

Sepsis is recognized as a global health problem worldwide and an important public health issue with considerable economic consequences. Sepsis can be the clinical manifestation of infections acquired both in the community setting and in health care facilities. Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) from 2016 defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection." This definition emphasizes the central pathogenetic role of the non-homeostatic host response to microorganisms rather than the infection *per se* [1]. Organ dysfunction was described using scoring systems such as the Sequential (Sepsis-related) Organ Failure Assessment score (SOFA score). A SOFA score ≥ 2 points were set as a criterion for more rapid identifying patients with sepsis in intensive care units (ICU). Patients with a SOFA score of 2 or more had an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Sepsis-3 has also introduced a new simpler score, called the quick Sequential Organ Failure Assessment (qSOFA) for use in non-ICU settings, to identify septic patients in out-of-hospital, emergency department, or general hospital ward setting. The qSOFA consists of three variables: respiratory rate ≥ 22 breaths per min, systolic blood pressure ≤ 100 mmHg, and altered mentation. A qSOFA score ≥ 2 was found to be significantly predictive of increased all-cause mortality in patients outside of the

ICU. According to Sepsis-3 definition, septic shock was defined as a subset of sepsis in which underlying circulatory and metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/l (>18 mg/dl) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40% [1].

Neonatal sepsis is a systemic condition of bacterial, viral, or fungal (yeast) origin that is associated with hemodynamic changes and other clinical manifestations and results in substantial morbidity and mortality. The symptoms are variable and nonspecific. Based on the onset neonatal sepsis could be classified into two types: (a) early-onset sepsis (EOS), which manifests as respiratory distress within 72 h of birth, and is mainly due to bacteria acquired before and/or during delivery (maternal-fetal infection); (b) late-onset sepsis (LOS), which manifests as septicemia after 72 h of birth and is due to bacteria acquired after delivery like nosocomial ones (community or hospital-acquired), and affects preterm and very-low-birth-weight neonates in particular [2].

The global burden of sepsis is difficult to ascertain. A meta-analysis of studies on adults admitted to hospitals from seven high-income countries suggested global estimates of 31.5 million sepsis (19.4 million severe sepsis cases), and 5.3 million sepsis-related deaths annually [3]. The recent article published by Rudd et al. [4] is the first comprehensive global report on the epidemiology of sepsis. It assessed the burden of sepsis across 195 countries and territories within the framework of all 282 underlying causes of death, both sexes, and 23 age groups for the years 1990 to 2017 in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 study. It is estimated that in 2017, there were 48.9 million cases and 11 million sepsis-related deaths worldwide, i.e., almost 20% of all global deaths. Approximately 85% of sepsis cases and sepsis-related deaths worldwide occurred in countries with low to middle sociodemographic indices that had much higher rates than those with higher indices. Nearly half of all sepsis-related deaths occur secondary to sepsis complicating an underlying injury or non-communicable disease. In 2017, almost half of all global sepsis cases occurred among children, with an estimated 20 million cases and 2.9 million global deaths in children under five years of age. The hospital mortality rate of sepsis was estimated to be 27% and mortality in ICU-treated sepsis was 42%. Among adult sepsis survivors, one in three died within a year, and one in six experienced significant, long-term morbidity [5]. Patients who survive sepsis often have long-term physical, psychological, and cognitive disabilities with significant health care and social implications.

Fleischmann-Struzek et al. [6] published an extensive systemic review analyzing the global burden of pediatric and neonatal sepsis. The review was based on 1270 studies published from 1979 to 2016. They performed the largest meta-analysis of population-based sepsis incidence in neonates and children, including 15 studies from 12 middle- and high-income countries on four continents. They estimated that 48 children per 100,000 population develop sepsis, 22 children per 100,000 population develop severe sepsis. Mortality ranged from 1.3% to 5.4% for sepsis, and 9–20% for severe sepsis. The population-level estimated for neonatal sepsis was 2202 per 100,000 live births, with mortality between 11% and 19%. This would translate to an incidence of 3 million cases of neonatal sepsis and 1.2 million cases of pediatric sepsis annually. These estimates are exploratory because of the considerable heterogeneity between data and the lack of population-based data from low-income and middle-income settings. Analyzing these alarming data, it is clear why the WHO, in 2017, listed sepsis as a key healthcare priority for the coming decade.

Sepsis is treatable, but early diagnosis is highly needed, due to significant clinical heterogeneity and the non-specificity of clinical symptoms. If it is not identified early and timely managed, sepsis may lead to severe and life-threatening complications such as septic shock, multiple organ failure, and death [7]. Early diagnosis is also important from an economic view since the earlier diagnosis of sepsis lowers the costs [8]. Sepsis-3 Task Force reiterates the concept that sepsis shall be identified using clinical criteria for life-threatening organ dysfunction and blood culture. Although blood culture has been considered the gold standard reference method for detecting and isolating pathogenic organisms from sterile body fluid specimens, its accuracy remains limited because of overall low diagnostic sensitivity, with high false negative rates in patients after initiation of antibiotic therapy, and in patients with severe localized infections or in the noninfectious cause of sepsis and preanalytical variables (inaccurate skin antisepsis, failure to use sterile gloves collection through central venous caterers, use of open blood collection systems, inadequate filling of blood culture bottles, long-term storage under inappropriate conditions, etc.). The drawbacks of blood culture are long turnaround time (its results are rarely available in a useful timeframe for decision-making), large sample volume, and frequent need for repeated testing [9, 10].

We have witnessed over the last years that an extensive variety of technologies for the identification of pathogens have been examined [11, 12]. Although some molecular diagnostic techniques, such as DNA/RNA rapid amplification followed by mass spectrometry or nuclear magnetic resonance are available and enable molecular identification of the causative organism in a few hours, limitations in their diagnostic performance still exist and must be overcome. Additional well-known drawbacks include: the need of dedicated often expensive equipment, high sensitivity of technique used for lysis and nucleic acids extraction, vulnerability to environmental contaminations, possible generation of false positive results due to deep-seated infections, doubts about the optimal sample matrix, interference from host nucleic acid and additional substances, amplification bias, off-target interactions, as well as to current limitedness and insufficient standardization of test panels [9].

Delays in the initiation of antimicrobial treatment are associated with a worse prognosis [13]. The current treatment guidelines for treating sepsis promulgate initiation of effective antibiotics within 1–3 h [14]. A large number of patients with sepsis still remain microbiologically undiagnosed in that period, thus, amplifying the risk of indiscriminate use of empiric antibiotics as broad-spectrum treatment. It contributes to the spread of antibiotic resistance genes, further exacerbating the emergence of multidrug-resistant microbial pathogens and secondary fungal infections [15]. Sometimes, empiric antibiotics are often administered to patients before arriving in the hospital and before exhibiting progressive signs of sepsis, thereby precluding an accurate microbial diagnosis by standard culture.

Due to explained limitations, there has been intense interest in identifying biomarkers of sepsis. Numerous serum/plasma sepsis biomarkers have been commercialized over the past decades. We are the witnesses that a growing body of literature over the last years revealed more than 250 sepsis biomarkers that offer utility for diagnosis, prognosis, early disease recognition, risk stratification, and appropriate treatment for patients with sepsis or suspected sepsis [16]. It is very well known that the ideal sepsis biomarker should be present at symptoms onset (or even earlier) and allow for an early diagnosis, should offer both high specificity and sensitivity for infections, be capable to identify the causative microorganism, be informative on the clinical course, provide valuable information on the prognosis, and guide therapeutic

decisions. Additionally, the ideal biomarker should be non/invasive, easily measured by a single, widely available test, reproducible, accurate, with defined optimal cut-off(s), known release kinetics, and cost-effective [17]. Despite a large number of biomarkers studied, no single biomarker emerged as a consistently reliable indicator for diagnosis and prognosis of sepsis. Given that none of these biomarkers fulfill all features of ideal sepsis biomarker, it is not surprising that the Sepsis-3 definition consensus states the role of biomarkers in sepsis diagnosis remains undefined [1], Surviving Sepsis Campaign guidelines for the management of sepsis mention that sepsis biomarkers can complement clinical evaluation [18].

Recent evidence suggests that an increased concentration of some sepsis biomarkers more reliably reflects the systemic host response to infection. Only a few biomarkers were reported to have a role specifically related to sepsis pathophysiology, rather than to a more general inflammatory reaction. However, only a handful of these has reached the point of clinical availability, i.e., validation in clinical practice. The measurement of some sepsis biomarkers in addition to blood culture or molecular biology further improves the diagnostic management of patients with possible sepsis. It appears that some sepsis biomarkers are favorable markers for the evaluation of sepsis severity, for garnering valuable prognostic information, and guiding therapeutic decision-making i.e., antibiotic stewardship.

Among the emerging biomarkers of sepsis, the soluble CD14 subtype (sCD14-ST) also known as presepsin received increasing attention as one of the most promising. This chapter will summarize our current knowledge of presepsin with emphasis on its clinical usefulness as a diagnostic and prognostic biomarker in sepsis.

2. Soluble CD14 subtype (sCD14-ST)–presepsin

Presepsin, which is also known as soluble CD14 subtype (sCD14-ST) (64 amino-acids, 13 kDa) is a glycoprotein fragment mostly synthesized and released in general circulation by macrophages or monocytes/macrophages in response to infections [19, 20]. The CD14 receptor is a pattern recognition receptor in the innate immune response that has the ability to identify different pathogen-associated molecular pattern molecules of both Gram-positive and Gram-negative bacteria such as lipopolysaccharide, peptidoglycan, lipoteichoic acid, etc. The best-studied ligand is lipopolysaccharide (LPS) of Gram-negative bacteria [21, 22].

CD14 has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). The first, mCD14 receptor (356 amino acids, 55-kDa), is a membrane glycoprotein [23], whose C-terminal leader sequence of 28–30 amino acids is replaced by a glycosyl phosphatidylinositol (GPI) anchor after translation [24]. Thus, mCD14 is anchored to the cellular membrane through GPI linkage. It does not possess an intracellular tail; it is not a transmembrane protein and is unable to transmit a signal by itself. Although CD14 is detected predominantly on the surface of myeloid-lineage cells; however, low amounts are also found in non-myeloid cells, e.g., hepatocytes, adipocytes, corneal, and intestinal epithelial cells. The circulating soluble form-sCD14 is found in plasma and is produced by mCD14 fall-off or cell secretion [25].

Various stimuli induce shedding of the GPI anchored mCD14, probably mediated by serine proteases such as leucocyte elastase [26] resulting in sCD14 with a molecular mass of 48–49 kDa. Some CD14 molecules stored intracellularly escape GPI anchor attachment and keep the C-terminal leader sequence, resulting in sCD14 with a molecular weight of 55–56 kDa [27]. After that, sCD14 is cleaved by cathepsin D and

other proteases in plasma or the phagolysosome and the truncated 13-kDa form of sCD14, called presepsin is generated and released into circulation.

After being released into circulation, lipopolysaccharide (LPS, endotoxin) of Gram-negative bacteria (the prevailing cause of severe sepsis in humans) binds to a specific plasma protein known as lipopolysaccharide-binding protein (LBP). LBP presents LPS to CD14 which is recruited to the receptor after ligand binding. The LPS/LBP complex after binding to CD14, mediated by myeloid differentiation factor 2 (MD2), finally binds to Toll-like receptor 4 (TLR4), resulting in its activation. Both membrane-bound and soluble CD14 can transfer the LPS molecule to the TLR4/MD-2 complex. TLR4 activation sequentially triggers two signaling cascades. The first one is the MyD88-signaling pathway at the plasma membrane, and the second is the TRIF-dependent signaling pathway. Dimerization of the receptor complex induces the assembly of TIRAP, MyD88, and IRAK kinases in a submembrane signaling complex called the myddosome at the TIR domain of TLR4 inducing a signaling pathway inducing expression of genes encoding pro-inflammatory cytokines (IL-6, TNF-α, etc.). The MyD88-dependent signaling is followed by internalization of TLR4 in endosomes. Simultaneously, TIRAP and MyD88 dissociate from the membrane allowing TLR4 to bind in the endosome the second set of TIR-containing adaptor proteins, TRAM and TRIF, controlling the production of type I interferons, CCL5/RANTES. Via activated NF-κB TLR4 also contributes to the activation of the cytosolic NLRP3 inflammasome [28]. Notably, while CD14 is marginally important for MyD88-dependent TNFα expression, it is essential for TRIF-mediated IFN expression because it regulates TLR4 endocytosis [29].

2.1 Kinetic of presepsin release

The kinetics of presepsin is extraordinarily rapid in blood. Presepsin levels increase in the blood within 2 h after the onset of any infection, with a maximum concentration after 3 h, and tended to decrease on day 7. The half-life of presepsin is 4–5 h at the plasma level [30]. In 2008, Nakamura et al. [31] in an experimental peritonitis model of sepsis in rabbits using cecum ligation and puncture, detected presepsin in the blood of animals 2 h after initiation of the procedure. Presepsin levels peaked at 3 h and decreased 4–8 h after initiation of the procedure. In 2016, Chenevier-Gobeaux et al. [32] measured presepsin levels after LPS stimulation in peripheral mononuclear cells (PMNC) and human cell line of mononuclear cells (THP-1), and found that In THP1 cells, presepsin levels increase after 1 h, reaching a peak after 3 h, and decreasing at 4 h after LPS exposure. In PMNC, exposure to LPS induced an increase of median presepsin levels as early as hour 1, concomitantly to IL-6 synthesis.

3. Measurement of soluble CD14 subtype (sCD14-ST)-presepsin

Different methods have been developed for the determination of presepsin. The first, presepsin concentrations were measured using a two-step sandwich enzyme-linked immunosorbent assay (ELISA). Large recombinant CD14 antigen (S286C, approximately 40 kDa) was used as standard. The dynamic range of the two-step assay was 3–150 ng/ml. The total assay time was 4 h. This test was sufficient to evaluate presepsin as a diagnostic marker for sepsis, but it lacked the speed and accuracy that are required for routine presepsin tests in ICU. Soon after, Shirakawa et al. [33] modified a traditional two-step into one-step ELISA. The standard used in the one-step method was recombinant presepsin, the sample dilution step was eliminated and two new anti-presepsin

antibodies were used: F1106-13-3 monoclonal antibody as the capture antibody and S68 polyclonal antibody as the detection antibody. The dynamic range of the one-step assay was 0.05–3.00 ng/ml. The total assay time was 1.5 h. This assay is suitable for clinical practice [33]. However, this method has low linearity and several endogenous (rheumatoid factor, cross-reactive substances, complement) and exogenous (specimen hemolysis, bacteria, and iatrogenic tube contamination) interfering factors [34].

In 2011, Okamura and Yokoi [35] have developed and evaluated the analytical and clinical performance of the highly sensitive, fully automated PATHFAST Presepsin test. This test performed on the PATHFAST instrument (Pathfast, Mitsubishi Chemical Medicine Corporation, Tokyo, Japan) is based on a noncompetitive chemiluminescent enzyme immunoassay combined with Magtration® technology. The principle of the test is as follows. The patient sample is dispensed into the reagent cartridge. The instrument combines the patient sample, the anti-presepsin monoclonal antibody-coated magnetic particles, and the alkaline phosphatase-labeled anti-presepsin polyclonal antibody and incubates the mixture for 5 min at 37°C. During this incubation, the analyte in the patient sample binds to the antibody on the coated particles, and the alkaline phosphatase conjugate binds to the analyte-antibody coated-particle. After the incubation, the instrument performs Bound/Free (B/F) separation using Magtration® technology to remove any excess unbound reagents, chemiluminescent substrate (CDP-Star Chemiluminescent Substrate) was added. The substrate is catalyzed by the bound alkaline phosphatase, which results in the emission of photons. The photo-multiplier tube in the PATHFAST instrument detects the photons that are emitted during the reaction. The chemiluminescent count is converted to analyte concentration values by the instrument based on the master calibration curve for the reagent lot [36]. According to the manufacturer's data assay range is 20–20,000 pg/ml. The assay reveals its result within 15 min in six samples simultaneously, using a sample volume of 100 μl. The calibrator for the PATHFAST Presepsin assay is recombinant presepsin (13 kDa). The sensitivity of the PATHFAST Presepsin assay was sufficient to detect the presepsin concentrations of the healthy group. It was higher than the recently reported one-step ELISA [37] The PATHFAST Presepsin assay correlated well with a previously reported two-step presepsin ELISA [33]. PATHFAST is applicable for use in the Emergency Department (ED), ICU, and surgical wards. No interference of presepsin was noticed for bilirubin, hemoglobin, lipids, triglyceride, or rheumatoid factors [35].

Recently, evaluation results of a new automated one-step sandwich chemiluminescent enzyme immunoassay for presepsin measurement on Sysmex HISCL-5000 (Sysmex, Japan) was published [38]. Briefly, biotinylated anti-presepsin monoclonal antibodies specifically react with presepsin in the sample. This complex binds to streptavidin-coated magnetic particles (MPs). After bound/free separation, alkaline phosphatase (ALP)-labeled anti-presepsin monoclonal antibodies specifically bind to the presepsin on an MP. Then, the ALP on the MP breaks down the CDP-Star® chemiluminescent substrate which produces a luminescent signal. Assay samples were tested undiluted, with an analytical measurement range of–30,000 pg/ml. Turn-around-time for measuring the first sample was 17 min and the total processing capacity was around 200 tests per hour. For the first time, Sysmex HISCL-5000 and PATHFAST presepsin tests were performed, and a high significant correlation was found. Also, SCD14-ST concentration picogram/milliliter (pg/ml) can be measured using CL1200i (Mindray, Shenzen, China), according to manufacturer protocol based on sandwich chemiluminescent enzyme immunoassay. The measurement range of the assay was 20–20,000 pg/ml [39].

4. Presepsin values in the reference population

Few studies measured presepsin concentrations in the reference population. They found that presepsin is present in low concentrations in healthy individuals. Mean concentrations were in range between 21.8 and 312 pg/ml, median was around 200 pg/ml [35, 37, 40–47].

However, current literature suggests an operational cut-off for the decision making process at the 95th percentile value. However, this value can be measured with enough statistical confidence (>95% CI) only if the studied population is >300 volunteers. Thus, this detection remains to be established for presepsin use today. Okamura and Yokoi [35] determined presepsin in the heparinized plasma of 127 healthy volunteers. The 95th percentile value was for plasma/whole blood 333 pg/ml/314 pg/ml. Carpio et al. [48] measured presepsin concentrations in EDTA plasma samples of 123 healthy volunteers and revealed a PSEP range of 58–339 ng/l and a 95% reference interval with an upper and lower reference limit of 236 ng/l (90% CI 222–250 ng/l) and 24 ng/l (90% CI 10–38 ng/l), respectively. Males showed slightly higher values than females. Median values were 133 and 101 ng/l, respectively ($P = 0.0435$).

Few studies published presepsin cut-off levels (pg/ml) expressed as medians (minimum-maximum) in healthy control infants, preterm and term infants. Mussap et al. [49] enrolled 26 consecutive non-septic preterm newborns with gestational age (GA) between 26 and 36 weeks admitted to NICU after the first day of life for various severe diseases. The obtained median presepsin value was 578 ng/l, the authors finally indicate preliminary reference ranges for preterm newborns 255–1144 ng/l. They did not find a correlation between GA and sCD14-ST presepsin blood levels between 26 and 36 weeks and they suggested adopting a unique reference range for preterm newborns. Pugni et al. [50] recently performed the first study that determined presepisn reference ranges in a large group (684 neonates) of term and preterm neonates (484 born at term and 200 were preterm (24–36 weeks' gestation). In term infants, presepsin median value was 603.5 pg/ml (interquartile range: 466.5–791 pg/ml; 5th and 95th centiles: 315 and 1178 pg/ml, respectively). In preterm infants, presepsin median value was slightly higher, equal to 620 pg/ml (interquartile range: 503–864 pg/ml; 5th and 95th centiles: 352 and 1370 pg/ml, respectively). The determined reference ranges of presepsin were much higher than those seen in healthy adults. No correlation between presepsin levels and postnatal age was observed, as well as no significant difference was demonstrated in preterm neonates at different gestational ages. None of the variables analyzed affected presepsin levels to a clinically significant extent. Poggi et al. [51] analyzed presepsin values in 183 preterm infants with ≤32 weeks of GA during the first 48 h of life and measured presepsin at four different time points. Presepsin median value within 6, 12, 24, and 48 h of birth was 583, 614, 604 and 513 ng/l, respectively. Presepsin values were negatively associated with GA at the first three time points. Recently, Nur Ergor et al. [52] in 144 neonates born at 24–42 weeks' gestation revealed, for the first time, the reference ranges of presepsin in healthy term and preterm neonates without infection with respect to gestational and postnatal age, sex, and body weight. Presepsin measurements included cord blood levels and serum levels on postnatal days 1, 3, 5, 7, 14, 21, and 28. The presepsin values corresponding to the 10th percentile ranged from 240.8 pg/ml (on day 1) to 129.9 pg/ml (on day 28), whereas those corresponding to the 90th percentile ranged from 725.8 pg/ml (on day 1) to 471.6 pg/ml (on day 28). Significantly higher presepsin levels were observed in cesarean deliveries than in spontaneous deliveries (P: 0.012 to <0.001), in gestational ages ≤32 weeks than in gestational ages ≥37 weeks (P: <0.05 to <0.001), and in

cases with a maternal history of chorioamnionitis than in those without (*P*: <0.05 to <0.001).

In the pediatric setting, mean presepsin plasma levels in healthy infants are much higher (720 ng/l) than in healthy adults, probably due to the passage after birth from the intrauterine environment to the new external environment rich in foreign antigens, which activates the innate immune system [53].

5. Presepsin values interpretation

Presepsin values are usually interpreted as follows [20]:

Presepsin, pg/ml	Diagnosis
<200	Sepsis excluded
<300	Systemic infection improbable
<500	Sepsis probable
<1000	Significant risk of severe sepsis
≥1000	High risk of severe sepsis/septic shock equivalent to SOFA≥8

Special care must be taken in interpreting altered presepsin levels. Presepsin concentrations increase with age, and the interpretation of presepsin is altered in elderly patients. Special attention should be paid on newborn presepsin values. Presepsin is a small protein, filtered by the glomerulus and reabsorbed and completely catabolized within proximal tubular cells. Since the kidney is involved in the presepsin excretion, the presepsin plasma levels are increased in patients with renal failure. Presepsin levels could rise above the cut-off value in patients with renal dysfunction, and in this case, presepsin concentrations should be interpreted with caution. For this reason, the cut-offs must be adapted in patients with chronic kidney disease and/or on hemodialysis treatment [43, 54].

Presepsin is also influenced by translocation of the intestinal microbial flora [55]. As presepsin is not only excreted through the kidney but also in the hepatobiliary system, its abnormalities may therefore be related to higher levels of presepsin level. Cholestasis significantly increases biliary enzymes, suggesting that presepsin is elevated in patients with cholestasis. Lin et al. [56] indicated an association between presepsin and the severity of cholangitis. This may indicate that an increase in the total bilirubin is associated with the presepsin level. A markedly high presepsin level may be associated with obstructive jaundice [57]. These findings highlight the need of establishing adapted cut-offs for specific populations/conditions.

6. Presepsin as a diagnostic and prognostic marker

Since 2005, when it was first reported that presepsin was increased in patients with sepsis [37], suggesting its utility as an early diagnostic marker of sepsis, numerous studies have been performed with the aim to evaluate the usefulness of presepsin as a diagnostic and prognostic biomarker in sepsis. Also, few meta-analyses have been published evaluating the diagnostic and prognostic value of presepsin. The first

meta-analysis published in 2015 mainly focused on validating the diagnostic value of presepsin in adult sepsis, and the newer analyses examined the prognostic values of presepsin value for adult sepsis. Recently published meta-analyses were performed mainly on neonates, examining the diagnostic and prognostic value of presepsin in sepsis. Some of them analyzed the prognostic value of presepsin in comparison and combination with traditional sepsis biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT).

6.1 Presepsin as a diagnostic marker

Numerous studies, mainly conducted in the last decade, have assessed the diagnostic value of presepsin for sepsis, with conflicting results. The studies reported that presepsin efficiency depends on the cut-off used. Different cut-off values reported by these studies may be caused by the heterogeneity of the studies in the clinical setting (ED vs. ICU), the sepsis criteria adopted (before or after Sepsis-3), study design (prospective vs. retrospective), comorbidities, or the type of sample used (plasma vs. whole blood vs. serum) for measurement of presepsin. Optimal cut-off values (sensitivity and specificity, respectively) to discriminate sepsis from non-sepsis were 907 (70%, 83%) [30], 686 (47%, 91%) [58], 729 (81%, 63%) [59], 600 (79%, 62%) [60], 542 (77%, 76%) [61], 430 (88%, 82%) [45], 466 (90%, 55%) pg/ml [62]. In the study by Shozushima et al. [40] the optimal cut-off value of presepsin was 399 pg/ml, until, in Liu et al. [42], the optimal cut-off value of presepsin was 317 pg/ml.

Several studies revealed the potential greater utility of presepsin over PCT in the early diagnosis of sepsis. Some studies have shown that presepsin has diagnostic and prognostic power substantially similar to PCT, but, unlike PCT, presepsin increases earlier in bacterial infection and can be measured effectively and accurately within 15 min using a POCT analyzer. Rare studies showed the opposite results.

In a 2013 prospective cohort study [42] in consecutive ED patients with at least two diagnostic criteria for SIRS in the ED (prior Sepsis-3), presepsin was the superior diagnostic marker of sepsis than PCT. In patients with bacterial and non-bacterial infection in acute abdominal conditions, Vodnik et al. [63] reported that presepsin discriminates SIRS from sepsis much better than PCT, CRP, or WBC. They also reported that presepsin was superior to PCT and CRP in discriminating sepsis from SIRS in acute abdominal conditions. Kweon et al. [45] found higher diagnostic accuracy of presepsin compared to PCT, IL6, and CRP in patients presenting to the ED with suspected sepsis. Hou et al. [64] reported that presepsin had a higher diagnostic value compared with both PCT and CRP patients with nephrolithiasis presenting with SIRS. In another 2015 study, using a cut-off of 413 ng/L for diagnosing bacterial infections in ICU patients, Godnic et al. [65] reported that presepsin has a higher area under the curve (AUC) compared to PCT (0.705 vs. 0.630) but lower than CRP (0.705 vs. 0.734). In a study conducted on ICU patients, presepsin was effective in predicting sepsis with sensitivity and specificity values of 84.6% and 62.5%, respectively, which were significantly related to the APACHE II score (P-value = 0.016).

The multicenter prospective study that included 207 suspected sepsis patients demonstrated that presepsin is useful for the diagnosis of bacterial infections as PCT [46]. The cutoff value of presepsin for discrimination of bacterial and nonbacterial infectious diseases was determined to be 600 pg/ml, with sensitivity 87.8% and specificity 81.4%. A study performed by de Guadiana Romualdo et al. [59] in 2014, has included 226 patients admitted to the ED with SIRS criteria, of which 37 had positive blood culture (bacteremic SIRS group) and 189 had negative blood culture

(non-bacteremic SIRS group). They showed that presepsin values can be used to rule out the diagnosis of bacteremia in SIRS patients in the ED setting (cut-off value 729 pg/ml, sensitivity 81.1%, specificity 63%, PPV 30%, and NVP 94.4%). In this study, presepsin showed a similar diagnostic accuracy to PCT. A few years later, the same authors examined 223 patients admitted in ED with suspected sepsis, using two cut-offs (312 and 849 ng/l) and found sensitivity 97.1% and 67.1% and specificity 16.9% and 80.8%, respectively. They also reported that the diagnostic accuracy of presepsin does not improve that of PCT [58]. Cakır Madenci et al. [61] revealed that presepsin levels had comparable performances with PCT, CRP, and WBC levels in burn sepsis. In 2016, Alli et al. [30] and Leli et al. [66] in prospective cohort studies of patients with SIRS/suspected sepsis/healthy controls, and patients with suspected sepsis, respectively showed that presepsin and PCT had good diagnostic accuracy, whereas presepsin was superior to CRP.

Contenti et al. [67] using Sepsis-3 reported that presepsin can effectively discriminate sepsis from non-infectious SIRS and that presepsin and PCT were superior to CRP and lactate in discriminating sepsis, including shock, from non-sepsis with SIRS and a SOFA score ≥ 2. The study showed that the AUC values used to discriminate sepsis from non-sepsis were 0.88 for presepsin. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of presepsin for diagnosing sepsis (including shock) using a cut-off value of 508 pg/ml were 87%, 86%, 93%, 76%, and 87%, respectively. A recently published study by Lee et al. [68] performed the largest prospective observational study on the diagnostic value of presepsin in non-infectious organ failure, sepsis, and septic shock, in accordance with the latest Sepsis-3 definitions. They reported that presepsin has good accuracy in discriminating sepsis from non-infectious organ failure and had fair accuracy in discriminating septic shock from sepsis. Presepsin best cut-off to discriminate sepsis and non-infectious organ failure was 582 pg/ml (sensitivity 70.1%, specificity 89.4%, AUC 0.877, $P < 0.001$) and sepsis and septic shock 1285 pg/ml (sensitivity 50.4%, specificity 76.6%, AUC 0.618, $P < 0.001$). The discriminating power of presepsin was comparable with that of PCT among patients with non-infectious organ failure/sepsis/septic shock.

Two center studies published in 2013 [60], including patients in the ED with suspected sepsis/septic shock, and patients with SIRS without clinical evidence of infection, found that the diagnostic accuracy of presepsin was generally lower than PCT. Sargentini et al. [69] showed that presepsin can accurately differentiate septic and non/septic patients in ICU, but it is inferior compared to PCT. At the same time, Claessens et al. [41] also confirmed that presepsin was less accurate than PCT to predict bacteraemia in patients with acute pyelonephritis and bacteremia.

The level of presepsin will rise significantly in early-onset sepsis. Whether presepsin can indicate Gram-positive and Gram-negative bacterial infection is still controversial. Lu et al. [70] reported that the cut-off value of presepsin for discrimination of sepsis and nonbacterial infectious SIRS was determined to be 407 pg/ml, with a sensitivity 98.6% and specificity 82.6% in patients with sepsis and SIRS in the ED. They compared presepsin levels in septic patients infected with various kinds of pathogens and did not find a significant difference in patients with Gram-positive, Gram-negative, mixed (bacterial and fungal), fungal infection and unknown infection. But, presepsin was significantly different between Gram-positive and Gram-negative bacterial infections ($P < 0.05$), enabling distinguishing Gram-positive and Gram-negative bacterial infections. Besides, Masson et al. [71] in 997 patients with severe sepsis or septic shock in the multicenter Albumin Italian Outcome Sepsis

(ALBIOS) trial reported that patients infected with Gram-negative bacterial infections had higher levels of presepsin than those with Gram-positive infections. Also, presepsin concentration was significantly higher in patients with bacterial infection (according to the site or blood culture) than in those with negative culture or in those with no culture available. However, Endo et al. [46] have gained the opposite results; there was no significant difference between Gram-positive and Gram-negative bacterial infections, as well as no significant differences in presepsin levels between the blood culture-positive and culture-negative groups.

It was found that presepsin should also be useful for the diagnosis of bacteremia in hematological patients undergoing stem cell transplants with a cutoff value of 218 pg/ml [72]. The same authors two years later in another study of hematological patients undergoing chemotherapy reported that presepsin is useful for the differentiation between bacterial and fungal infection. They found that elevated CRP in conjunction with presepsin within the normal reference range was in favor of fungal infection in this group of immunocompromized individuals [73].

Klouche et al. [62] reported greater specificity of presepsin and PCT in combination for the diagnosis of sepsis, septic shock and pneumonia, compared to using PCT alone or presepsin alone. In 2016, Plesko et al. [74] reported that in hematologic patients the association of presepsin with IL-6 increases sensitivity compared to the use of presepsin alone in detecting sepsis, while the association of presepsin with PCT and CRP did not show better accuracy than presepsin alone in detecting sepsis in this type of patients. Chan et al. [75] reported that a cut-off value of 1025 pg/ml presepsin had 83% specificity and 85% sensitivity for the diagnosis of sepsis. This case–control study (60 patients admitted to ICU with sepsis/60 controls) showed that presepsin and sTREM-1 were more sensitive for the diagnosis of sepsis compared to PCT and CRP. The most accurate indicator was a composite biomarker of presepsin and sTREM-1. In 2015, Carpio et al. [48] performed a single-center prospective observational study (120 patients with SIRS or sepsis criteria (before Sepsis-3) and 123 healthy controls) confirmed that presepsin at a cut-off of 581 ng/l is effective in diagnosing sepsis, graduating severity of disease and differentiating between SIRS and sepsis in ED, with the sensitivity of 61% and specificity of 100%. The performance of presepsin varies according to the cut-off considered: using a cut-off of 273 ng/l, a sensitivity of 95.5% and specificity of 21.7% were found, while using a cut-off of 686 ng/l, these values were 46.5% and 91.3%, respectively. This study showed that the combination of presepsin and MEDS score improved discriminatory power compared with presepsin or MEDS score alone. In a single center study of 250 patients older than 75 years admitted in ED with suspected sepsis, Ruangsomboon et al. [76] revealed that presepsin had a similar diagnostic accuracy as PCT and the early warning score. Presepsin was found to be an accurate biomarker for sepsis diagnosis in geriatric persons older than 75 years in combination with PCT and the early warning score.

Among the biomarkers identified as a potential diagnostic markers for neonatal sepsis, presepsin seems to be promising. A recently published review analyzed literature data about presepsin as a biomarker for the diagnosis of neonatal sepsis [77]. In 2015, 13 studies [78–90] were assessed presepsin accuracy as an early diagnostic biomarker of sepsis in infants preterm and term infants. Ten out of the 13, performed longitudinal presepsin monitoring from birth up to the first week of life. Cut-offs were 300–987 ng/l sensitivity 67–100%, specificity 75–100%, Presepsin accuracy as a diagnostic test for perinatal sepsis, and a comparison with the standard of care parameters such as CRP and PCT was provided. The research strategy allowed for the selection of seven studies in which presepsin, CRP, and PCT accuracy were

investigated according to different outcomes [78, 81, 82, 84, 86–88]. It was shown that presepsin is a valuable diagnostic test for sepsis (EOS and LOS) with higher sensitivity and specificity values than PCT and CRP [81, 87, 88], or similarly accurate as a diagnostic test of EOS to CRP and PCT [78, 86].

6.1.1. Systematic reviews and meta-analyses

The first comprehensive meta-analysis [91], published in 2015 included 11 studies [37, 40, 42, 45, 46, 55, 59–61, 63, 92] (1630 sepsis cases, 1422 controls) with heterogenous inclusion criteria. It revealed the overall diagnostic sensitivity of presepsin for sepsis was 0.83 (95% CI: 0.77–0.88) and the specificity was 0.78 (95% CI: 0.72–0.83). The diagnostic odds ratio was 18 (95% CI: 11–30). The area under the summary receiver operating characteristic curve (sROC) was 0.88 (95% CI: 0.84–0.90), until the positive and negative likelihood ratios of presepsin for revealing sepsis were 3.9 (95% CI: 2.9–5.0) and 0.21 (95% CI: 0.15–0.30), respectively. When presepsin was introduced as a diagnostic test for sepsis, sepsis probability increased from 56% (pretest probability among all subjects) to 81% (post-test probability for a positive result). Presepsin is an effective adjunct biomarker for sepsis diagnosis, but presepsin alone is insufficient to rule out or confirm sepsis, and its results should be interpreted within the clinical context.

In 2015, Wu et al. [93] published a systematic review and meta-analysis of 10 trials (9 studies) [40, 42, 44, 45, 55, 60, 63, 94, 95], conducted in internal care unit, critical care unit, in the emergency department in Eastern Asia and Western Europe. It included 1320 sepsis patients, 512 with SIRS of non-infectious origin, and 327 healthy persons. The pooled sensitivity of presepsin for sepsis was 0.78 (0.76–0.80), pooled specificity was 0.83 (0.80–0.85), pooled diagnostic odds ratio was 21.73 (12.81–36.86), pooled positive likelihood ratio was 4.63 (3.27–6.55), and pooled negative likelihood ratio was 0.22 (0.16–0.30). Wu et al. [93] found similar sensitivity (0.85 vs. 0.84), but lower specificity in the cut-off values greater than 700 pg/ml studies, compared to values smaller than 700 pg/ml studies (0.59 vs. 0.80). This meta-analysis showed that presepsin could be helpful in sepsis early diagnosis, and has only moderate diagnostic value in differentiating sepsis from other non-septic inflammatory conditions.

In the same year, meta-analysis [96] of eight studies [42, 44–46, 59, 60, 63, 97] from Europe and Asia were published. It included 1815 patients, from whom SIRS criteria were fulfilled in 1690 patients (1165 patients with sepsis and 525 patients with non-infectious SIRS)). This meta-analysis revealed very good diagnostic accuracy of presepsin (AUC 0.89 (95% CI: 0.86–0.92)) for the diagnosis of sepsis in SIRS patients. The pooled sensitivity was 0.86 (95% CI: 0.79–0.91), specificity was 0.78 (95% CI: 0.68–0.85), diagnostic odds ratio 22 (95% CI: 10–48), positive likelihood ratio 3.8 (95% CI: 2.6–5.7), and negative likelihood ratio 0.18 (95% CI: 0.11–0.28). According to this meta-analysis, presepsin cannot be recommended as the single definitive test for diagnosis of sepsis.

The systematic review and meta-analysis of Zheng et al. [98] included eight studies [42, 44–46, 59, 60, 65, 97] with 1757 patients who evaluated the accuracy of presepsin for the diagnosis of sepsis from SIRS patients. The pooled sensitivity was 0.77 (95% CI 0.75–0.80), specificity 0.73 (95% CI 0.69–0.77), and diagnostic odds ratio was 14.25 (95% CI 8.66–23.42). The summary receiver operating characteristic curve (sROC) AUC was 0.8598, indicating that the presepsin had a moderate diagnostic efficiency.

A bivariate meta-analysis of Tong et al. [99] of 11 publications [40, 42, 44–46, 60, 61, 63, 92, 97, 100] examined the use of presepsin to diagnose sepsis with 3106 subjects. The sensitivity was 0.83 (95% CI 0.77–0.88), specificity 0.81 (95% CI 0.74–0.87), DDR 21.56 (95% CI 10.59–43.88), PLR 4.43 (95% CI 3.05–6.43), NLR 0.21 (95% CI 0.14–0.30). The area under the curve was 0.89 (95% CI 0.86–0.92). Estimated positive and negative post-probability values for a sepsis prevalence of 20% were 53% and 5%, respectively. This analysis showed the valuable role of presepsin in the diagnosis of sepsis, but stated that presepsin values should be interpreted carefully in a clinical context considering traditional markers.

Li et al. [101] conducted a large systematic review and meta-analysis of nine studies [40, 46, 48, 59, 60, 63, 65, 97, 100] comprised of 1510 participants to evaluate the diagnostic value of potential biomarkers (among them presepsin) for the differential diagnosis of non-infectious SIRS and sepsis. The obtained sensitivity for presepsin was 0.84 (95% CI 0.79–0.88), specificity (0.77 (95% CI 0.68–0.84), AUC was 0.88 (95% CI 0.85–0.90). It was shown that presepsin has moderate diagnostic utility in differentiating sepsis from SIRS. This analysis showed a similar diagnostic accuracy of presepsin in detecting sepsis as PCT, CRP, IL6, sTREM-1, LBP, and CD64.

Next year Wu et al. [102] published a systematic review and meta-analysis of 18 studies [40, 42, 44–46, 48, 55, 58–63, 65, 92, 97, 100, 103] including 3470 patients with the aim to assess the accuracy of presepsin for the diagnosis of sepsis in adult patients and compare the performance of presepsin, and traditionally examined biomarkers CRP, PCT. The pooled diagnosis sensitivity of presepsin for sepsis was 0.84 (95% CI 0.80–0.87), specificity was 0.76 (95% CI 0.67–0.82), the pooled DOR was 16 (95% CI 10–25), PLR 3.4 (95% CI 2.5–4.6), NLR 0.22 (95% CI 0.17–0.27), and AUC 0.88 (95% CI 0.85–0.90). It showed that presepsin is a good predictor for sepsis but there are no significant variations compared to PCT or CRP. Presepsin has similar diagnostic accuracy as PCT or CRP.

Although Hayashida et al. [104] in 2016, first decided to conduct a systematic review and meta-analysis to evaluate the diagnostic accuracy of PCT and presepsin to a reference standard of sepsis/infection and to compare the diagnostic accuracy with each other in critically ill adult patients, their work was published three years later [105]. It included 10 studies [30, 44, 46, 59, 61, 62, 65, 66, 106, 107] that enrolled 1389 patients with established infection in the critical care setting. It was focused only on studies evaluating participants with critical illnesses, such as acute respiratory distress syndrome and sepsis, but not healthy volunteers. Diagnostic accuracy in detecting infection is similar for PCT and presepsin (sensibility 0.80 and 0.84, specificity 0.75 and 0.73, respectively). It was shown that both biomarkers are useful for early diagnosis of sepsis and reduction of mortality in critically ill adults. It was shown that the diagnostic accuracy of both biomarkers in detecting infection was similar, also both are useful for early diagnosis of sepsis and reduction of mortality in critically ill adults.

Few meta-analyses regarding presepsin diagnostic accuracy in detecting neonatal sepsis were recently published. The first meta-analyses performed by Bellos et al. [108] evaluated the diagnostic accuracy of presepsin in neonates with suspected sepsis. This meta-analysis consisted of 11 studies [80, 84, 85, 87, 88, 90, 109–113] with a total number of 783 neonates (391 with neonatal sepsis, 392 controls). The pooled sensitivity of presepsin for the prediction of neonatal sepsis was 0.91 (95% CI [0.87–0.93]), pooled specificity was 0.91 (95% CI [0.88–0.94]), with a diagnostic odds ratio of 170.28 (95% CI [51.13–567.11]) and the AUC was 0.9751 (SE 0.0117). A head-to-head comparison with AUC values of CRP (0.9748 vs. 0.8580) and PCT (0.9596 vs. 0.7831) revealed that presepsin was more sensitive in detecting neonatal sepsis.

According to this meta-analysis, presepsin can help clinicians in identifying neonates at risk. Ruan et al. [114] performed a meta-analysis of 28 studies (2661participants) with the aim to compare the diagnostic accuracy of PCT, CRP, PCT combined with CRP (PCT + CRP), and presepsin in diagnosing neonatal sepsis. A total of six studies [84, 85, 87, 88, 90, 115] enrolling 463 neonates were included in this presepsin meta-analysis. The pooled sensitivity of presepsin (0.94 (95% CI 0.80–0.99)), the pooled NLR of presepsin (0.06 (95% CI 0.02–0.23)) and the AUC for presepsin (0.99 (95% CI 0.98–1.00)). The main finding of this meta-analysis was that presepsin alone or PCT plus CRP have better diagnostic power than CRP and PCT alone in neonatal sepsis. One of the largest reviews and meta-analyses [116] investigating the diagnostic accuracy of presepsin in detecting sepsis, performed on neonates include nine [78, 80, 83–85, 87, 90, 111, 113] high-quality studies, comprising 712 neonates. Meta-analysis results showed an overall sensitivity of 90% and an overall specificity of 90%, with an AUC of 0.968, indicating a high level of diagnostic accuracy in detecting neonatal sepsis. The pooled sensitivity was 0.90 (95% CI 0.86–0.93), pooled specificity was 0.90 (95% CI 0.86–0.93), the pooled DOR was 120.94 (95% CI 40.11–364.69), and AUC was 0.968 (SE 0.0136). Using cut-off values <600 ng/l, sensitivity was 0.93, specificity of 0.81 and AUC 0.8195, while using a threshold >600 ng/l, sensitivity was 0.87, specificity 0.97, with higher diagnostic accuracy (AUC 0.976). Diagnostic accuracy of presepsin resulted high in detection of neonatal sepsis. Even though it cannot be recommended as a single diagnostic test, presepsin could be a helpful and valuable biomarker in neonates with suspected sepsis.

However, these meta-analyses analyzed together studies that included EOS and LOS. They did not take into account that different timing of presepsin measurements may affect results and that a single cut-off value for EOS and LOS may be inappropriate, as presepsin values change during the first month of life [52]. Patient populations may also significantly differ, because LOS occurrence is definitely prevalent in hospitalized preterm newborns, and gestational age affects presepsin values [51].

Van Maldeghem et al. [117], in a published systematic review and meta-analysis, for the first time, evaluated the differences in diagnostic accuracy of presepsin between EOS and LOS. Twelve articles [49, 50, 80, 83–85, 87, 90, 109, 111, 113, 118] were included in the systematic review and ten in the meta-analysis. At sepsis onset, a consequently higher level of sCD14-ST was found in septic neonates compared to healthy controls with significantly higher levels in LOS compared to EOS. sCD14-ST levels increase in the first 24 h in EOS, but not in LOS. This underlines the importance to consider EOS and LOS as two different disease entities. Optimal cut-off values ranged from 305 to 672 ng/l for EOS cases vs. healthy controls. The pooled sensitivity was 81% (95% CI 0.76–0.85), pooled specificity 86% (95% CI 0.81–0.89) with an AUC of 0.9412 (SE 0.1178). In LOS optimal cut-off values ranged from 801 to 885 ng/l with a pooled sensitivity of 81% (95% CI 0.74–0.86) and a pooled specificity of 100% (95% CI 0.98–1.00). An AUC and sROC were not estimable in LOS because of the low number of studies.

Recently published the largest systematic review and meta-analysis on presepsin diagnostic performance in the neonatal population [119], and for the first time specifically assessed presepsin accuracy for the diagnosis of neonatal EOS. Twelve studies [79, 80, 83, 84, 109–111, 118, 120–123] and 828 newborns (including 460 with EOS and the rest uninfected) met the inclusion criteria for the primary analysis (positive blood culture). Ten of the studies included a mix of EOS and LOS, four only included infants born at term, two were restricted to preterm infants, and the rest had a mix. Half of the studies were performed in Egypt, while the remaining were conducted in

Europe and Asia. Presepsin had a pooled sensitivity of 0.93 for the primary analysis of culture-proven sepsis (95% CI 0.86–0.96), a pooled specificity of 0.91 (95% CI 0.85–0.95), and a pooled diagnostic odds ratio (DOR) of 131.7 (95% CI 54.9–310.9). Presepsin showed high pooled sensitivity and specificity; presepsin specificity was influenced by the inclusion of only early-onset or all neonatal sepsis. Accuracy was not affected by gestational age, test type, country of the study, or risk of bias of the included studies. The secondary analysis included 23 studies [78–80, 83, 84, 86–88, 109–113, 115, 118, 120–127] that met the broader criteria for sepsis (either positive blood culture or clinical sepsis) and involved 1866 newborns (1040 newborns with EOS and the rest uninfected), with seven of the trials involving only newborns with EOS produced similar results. Results of the secondary analysis were similar, with a pooled sensitivity of 0.93 (95% CI 0.89–0.96), a pooled specificity of 0.91 (95% CI 0.87–0.94), and a pooled DOR of 141.9 (95% CI 68.6–293.5), though the authors cautioned that "the risk of misdiagnosis remains considerable among studies enrolling clinical sepsis, as noninfectious conditions likely account for a certain proportion of cases, possibly leading to overestimation of presepsin accuracy." The findings suggest presepsin "was a robust biomarker" of EOS and warrant trials to assess its usefulness in guiding early empirical antibiotic treatment, especially for newborns born preterm.

Yoon et al. [128] performed the first systematic review and meta-analysis that evaluated the diagnostic value of presepsin for pediatric sepsis (not including neonates) and compare it with other biomarkers. A total of four studies [74, 129, 130] (one in Turkey, one in Egypt, and two in Slovakia) were published between 2016 and 2018. Three hundred eight patients (101 patients with sepsis, 127 non-sepsis patients, and 80 healthy volunteers) aged between 1 month and 18 years were included. The pooled diagnostic sensitivity of presepsin was 0.94 (95% confidence interval [CI]: 0.74–0.99,) specificity 0.71 (95% CI: 0.35–0.92), pooled DOR 32.87 (95% CI: 2.12–510.09), PLR 3.24 (95% CI, 1.14–12.38), and NLR 0.08 (95% CI, 0.01–0.74). Presepsin has higher sensitivity and diagnostic accuracy, but lower specificity, than PCT or CRP in detecting sepsis in children. The pooled sensitivity of presepsin (0.94) was higher than that of CRP (0.51) and PCT (0.76), whereas the overall specificity of presepsin (0.71) was lower than that of CRP (0.81) and PCT (0.76). The AUC of presepsin (0.925) was higher than that of CRP (0.715) and PCT (0.820). The high sensitivity of presepsin could be very useful for the exclusion of sepsis in pediatric patients when the level of this biomarker is normal or lower than the cut-off value. But, this result must be interpreted with caution, because the meta-analysis included only a few heterogeneous studies.

6.2 Presepsin as a prognostic marker

A growing body of literature indicates the potential of presepsin as a suitable biomarker for the assessment of severity, risk stratification especially for Gram-negative bacterial infection, the prognosis of sepsis and aid clinicians with the choice of appropriate treatment strategies at an early stage for optimal resource allocation. A change in presepsin levels may be an appropriate indicator for monitoring antibiotic therapy that improves the prognosis and increases the survival rate in severe sepsis or septic shock. Serial presepsin measurement can be used to evaluate changes in a patient's condition in the ICU. Patients with ≥50% decreased presepsin in ICU survived more than 90 days [131]. Reduction in presepsin levels on day 7 strongly correlates with the efficacy of antibiotic therapy [71]. The trend of presepsin decrease during

serial prespsin measurement is a good prognostic sign, until an increase hints worse prognosis. The first few days in ICU are critical for the development of most severe complications, and elevated presepsin levels may be associated with the occurrence of severe sepsis complications and subsequent mortality in ICU. Shimoyama et al. [132] in the prospective cohort study, single-center ICU, with 83 patients reported that presepsin elevation upon ICU admission and on day 2 is a predictor of septic acute renal failure, presepsin on days 1 to 3 acute respiratory distress syndrome, presepsin on day 2 and Δ presepsin (day 2-day 1) for septic disseminated intravascular coagulation (DIC). Multivariate analysis revealed presepsin on day 2 to be a predictor of septic DIC. Combining presepsin with Glasgow Prognostic Score improved the specificity for predicting septic ARDS relative to using baseline presepsin values alone. The same authors [133] demonstrated that presepsin value on day 1 predicts 28-day mortality and death within 7 days of ICU admission.

In Hassan et al. [134] study, ICU patients with sepsis reported that presepsin levels within the first week had better prognostic accuracy than hsCRP in the prediction of sepsis-related in-hospital mortality. Patients who had higher levels of presepsin at admission than the cut-off value (>607 pg/ml) had a shortened survival period compared to patients who had lower levels. Klouche et al. [62] aimed to assess the prognostic value of presepsin in ICU patients with severe sepsis, septic shock, and severe community-acquired pneumonia. They identified presepsin levels that best predict ICU mortality in septic patients (1925 pg/ml), and those with community-acquired pneumonia at cutoff values (714 pg/ml). Kim et al. [135] performed a retrospective study included 157 septic patients (112 patients with sepsis; 45 patients with septic shock) admitted to ICU or ED, with the aim to explore the prognostic utilities of multi-marker approach using PCT, presepsin, galectin-3, and sST2 in septic patients for predicting 30-days mortality. Although the presepsin was higher in non-survivors compared with survivors, presepsin alone was not a significant predictor of 30-day mortality. But, the combination of presepsin with PCT, galectin-3, and soluble suppression of tumorigenicity-2 showed better performance in predicting 30-day all-cause mortality than the single use of presepsin for sepsis patients.

Drăgoescu et al. [136] in a recently published study assessed the efficacy of presepsin at admission in the prognosis of sepsis useful marker for prognosis of sepsis severity and mortality risk in 114 patients admitted to the ICU in comparison to CRP, erythrocyte sedimentation rate, white blood cells, and SOFA score. Presepsin values were significantly higher ($P < 0.001$) in patients with septic shock 2403 (1974–3278) ng/ml compared with those with sepsis 1476 (963–2413) ng/dl, as well as in non-survivors 2975 (2551–3647) ng/ml compared to survivors 1258 (963–1971) ng/dl. Presepsin levels higher than 1932 ng/ml had a sensitivity 79% and specificity 63% in predicting in-hospital mortality. The AUC was 0.726 (95% CI 0.635–0.806) ($P < 0.0001$), and it was significantly better than SOFA score, but similar to CRP in predicting sepsis severity. They also found that presepsin levels higher than 2365 ng/dl had a sensitivity 74% and specificity 88%. The AUC was 0.861 (95% CI 0.784–0.919) ($P < 0.0001$). Presepsin was a significantly better predictor of sepsis mortality than CRP, SOFA score.

In the study of Matera et al. [137] that included ICU patients with suspected sepsis, multivariate logistic regression analysis showed that only presepsin (within 6 h after admission) is an independent predictor of mortality, until PCT and CRP were not significant predictors.

Behnes et al. [44] evaluated the prognostic accuracy of presepsin in 116 patients with suspected severe sepsis or septic shock during the first week of ICU treatment.

Presepsin revealed a valuable diagnostic capacity to differentiate sepsis severity compared to other used biomarkers for sepsis such as PCT, IL-6, CRP, and WBC. Presepsin and IL-6 also showed prognostic value regarding 30 days and 6 months of all-cause mortality throughout the first week of ICU treatment. Multicenter prospective cohort study of Endo et al. [46] included 103 patients with sepsis admitted to the ED or ICU and compared the clinical utility of presepsin with other sepsis biomarkers including PCT, IL6, and CRP for evaluating the severity of sepsis during follow-up. Presepsin was the only biomarker that remained elevated after treatment application in the unfavorable prognosis group that had the most severe initial presentation and retained an association with an elevated risk of 28-day mortality during the follow-up period.

Presepsin was evaluated as a potential biomarker for bacterial infection relapse in critical care patients during hospitalization in ICU. In patients with a clinical recurrence of sepsis, presepsin levels remained high while PCT levels were normalized during the transient remission phase. The existence of high presepsin levels could alert clinicians to continue with antibiotic therapy in patients with sepsis [55].

Jovanovic et al. [138] evaluated the prognostic value of presepsin for ventilator-associated pneumonia (VAP) and sepsis in critically injured patients requiring mechanical ventilation and treatment in ICU. Presepsin levels were significantly higher in patients who developed VAP compared to those with SIRS and significantly higher in patients with sepsis compared to those with VAP or SIRS.

In the Multicenter Albumin Italian Outcome Sepsis (ALBIOS) [71], the first analysis included patients with severe sepsis or septic shock, and reported the median concentration of presepsin at ICU admission as 2269 (1171–4300) pg/ml in deceased patients, that was significantly higher than 1184 (875–2113) pg/ml in survived. Baseline presepsin was independently associated with the risk of ICU and 90-day mortality. Increasing concentrations of presepsin from day 1 to day 2 predicted higher ICU and 90-day mortality (adjusted $P < 0.0001$ and $P < 0.01$, respectively). The second analysis from the ALBIOS trial (enrolling patients with severe sepsis or septic shock in ICUs) [139] demonstrated that presepsin level was independently associated with the number and degree of organ dysfunctions or failures, coagulation disorders and ICU mortality. Provide the first evidence that presepsin measurements may have useful prognostic information for patients with severe sepsis or septic shock. Results showed that presepsin was the only variable independently associated with ICU and 28-day mortality. It also showed better prognostic accuracy than PCT in the range of SOFA score.

Two prospective cohort studies found that presepsin is an independent predictor of in-hospital mortality in a cohort of patients hospitalized due to sepsis [140] and in patients with sepsis-related ARDS [141]. Wen et al. [140] also found that the combination of presepsin elevation and SOFA score was a predictor of in-hospital mortality compared with a marker or stroke used alone. A recently published study by Aliu-Bejta et al. [142] in 2020 performed also in a cohort of hospitalized patients outside of ICU, found significantly higher baseline presepsin concentrations in patients with septic shock compared to septic patients (according to the sepsis-3 definition), especially in the first 72 h, confirming that presepsin concentrations had a good capacity for distinguishing disease severity. PCT and CRP levels did not differ significantly between the two severity groups.

A recently published single-center prospective observational study by Lee et al. [68] reported prognostic value of presepsin among patients with non-infectious organ failure, sepsis, and septic shock (in accordance with Sepsis-3 definition) in ED. They identified the most useful presepsin cut-off value (821 pg/ml) for the prediction of 30-day mortality among patients with sepsis and septic shock. Multivariate Cox

proportional hazards model analyses of the 30-day mortality, identified presepsin as a significant predictor (HR 1.003; 95% CI 1.001–1.005; $P = 0.042$) together with lactate (HR 1.108; 95% CI 1.070–1.147; $P < 0.001$) and SOFA score (HR 1.264; 95% CI 1.167–1.369; $P < 0.001$).

Ulla et al. [60] reported that a higher level of presepsin at presentation in ED was correlated to 60-day mortality. Lu et al. [70] in 72 patients with sepsis in ED and 23 nonbacterial patients with SIRS reported presepsin's value as a prognostic marker of sepsis severity. They found that there was a significant difference in presepsin, among sepsis, severe sepsis, and septic shock group ($P < 0.05$). Statistically, a significant difference was noticed between the sepsis and severe sepsis group, as well as between the severe sepsis and septic shock group.

Presepsin may also retain significant predictive values in the ED, where initial evaluation may be a significant predictor of early mortality due to sepsis. The validity of presepsin as a prognostic marker of 30-day mortality in the ED was assessed in 123 patients with suspected infection in the ED and 123 healthy individuals [48]. Results showed that presepsin at admission had a similar outcome prediction as the clinical scores MEDS and APACHE II. The combination of presepsin with MEDS score improved the power for outcome prediction. Popa et al. [143] in a retrospective study of 95 patients with suspected infection in ED concluded that presepsin is an early marker of mortality in patients with sepsis. Ishikura et al. [97] evaluated 11 biomarkers in 82 patients with ≥1 SIRS criteria at admission to the ED, with the aim to define a biomarker panel to predict sepsis-induced DIC. The optimal panel was presepsin together with protein C is predictive of the severity of sepsis-induced DIC in suspected ED patients.

Three studies did not show so promising results about the relationship between presepsin and mortality. Enguix-Armada et al. [106] analyzed the prognostic value of CRP, PCT, presepsin mid-regional pro-adrenomedullin measured in the first 24 h from ICU admission. The outcome variables studied were 28-day mortality and length of stay in the ICU. The authors failed to detect any prognostic value presepsin measured in the first 24 h. Brodska et al. [144] in 30 consecutive patients admitted for sepsis to the mixed medical-surgical ICU, showed the opposite results, i.e., that presepsin did not outperform the traditional biomarkers (PCT, CRP, lactate) in mortality prognosis in critically ill patients with sepsis and SIRS. Koh et al. [145] evaluated the performance of presepsin as a biomarker for predicting in-hospital mortality in 153 patients with sepsis or sepsis shock admitted to ICU directly from ED. Although presepsin values were higher in the non-survivor compared to the survivor group, ROC analysis revealed poor performances of presepsin in predicting the prognosis of sepsis (AUC = 0.656, $P = 0.001$). Presepsin levels higher than 1176 pg/ml had a 66.7% sensitivity and 61.1% specificity in predicting in-hospital mortality.

The prognostic value of presepsin has also been evaluated in patients who are hospitalized with a known cause of infection. Two studies examined presepsin in confirmed pneumonia. Titova et al. [146] in 75 patients with pneumonia, sepsis, and other inflammatory diseases found that presepsin in patients with pneumogenic sepsis was higher compared to presepsin in patients with severe pneumonia and non-severe pneumonia. The high level of presepsin reflects the severity of pneumonia and the development of sepsis. Ugajin et al. [147] reported that presepsin levels on admission could be a useful predictor of 30-day mortality in hospitalized patients with pneumonia. Song et al. [148] examined if presepsin has some prognostic value in patients with enterocutaneous fistula and abdominal sepsis. Patients with higher

presepsin levels had a more severe intra-abdominal infection, higher risks of complications, and failure of fistula closure compared with patients with low presepsin admission values group. Current evidence suggests that presepsin could be also a useful predictive marker for newly developing sepsis after abdominal surgery [149]. Prospective study by Bamba et al. [150] revealed that presepsin could also be a useful biomarker of sepsis secondary to fungal infections. Presepsin levels were increased in those patients with fungal bloodstream infection, with a positive association with the disease severity.

Presepsin has also been tested in an antimicrobial stewardship program. In a recent prospective, multicenter, not randomized trial from China Xiao et al. [151] compared presepsin guidance to control (standard of care) in sepsis. In the presepsin group, physicians were advised to stop the antibiotics by serum concentrations lower than 350 pg/ml or any baseline decrease of more than 80%. The antibiotic adjustment was encouraged when the blood presepsin concentration did not decline. Patients in the presepsin group had significantly ($P < 0.001$) more days without antibiotics [14.54 days (SD 9.01) compared with the control group 11.01 days (SD 7.73),]. Although the primary outcome (days without antibiotics at day 28) was achieved, mortality did not differ between treatment arms. Mortality in the presepsin group was not significantly different compared to control group at day 28 (17.7% vs. 18.2%; $P = 0.868$) and day 90 (19.9% vs. 19.5%; $P = 0.891$). Patients in the presepsin group had a significantly shorter hospital length of stay and lower healthcare costs compared with the control group.

6.2.1. Systematic reviews and meta-analyses

Two meta-analyses that evaluated the prognostic value of presepsin in adult septic patients have been recently published. The first of Yang et al. [152] included 10 studies [30, 42, 44, 48, 62, 135, 139, 153–155] with 1617 patients (580 non-survivors and 1037 survivors). Five out of ten included studies were conducted in ICU, three studies in ED, and six studies exclusively contained severe sepsis or septic shock. This is the first meta-analysis, that demonstrated that presepsin can predict mortality in patients with sepsis. Presepsin levels in samples taken within the first 24 h were significantly higher in non-survivors as compared to survivors: a weighted pooled SMD of 0.92 (0.62–1.22) for over-all mortality and 1.09 (0.78–1.41) for in-hospital or 30-days mortality ($P < 0.01$). In subgroups, divided by the sepsis severity or study site (ICU, ED), pooled SMD was consistently noting higher presepsin levels in non-survivals ($P < 0.05$).

Zhu et al. [156] further evaluate the relationship between presepsin and hospital mortality and provide additional information on pooled sensitivity and specificity to determine its prognostic performance. Nine publications [30, 42, 48, 135, 137, 139, 144, 154, 157], comprising 1561 patients, were included in this study. Since PCT was a widely used predictor of mortality, they performed a head-to-head comparison of presepsin and PCT in predicting all-cause mortality in these patients. The overall AUC of presepsin was 0.77 (95% CI, 0.73–0.81) with a pooled prognostic sensitivity 0.83 (95% CI, 0.72–0.90) and specificity 0.69 (95% CI, 0.63–0.74). Additionally, the PLR, NLR, and DOR of presepsin were 2.6 (95% CI, 2.1–3.3), 0.25 (95% CI, 0.15–0.44), and 10 (95% CI, 5–22), respectively. It was found that there is no statistically significant difference between presepsin and PCT, implying that both predictors are promising prognostic biomarkers of sepsis.

7. Conclusions

Within the last decade, a broad range of molecular biomarkers for sepsis has been reported. One of the most promising emerging biomarkers is presepsin, gaining relevance year by year. After the initial report in 2005, a strong body of literature comprised of more than 280 clinical studies, systematic reviews, and meta-analyses, indicated that presepsin could be used as a relevant routine daily clinical tool for early diagnosis, risk stratification, and predicting clinical progression, short-term and long-term outcomes, and guiding therapeutic management in adult, neonates, and pediatric sepsis patient. That presepsin is still a marker in focus, is shown by the fact that almost 70% of studies were published in the last 5 years. With the change of sepsis definition in Sepsis-3, the utility of presepsin is currently being reevaluated, with consistently encouraging results. In addition, presepsin concentration can now be routinely measured in whole blood, in approximately 15 min, using point-of-care devices in different clinical settings (ED, ICU). A potential advantage of presepsin resides in the possibility of its measuring in non-invasive biological fluids such as urine, saliva, as well as tracheal aspirate for adults, children, and infants.

Despite presepsin represents a promising biomarker, it still faces numerous challenges and criticisms that require further elucidation. The studies in favor of the use of presepsin are heterogenous in the sense they use the sepsis-2 definition, and examine clinically heterogenic patient groups at risk of sepsis in a variety of different settings, with the small sample size as a common limitation.

Inter-assay disagreement can represent a confounding factor in the interpretation of test results in different studies. The definition of an optimal cut-off is very important. Instead of using static threshold presepsin concentrations, serial monitoring of presepsin levels would prove more helpful to clinicians to follow an individual patient's response to therapy. Further prospective studies with larger and more diverse populations are required to establish the presepsin cut-off for the diagnosis and prognosis of infections. Consensus regarding time sampling strategy in infants is particularly of great importance. Also, conversion of presepsin level from pg/ml to multiple medians as measurement units will be more than justified in the assessment of perinatal sepsis. Studies that evaluated the impact of presepsin on therapeutic decisions are still limited. Specifically designed randomized clinical trials are needed to determine the usefulness and safety of early measurement of presepsin to guide early empirical antibiotic treatment, particularly in preterm newborns. Will presepsin be incorporated in antimicrobial stewardship programs that will contribute to reducing antimicrobial overuse in septic patients without compromising the clinical outcome, remains to be seen. Although, current evidence on biomarkers and pharmacokinetic optimization of antibiotics in critically ill patients is limited, maybe in the future, presepsin-based drug monitoring for dose optimization will be proposed.

As it has already been touched on in the chapter, in some clinical conditions (renal failure, burns, etc.), presepsin levels can be altered in the absence of sepsis. Presepsin levels may be higher in some physiological conditions like in preterm newborns and advanced age patients, in which concentrations reach the threshold at which the diagnosis of sepsis would be highly suspected in human beings. Presepsin is also affected by the translocation of intestinal microbial flora. Future studies are necessary, for the identification of these conditions and the determination of appropriate cut-off values based on age and associated diseases.

Many studies in different clinical settings that compared the diagnostic and prognostic efficacy of presepsin with CRP and/or PCT, reported controversial results. Presepsin does not appear to be clearly superior to the biomarkers commonly used in the assessment of sepsis, although mainly performances place presepsin at the level of PCT. Compared to PCT, the significance of presepsin elevation is easy to understand, as it results from a dose–response mechanism of the host-pathogen interaction. Presepsin increases with every type of bacteria and fungi. In neonatal sepsis, presepsin compared to PCT is more effective in diagnosing and guiding therapy.

The combination of presepsin with traditional sepsis biomarkers CRP and/or PCT, or with other novel biomarkers (triggering receptor expressed on myeloid cells-1, neutrophil cluster of differentiation-64, soluble urokinase-type plasminogen activator receptor, mid-regional pro-adrenomedullin, cell-free DNA, microRNAs, interleukin-27, etc) into a bio-score, together with physician expertise and clinical judgment, may be particularly useful in the diagnosis of sepsis or the risk stratification of patients with sepsis. High-quality prospective studies with larger, diverse populations with an eye on specific subgroups are more than warranted. It seems that presepsin merits further study to delineate its specific area of utility.

Conflict of interest

The author declares no conflict of interest.

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