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Clinical Assays in Sepsis: Prognosis, Diagnosis, Outcomes, and the Genetic Basis of Sepsis

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Abstract

Sepsis is the most widespread medical disorder of the intensive care unit (ICU) and the most common cause of death in hospitalized patients. Several endothelium-related molecules have been investigated as potential biomarkers for early diagnosis and/or prognosis of sepsis, providing different results depending on study designs. Therefore, it seems that we are still far from the right combination of sepsis markers to be used in clinical practice. It is more probable that a panel of diverse biomarkers will be more efficient in clinical practice. More recently, the potential use of genetic biomarkers for prognostic purposes started emerging for sepsis, in the form of genome-wide association studies. The successful use of modern molecular diagnostics could enable rapid identification of particularly susceptible or less susceptible individuals, leading to tailored therapeutic treatments.

Keywords: sepsis, biomarkers, polymorphisms

1. Introduction

Sepsis, as defined by the third consensus definitions for sepsis and septic shock, is a life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [1]. However, in the studies used to establish the sepsis-3 guidelines, patient populations were primarily characterized by the previous definitions of sepsis, severe sepsis, and septic shock [2].

Sepsis is the most common medical disorder of the intensive care unit (ICU) and the most frequent cause of death in hospitalized patients; it accounts for 1,000,000 cases and 200,000 deaths annually in the United States alone [3]. Unlike other major epidemic illnesses, treatment for sepsis is nonspecific. The new surviving sepsis guidelines [4], that provide an update to the older guidelines [5, 6], presented statements on early management and resuscitation, limited primarily to support organ function and administration of intravenous fluids, antibiotics, and oxygen. Sepsis is a syndrome, not a disease [7] and it occurs in patients with infection [8]. There are no approved drugs that specifically target sepsis. Drotrecogin alfa (activated protein C), the only approved drug specifically indicated for the treatment of severe sepsis, was withdrawn from the market in 2011 [5, 9].

Hence, in the last several years, the search for prognostic and diagnostic markers of sepsis for their use in clinical practice reached its peak. Indeed, the 2001 International Sepsis Definitions Conference [2] introduced C-reactive protein (CRP) and procalcitonin (PCT) as inflammatory markers in the diagnostic criteria for sepsis. However, the new sepsis-3 definitions [1] recognized that sepsis is a syndrome without as yet a validated standard diagnostic test. Sepsis is recognized to involve early activation of both pro- and anti-inflammatory responses [10] along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation [11], all of which have prognostic significance. The use of biomarkers for the early diagnosis of sepsis may permit early intervention which may reduce the risk of death. Combinations of pro- and anti-inflammatory biomarkers in a multimarker testing kit may help identify patients who develop severe sepsis before organ dysfunction has advanced too far [12]. Biomarker-guided immunotherapy that is administered to patients at the proper immune phase of sepsis may potentially be a major advance in the treatment of sepsis.

In the first part of the chapter, the most commonly studied biomarkers of sepsis are reviewed for their current uses and diagnostic accuracies, including C-reactive protein, procalcitonin, various cytokines and chemokines, endothelial biomarkers, and lactate. The second part of the chapter will focus on the genetic markers of sepsis.

2. Sepsis biomarkers

2.1. Pro-inflammatory biomarkers (acute-phase)

2.1.1. C-reactive protein (CRP)

Proteins, such as C-reactive protein and procalcitonin, are synthesized in response to infection and inflammation. CRP, named after its ability to precipitate the somatic C-polysaccharide of *Streptococcus pneumoniae*, was the first acute-phase protein to be described and comprises a very sensitive systemic marker of inflammation and tissue damage [13]. Currently, CRP is used as a clinical marker to assess the presence of infection and can help discriminate bacterial and viral infections [14]. Various studies have shown CRP to be a valuable marker for the diagnosis of sepsis [15–19] and disease severity [15, 20]. Besides its use in the diagnosis of

sepsis, CRP has also been evaluated as a prognostic marker. More specifically, in ICU patients, elevated concentrations of serum CRP on admission have been associated with increased risk of organ failure and mortality [21, 22]. There have been studies, however, that have not been able to demonstrate that CRP levels are indicative of survival in septic patients [23, 24].

2.1.2. Procalcitonin (PCT)

PCT is a protein consisting of 116 amino acids with a molecular weight of 13 kDa and is a precursor of calcitonin produced by C-cells of the thyroid gland, which is intracellularly cleaved by proteolytic enzymes into the active hormone [25]. In 1993 when its elevated level was found in patients with bacterial infection, PCT became an important protein in the detection and differential diagnosis of inflammatory states [26]. The highest levels of PCT are achieved in acute bacterial infections and sepsis. Since then, it has been widely investigated for its prognostic value in sepsis, and has become the most widely used biomarker in the management of infection and sepsis in Europe [27]. The efficacy of serial PCT concentrations has been evaluated as a prognostic biomarker of outcome in sepsis [28, 29]. PCT clearance has also been extensively studied as a biomarker for monitoring sepsis outcomes; at this end various reports have demonstrated significant improvement in PCT clearance in survivors compared to nonsurvivors in both severe sepsis and septic shock patients [28, 30–32]. A large meta-analysis comprising 23 studies with 3944 patients concluded that PCT nonclearance was a prognostic factor of death in patients with sepsis [33]. Hence, it has been suggested that PCT clearance could be indicative of patient outcome and serial PCT concentration measurements throughout hospitalization could facilitate treatment planning to improve patient outcome.

Several meta-analyses have investigated the value of PCT as a diagnostic marker of sepsis. However, this vast number of studies and meta-analyses has produced conflicting results. Uzzan *et al.* found that PCT represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock and suggested that procalcitonin should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units [34]. The findings of Tang *et al.* on the other hand do not support the widespread use of the procalcitonin test in critical care settings [35]. Another large meta-analysis consisting of 3244 patients suggested that PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients [36]. As far as prognosis is concerned, a meta-analysis of 2353 patients proved that there is a significant difference between PCT levels as early as day 1 between survivors and nonsurvivors among septic patients [37].

The efficacy of procalcitonin-guided antibiotic treatment has also been studied. A meta-analysis of 1075 patients concluded that procalcitonin is a helpful method to guide antibiotic therapy and surgical interventions without, however, exhibiting a beneficial effect on mortality [38]. The major benefit was shorter antibiotic treatment duration.

In conclusion, PCT in some studies has been found to be a superior marker of infection than CRP in critically ill patients, and nonetheless is a useful marker of the severity of infection [15, 39–43].

2.2. Cytokine/chemokine biomarkers

Cytokines are immuno-regulators produced in response to an infection or injury. A more clear understanding of the pathophysiological basis of sepsis, including the pro- and anti-inflammatory response during the hyperinflammatory and immunosuppressive phase of the disease, respectively, can lead to an alternative treatment approach. In septic patients, secretion of pro-inflammatory cytokines at the systemic inflammatory response syndrome or SIRS and anti-inflammatory cytokines, at the compensatory anti-inflammatory response syndrome (CARS) [44], occurs in a simultaneous manner from the very first instant of infection [45]. Mean serum levels of cytokines are higher in septic compared to nonseptic patients. Cytokines have therefore been proposed to be sepsis biomarkers in cases of neonatal and adult sepsis [46, 47]. Interleukin-6 (IL-6), IL-8, and IL-10 are the most extensively studied cytokines in diagnosing sepsis, evaluating the intensity of the inflammatory response and determining the prognosis for the patient. IL-6 comprises a pro-inflammatory cytokine, IL-8 is a major chemokine, and IL-10 represents an anti-inflammatory cytokine.

2.2.1. Pro-inflammatory cytokines and chemokines

Tumor necrosis factor-alpha (TNF- α), IL-1 β , and IL-6 are the cytokines that mediate the initial response of the innate immune system to injury or infection. Neutrophils are the first and most important cellular host defense against invading pathogens. Neutrophils migrate rapidly from the blood to the site of infection and this recruitment is mediated by pro-inflammatory mediators, such as TNF- α , IL-1 β , and neutrophil-active chemoattractants, like IL-8. Therefore, these cytokines are essentially responsible for the features of SIRS and could be potentially useful as biomarkers of sepsis. IL-6 enhances the liver's production of the so-called acute phase reactants, including CRP, and also stimulates a shift in the production of cells in the bone marrow so that more polymorphonuclear cells (PMNs) are produced. However, it is also possible that the cells entering circulation could disseminate inflammation into other organs, eventually leading to damage [48]. Impairment of neutrophil migration has been described in sepsis, suggesting that in human sepsis, failure of neutrophil migration is associated with a poor prognosis. In human sepsis, lipopolysaccharide (LPS) is known to induce TNF- α production by activating various kinases, leading to NF κ B (nuclear factor kappa light chain enhancer of activated B cells) activation.

Levels of circulating cytokines are frequently increased in sepsis [49–57]. IL-6 levels are increased in patients with infectious complications and have been used to differentiate SIRS from sepsis [58]. Studies have shown that high concentrations of TNF- α and IL-6 are predictive of organ failure and increased mortality in septic patients [55, 57, 59]. IL-8 has been used to predict the severity of sepsis in pediatric patients, although the use of IL-8 has not been confirmed in adults [60, 61]. A very recent study showed that the interleukin-1 receptor 2 (IL1R2) might be a better biomarker not only for sepsis diagnosis but also for differentiation of sepsis infected with G-positive or G-negative bacteria compared to PCT, Acute Physiology and Chronic Health Evaluation II (APACHE II), and CRP [62].

In line with this, clinical trials with an anti-TNF- α monoclonal antibody in septic patients did not show any advantage [63]. Interestingly, it was demonstrated in subsequent studies that blocking IL-6 caused a complete inhibition of endotoxin-induced activation of coagulation [64]. Administration of an IL-1 receptor antagonist partly blocked the pro-coagulant response in experimental sepsis models and inhibited thrombin generation in patients [65]. Overall, anti-TNF- α and IL-1 β clinical trials undertaken in patients with sepsis have been unsuccessful [66].

2.2.2. IL-27

IL-27, a bioactive member of the IL-12 cytokine family, may serve as a useful biomarker in estimating risk of bacterial infection among critically ill pediatric and adult patients [67–70]. Moreover, when used in combination with PCT, IL-27 may improve classification of critically ill adults with sepsis [68, 71].

2.2.3. Anti-inflammatory cytokines

Just as described above how the pro-inflammatory syndrome is characterized by many different and sometimes redundant cytokines, the CARS response also seems to involve many cytokines. The most important, however, is IL-10 [72]. It now has been established that IL-10 has multiple immunosuppressive roles [73] with its most important being the downregulation of TNF- α . Poor patient outcome has been associated with increased blood levels of the anti-inflammatory cytokine IL-10 [74]. IL-10 has been shown to protect endotoxemic mice [75–77], whereas in models of polymicrobial sepsis it seems to be deleterious [78, 79]. These inconsistent results likely depend on the time of administration and the severity of infection. Indeed, in view of these contradicting results, studies have documented that administration of anti-IL-10 monoclonal antibodies beyond the initial pro-inflammatory state of polymicrobial sepsis improves survival of animals subjected to sepsis [80], and furthermore, it is the timing and scale of the anti-inflammatory response that predicts severity of infection in murine model of sepsis [81].

To summarize, pro- and anti-inflammatory cytokines and chemokines have some value in the evaluation of the inflammatory response; however, they lack discriminative power to differentiate between infectious and noninfectious systemic inflammation. Elevated levels of pro- and anti-inflammatory cytokines are found mostly in nonsurvivors, whereas reduced levels are found in survivors of sepsis [82]. Even though they play an important part in the pathogenesis of sepsis, the role of cytokines as sepsis biomarkers remains to be established.

2.3. Endothelial proteins as potential biomarkers

Since early widespread endothelial dysfunction and/or damage appear to be directly involved in sepsis [83], there is a strong biological rationale for targeting markers of endothelial activation and dysfunction as biomarkers of the septic syndrome.

2.3.1. Angiopoietins

Angiopoietin-1 (Ang-1) and angiopoietin-2 are antagonistic factors that trigger endothelial cell (EC) activation; the role of angiopoietin-1 is to maintain vessel integrity and block vascular leakage, while angiopoietin-2 (Ang-2) counteracts the protective effects of Ang-1-Tie2 signaling [84, 85]. Ang-2 has been proposed as a biomarker in sepsis, since its release directly reflects vascular barrier breakdown [86–88]. More specifically, Ang-2 levels have been found to be elevated in patients with severe sepsis compared to patients with sepsis or not [89–91], higher Ang-2 levels have been reported in septic patients with worse clinical outcome [92–94], and increased Ang-2 levels have been demonstrated in nonsurvivors compared to survivors [95, 96]. Fewer studies have examined the role of Ang-1 in sepsis; those reports have shown either decreased levels of Ang-1 in critically ill patients compared to healthy controls, or have associated decreased levels at ICU admission with higher mortality [94, 97].

2.3.2. Selectins

Prior to the firm adhesion of leukocytes to the vascular endothelium and their transmigration to the sites of injury and inflammation, capture and rolling of leukocytes along the endothelium occurs. This is mediated by a family of cell adhesion molecules (or CAMs), called the selectin family [98]. Levels of soluble (s)E-selectin are very low in healthy individuals, whereas increased concentrations have been reported in various inflammatory pathologies [99–102]; other investigations have shown higher levels in nonsurvivors than survivors [103, 104]. Recently, it was demonstrated that sE-selectin levels may be used as predictor of fatal outcome in patients with SIRS [105]. Moreover, sE-selectin has also been proposed as a predictor of bacteremia in severe sepsis patients [106]. P-selectin has a similar function, but is constitutively expressed in lung ECs, and correlates with lung endothelial injury [107]. A recent study by Wang *et al.* [108] demonstrated in patients hospitalized for infections that higher baseline levels of interleukin-6, sE-selectin, and soluble intercellular adhesion molecule-1 (sICAM-1) may differentiate those patients who will develop a mild response to infection from those who will develop full-blown sepsis. A most recent study showed that high levels of the circulating endothelial adhesion molecules sE- and sP-selectin, measured at ICU admission, appear to be associated with sepsis development in time [109].

2.3.3. Soluble intercellular adhesion molecule-1 (sICAM-1)

Both the innate and adaptive immune responses depend on the migration of leukocytes across endothelial cells [110]. Specific adhesion glycoproteins are required for the binding of leukocytes to ECs. One such glycoprotein, intercellular adhesion molecule-1 (ICAM-1), controls the firm adhesion of neutrophils on endothelium and consequently their transmigration to the sites of infection. ICAM-1 has been studied as a biomarker of sepsis severity and outcome. These studies have produced inconsistent and conflicting results, possibly reflecting the time

point at which they were measured [105]. ICAM-1 production has been shown to be induced by endotoxins and has been associated with sepsis severity [102, 111] or mortality [111, 112], while sICAM-1 seems to be a reliable biomarker for distinguishing patients with sepsis from those with noninfectious SIRS [105].

2.3.4. Soluble platelet/endothelial cell adhesion molecule-1 (sPECAM-1)

Platelet/endothelial cell adhesion molecule-1 (PECAM-1, CD31) is a 130-kDa cell adhesion molecule that is expressed on the surfaces of leukocytes, such as monocytes, neutrophils, and some T-cell subsets, as well as on platelets and the intercellular junctions of endothelial cells [113]. Serum levels of sPECAM-1 have been demonstrated to be higher in septic patients compared with nonseptic patients at admission and are also higher compared to healthy controls [114, 115].

2.3.5. Endocan

Endocan is a proteoglycan expressed and secreted by the vascular endothelium in the lung and kidney, in response to pro-inflammatory cytokines and pro-angiogenic factors, which inhibits leukocyte migration [116]. The molecule is cleaved through the activity by cathepsin G generating a novel endocan peptide fragment of 14 kDa, named p14, which exhibits higher concentrations in septic patients compared to healthy volunteers [117]. Several studies have shown that this glycoprotein can be used as a strong and significant predictor of sepsis severity and outcome [118–122].

2.4. Receptor biomarkers

2.4.1. Soluble urokinase-type plasminogen activator receptor (suPAR)

The soluble urokinase-type plasminogen activator receptor (suPAR) was first identified in 1985 as a cellular binding site for urokinase [123]. Since then suPAR has been investigated as a potential prognostic marker in the ICU. In critically ill patients, several studies have reported elevated suPAR in SIRS, bacteremia, sepsis, and septic shock, in which high circulating suPAR levels indicated a poor prognosis, including organ dysfunction and mortality [124–127].

Systematic reviews have concluded, however, that the diagnostic value of suPAR in sepsis is limited [128] and suPAR does not appear to be better in diagnosing sepsis compared to other biomarkers, like CRP and PCT [129, 130]. Plasma suPAR levels are, however, a sensitive and specific independent prognostic biomarker in patients with bacteremia. This plasma protein may be used to identify patients who are severely ill with pneumococcal bacteremia, and predict mortality [131–133].

2.4.2. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

Triggering receptor expressed on myeloid cells-1 (TREM-1) is an immunoglobulin whose signaling induces the production of cytokines, chemokines, and reactive oxygen species, all of which contribute to the inflammatory response. Furthermore, TREM-1 signaling leads to degranulation of neutrophils and increased phagocytosis. A soluble form of TREM-1 (sTREM-1) can be measured in body fluids and has potential as a diagnostic and prognostic biomarker of sepsis [134–139]. Other studies, however, have not been able to demonstrate sTREM-1 as a single marker sufficient for sepsis diagnosis and prognosis [140–142].

Systematic reviews of the literature have shown that elevated sTREM-1 concentrations have a moderate diagnostic performance in differentiating sepsis from SIRS and were not sufficient for sepsis diagnosis in systemic inflammatory patients [140]. Furthermore, it exhibits a moderate prognostic significance in assessing the mortality of infection in adult patients and sTREM-1 alone is insufficient to predict mortality as a biomarker [142]. However, sTREM-1 represents a reliable biological marker of bacterial infection [143].

2.4.3. Soluble endothelial protein C receptor (sEPCR)

The protein C (PC) anticoagulant system provides important control of both blood coagulation and inflammatory pathways [144]. This system also involves protein S (PS), and the endothelial receptors thrombomodulin (TM) and endothelial protein C receptor (EPCR). Conversion of PC to activated PC (APC) is generated by TM-bound thrombin and is drastically augmented by the presence of EPCR [145]. The presence of a soluble form of EPCR (sEPCR) that exists under normal conditions and which is elevated in conditions marked by enhanced inflammation [146], supports the notion of EPCR shedding. While the role of membrane EPCR is clearly antithrombotic and anti-inflammatory, the physiological significance of circulating sEPCR *in vivo* is as yet not fully understood and it is still unknown whether soluble EPCR levels may have a predictive value in the appearance of sepsis.

In previous studies, sEPCR levels in septic patients were found to be significantly higher [146, 147], unchanged [148], or even lower [149] than in healthy volunteers. A study by Kager *et al.* [150] showed that increased plasma sEPCR levels correlate with accelerated mortality in patients with melioidosis, while overexpression of EPCR in transgenic animals aggravates outcome during Gram-negative pneumonia-derived sepsis. In another recent report, early kinetics of sEPCR levels in severe sepsis was correlated with outcome [151], by a proposed mechanism of counteracting the anticoagulant action of membrane EPCR. The authors suggested that sEPCR could provide an early biological marker of outcome in severe sepsis. Vassiliou *et al.* [152] showed that levels of soluble EPCR at ICU admission are higher in originally nonseptic patients who subsequently become septic compared to those who will not.

2.4.4. Presepsin

Cluster of differentiation 14 (CD14) is a glycoprotein expressed on monocytes and macrophages, which serves as a receptor for lipopolysaccharides. As a pattern recognition molecule

it plays a role in the innate immune system by activating a pro-inflammatory signaling cascade upon contact with microorganisms [153]. During inflammation, protease activity releases soluble CD14 (sCD14) fragments, one of which has been identified as presepsin (sCD14-ST).

Presepsin was discovered as a new marker in Japan in 2002 [154], as a molecule whose levels were elevated specifically in the blood of patients with sepsis, and in the last few years has been extensively studied as a diagnostic and prognostic sepsis biomarker. In 2012, a multicenter prospective study investigated the clinical usefulness of presepsin for discriminating between bacterial and nonbacterial infections and compared it with PCT and IL-6 [155]. The study concluded that presepsin is useful for the diagnosis of sepsis and that it was superior to conventional markers and blood cultures. Ulla *et al.* [153] evaluated the diagnostic and prognostic value of presepsin in the emergency department and found that presepsin was useful in the early diagnosis of infection in a population of patients with SIRS, sepsis, severe sepsis, and septic shock. Moreover, presepsin exhibited a prognostic value, since its initial levels were correlated with mortality. In ICU patients, presepsin demonstrated diagnostic capacity in differentiating sepsis severity and prognostic value in mortality [156], while Masson *et al.* [157] found that presepsin measured on the first day in ICU in patients with severe sepsis or septic shock was higher in nonsurvivors compared to survivors, thus exhibiting useful prognostic importance. In 2015, three large meta-analyses concluded that presepsin has moderate diagnostic capacity for the detection of sepsis and it is an effective adjunct biomarker, but is insufficient to detect or rule out sepsis when used alone [158–160].

Since then, more studies have been performed, comparing presepsin to markers such as PCT and CRP. Results from these studies have shown that presepsin could differentiate between septic and nonseptic patients with comparable accuracy to CRP and PCT [161, 162], while presepsin and CRP showed similar performance for predicting 28-day mortality [161]. In patients with suspected sepsis, presepsin and PCT showed a good diagnostic accuracy in predicting bacteremia and bacterial DNAemia, superior to CRP [163]. In two very recent studies, presepsin seemed to be as valuable a biomarker as PCT or CRP in the evaluation of infectious complications in patients after heart transplantation [164], while another study concluded that the introduction of presepsin in clinical practice is not justified, since although it is a valuable biomarker for diagnosis of infection and sepsis, its diagnostic accuracy does not improve that of PCT [165].

Presepsin has been shown to be beneficial as a sepsis marker in adults. Nevertheless, very few data are available in neonates. Recent studies have shown that presepsin is significantly higher in preterm infants with early onset sepsis (EOS) compared with uninfected infants [166] and that it may be used as a reliable and accurate marker for both diagnosis and follow-up of EOS [167]. Pugni *et al.* [168] provided reference ranges for presepsin as an effective sepsis marker in neonates.

2.5. Lactate

Lactate is currently the most commonly used biomarker to identify sepsis. In the last years, several studies have emphasized the prognostic value of initial lactate levels or lactate

clearance [169, 170]. Lactate, apart from being the end product of anaerobic glycolysis reflecting tissue oxygen delivery-utilization, is also increased during stress and critical illness [171]. Elevated serum lactate levels are associated with poor outcomes in diverse populations of critically ill patients, such as multiple organ failure, morbidity, and mortality [172–175]. Clinically, serum lactate is a potentially useful biomarker to risk-stratify patients with severe sepsis presenting to the emergency department [170, 174, 175], so it has been hypothesized that early detection of elevated lactate levels may result in early identification of patients at risk of adverse outcomes [176]. In sepsis these elevated levels may be due to either impaired lactate clearance or excessive production [177, 178]. Two very recent studies [176, 179] utilized serum lactate levels at admission in order to diagnose sepsis in undifferentiated patients with suspected sepsis, emphasizing on the utility of early lactate measurement in such context, while Vassiliou *et al.* demonstrated that combining sE- and sP-selectin with serum lactate offers better prognostic value for sepsis development in initially nonseptic ICU patients [180].

Lactate kinetics has proved a valuable marker for response to resuscitative handlings in septic patients, associated with clinical outcome and mortality. Thus, according to the new sepsis-3 guidelines “patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg 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].

2.6. Biomarker panels

Since as yet no single accepted biomarker or combination of biomarkers can be clinically used to diagnose patients with suspected sepsis, the multi-marker or panel approach has been suggested to improve clinical utility. Many groups have studied such biomarker panels. Kofoed *et al.* [181] showed that combining data from several markers improves diagnostic accuracy in detecting bacterial versus nonbacterial causes of inflammation. Another study identified a panel of three different biomarkers that could assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis [182].

Another panel including both pro-inflammatory and anti-inflammatory markers, comprising IL-6, IL-8, and the anti-inflammatory cytokine IL-10 was associated with a worse outcome for patients with sepsis [183]. As mentioned earlier, high concentrations of TNF- α and IL-6 are predictive of organ failure and increased mortality [55, 57], but poor patient outcome is also associated with increased levels of the anti-inflammatory cytokine IL-10 [74]. This apparent paradox is explained by the proposal that infection induces an initial stage of systemic inflammation (SIRS), with elevated blood levels of pro-inflammatory cytokines (e.g., TNF- α and IL-1 β), that is followed by a compensatory anti-inflammatory response (CARS) defined by high circulating levels of anti-inflammatory cytokines (e.g., IL-10 and IL-13), and it is indeed the sustained overproduction of the anti-inflammatory cytokine IL-10 that is the main predictor of severity and fatal outcome [184].

Figure 1 summarizes all major biomarkers involved in the inflammatory response in sepsis.

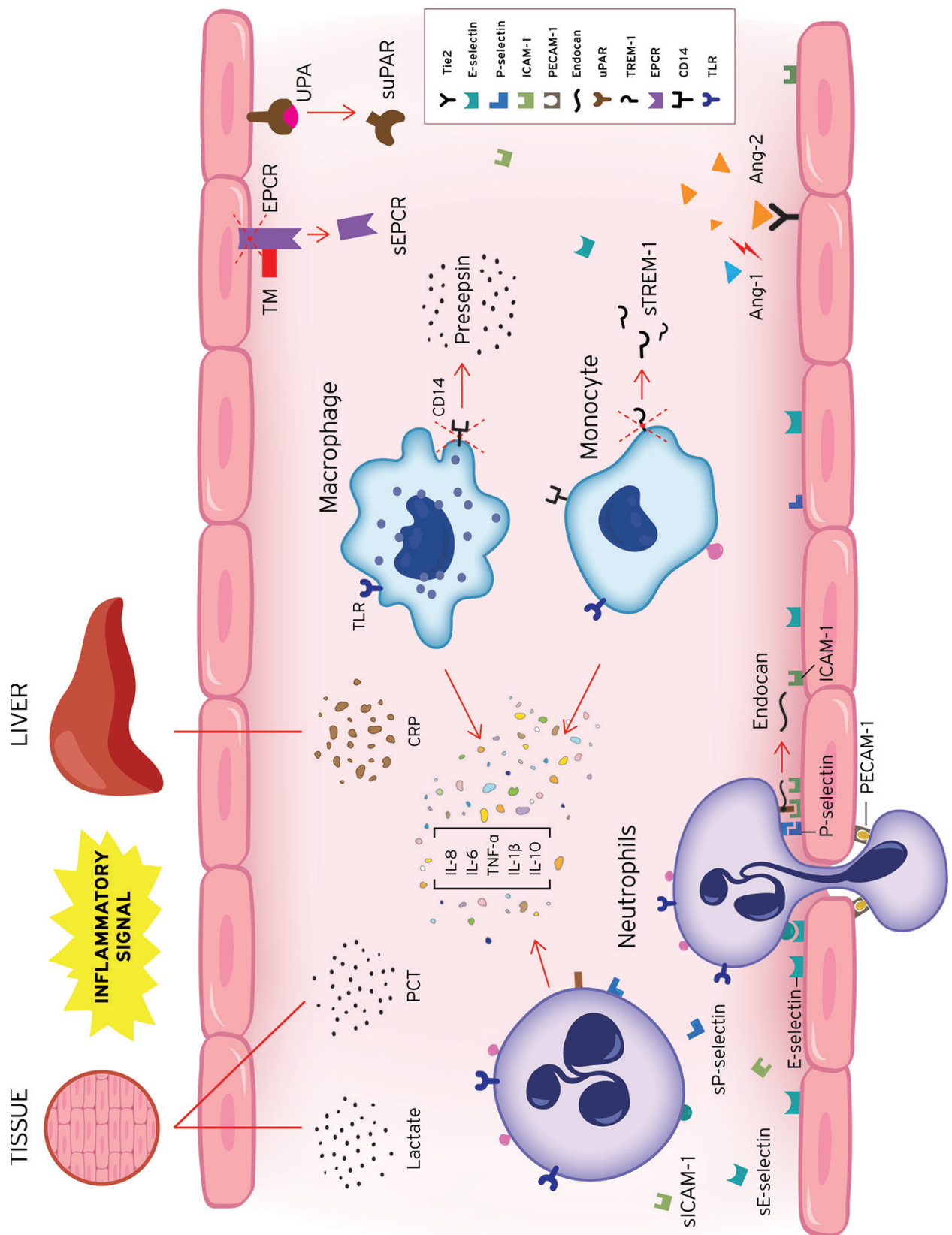


Figure 1. Major biomarkers in sepsis. During the inflammatory response a large number of cytokines, chemokines, and soluble molecules are secreted, affecting coagulation, endothelial activation and dysfunction, and vascular barrier permeability. The result is immune dysregulation and persistent immune suppression. The host immune response to sepsis includes activation of both pro- and anti-inflammatory stages and excessive activation of immune cells. Proteins, such as CRP and PCT are synthesized in the acute phase in response to infection and inflammation. The cells of the innate immune system release large amounts of pro- and anti-inflammatory cytokines, such as IL-1 β , IL-6, IL-8, TNF- α , and IL-10, during the hyper-inflammatory and immunosuppressive phase of the disease, respectively, from the very first instant of infection. The high levels of circulating cytokines can potentiate organ damage by endothelial injury and other routes. Ang-2 disrupts the protective effects of Ang-1-Tie2 signaling that maintains vessel integrity and inhibits vascular leakage. In critically ill patients, the release of Ang-2 directly reflects vascular barrier breakdown. Endothelial damage is associated with activation of neutrophils and expression of neutrophil and endothelial adhesion molecules. These molecules help localize leukocytes to the area of injury; however, before leaving the blood vessel, inflammatory molecules released by activated neutrophils can produce additional endothelial injury. Both the innate and adaptive immune responses depend on the migration of leukocytes across endothelial cells. The selectin family, including E-selectin and P-selectin, is an early mediator of the adhesion of activated neutrophils to endothelia in inflammatory states, before their firm adhesion and diapedesis at sites of tissue injury and inflammation. ICAM-1 controls the firm adhesion of neutrophils on endothelium and consequently transendothelial neutrophil migration response to sites of infection. PECAM-1 is a phosphoprotein highly expressed on endothelial cells and leukocytes, and comprises an important component in the regulation of neutrophil transendothelial migration. Endocan is a proteoglycan expressed and secreted by the vascular endothelium in response to pro-inflammatory cytokines and pro-angiogenic factors, and inhibits leukocyte migration. The soluble forms of these proteins have been found increased in the sera of septic patients. uPAR is a part of the plasminogen activation system, which is involved in tissue reorganization events. The soluble form of uPAR, suPAR, forms when UPA binds to uPAR, and its levels are increased in sepsis. TREM-1 is an inflammatory immunoglobulin superfamily member, which is expressed in neutrophils, monocytes, and macrophages. TREM-1 triggers and expands the inflammatory response, with promoted production of inflammatory mediators, inhibited expression of anti-inflammatory mediators, and activated and amplified inflammatory cascade. sTREM-1 is a subtype of secreted TREM-1, which has been shown to be released into the blood during infection. The protein C anticoagulant system also involves protein S, and the endothelial receptors TM and EPCR. Conversion of protein C to the anticoagulant APC is generated by TM-bound thrombin and is drastically augmented by the presence of EPCR. The presence of a soluble form of EPCR (sEPCR) is elevated in conditions marked by enhanced inflammation, of unknown physiological significance. CD14 is yet another glycoprotein expressed on monocytes and macrophages, and serves as a receptor for lipopolysaccharides. As a pattern recognition molecule it plays a role in the innate immune system by activating a pro-inflammatory signaling cascade upon contact with microorganisms. During inflammation, protease activity releases soluble CD14 (sCD14) fragments, one of which has been identified as presepsin. Other pattern recognition receptors involved in immunity are TLRs. Stimulation of TLRs by microbial components triggers expression of several genes that are involved in immune responses. Finally, lactate is also increased due to production by various tissues through aerobic and anaerobic glycolysis, and from a decreased lactate clearance. Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; APC, activated protein C; CD14, cluster of differentiation 14; CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; sEPCR, soluble endothelial protein C receptor; sICAM-1, soluble intercellular adhesion molecule-1; sPECAM-1, soluble platelet/endothelial cell adhesion molecule-1; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; suPAR, soluble urokinase-type plasminogen activator receptor; TM, thrombomodulin; TNF- α , tumor necrosis factor-alpha; TLR, Toll-like receptors; UPA, urokinase-type plasminogen activator.

3. Genetic polymorphisms in sepsis

The prospective of genetic biomarkers for prognostic use is well-known for mostly uncommon/rare inherited disorders, but is also emerging for sepsis [185, 186]. Most genes carry single-nucleotide polymorphisms (SNPs) at specific exonic or intronic regions.

In order to identify potential markers of susceptibility, severity, and clinical outcome, potential markers for survivors and nonsurvivors, and ultimately to identify targets for therapeutic intervention, gene polymorphisms have become the most widely used form of experimental study. In an attempt to deal with the limitations of these studies, such as small sample size and bias in selecting candidate polymorphisms and genes, genome-wide association studies (GWAS) are now emerging. GWAS concern large, well-conducted, multicenter studies that do not involve a prior hypothesis of candidate genes to test for association with disease.

3.1. Cell signaling pathways of the innate immune system

3.1.1. Pattern recognition receptors (PRR)

3.1.1.1. Toll-like receptors (TLRs)

Functional characterization of Toll-like receptors (TLRs) has established that innate immunity is an adept system that detects invasion of microbial pathogens. Stimulation of TLRs by microbial components triggers expression of several genes that are involved in immune responses [187]. TLR4 is an essential receptor for Gram-negative enteric LPS recognition [188, 189]. The Asp299Gly mutation in human TLR4 impairs LPS signaling in homozygous and heterozygous individuals [190], while Smirnova *et al.* [191] observed that rare heterozygous missense mutations of TLR4 contribute to the development of systemic meningococcal disease. The D299G allele of the *TLR4* gene has also been associated with increased susceptibility to severe bacterial infections and Gram-negative sepsis [192, 193].

3.1.2. Cellular innate immune response

3.1.2.1. IL-8

The 251A/T allele (rs4073) of the *IL-8* gene has been studied for its implication in sepsis and outcomes. Results until now have shown association of the allele with higher plasma IL-8 levels, as well as with survival [194]. The A allele has been suggested to be associated with protection against sepsis [195], and also with increased risk of sepsis [196]. The heterozygote AT genotype has been associated with increased risk of developing severe sepsis [197]. In a more recent study, the male population carrying the homozygote TT genotype was found to be more susceptible to sepsis, while no association was determined between the 251A/T allele and IL-8 serum levels in septic patients [198].

3.2. Adaptive immune response

3.2.1. Cytokines

3.2.1.1. Tumor necrosis factor- α promoter polymorphisms

Initially, the G-to-A polymorphism at position 308nt in the promoter region of the *TNF- α* gene was found to be associated with adverse outcome in patients with severe sepsis and septic shock [199, 200]. A large meta-analysis [201] concluded that the polymorphism is associated with sepsis, but is not associated with sepsis mortality. However, several studies later were not able to show association of *TNF- α* -308 SNP and development of sepsis [202, 203].

3.2.1.2. *IL-6* polymorphisms

A key inflammatory cytokine that has been examined in genetic association studies in infectious diseases is , producing also conflicting results. First of all, studies on the C allele of the G/C polymorphism at position 174nt of the *IL-6* gene have shown its association with both high and low plasma *IL-6* levels [204, 205], or even no association at all [206]. One study in critically ill patients did not find association between the 174 G/C polymorphism and sepsis appearance, but associated the polymorphism with improved survival rates in patients with sepsis [207]. A different study reported that the same polymorphism was not associated with survival [208]. A meta-analysis on the position 174nt polymorphism and the risk of sepsis in very low birth weight infants concluded that the available data are not consistent with more than a modest association between the *IL-6* polymorphism and neonatal sepsis [209].

3.3. Systemic effectors of inflammation and coagulation

3.3.1. Angiotensin-converting enzyme (ACE)

Studies have compared the effects of the angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) polymorphisms on the incidence and outcome of sepsis and acute respiratory distress syndrome (ARDS). In ventilated low birth weight infants the *ACE* insertion/deletion (I/D) polymorphism does not have a significant effect on the incidence or outcome of sepsis [210, 211]. Studies and meta-analyses showed that carriers of I allele (D/I genotype and I/I genotype) were at increased sepsis risk [212–214], but the polymorphism is not associated with outcome in critically ill septic patients [214, 215]. With regard to ARDS, the data of Villar *et al.* [216] do not support an association of the *ACE* gene I/D polymorphism with susceptibility or mortality in severe sepsis or with sepsis-induced ARDS in Spanish patients, but Cardinal-Fernandez *et al.* demonstrated that the presence of the allele D of the *ACE* gene is associated with ARDS in patients with severe sepsis [217].

3.3.2. Endothelial protein C receptor (EPCR)

A few studies have compared the effects of the *EPCR* haplotypes on the incidence and outcome of sepsis. Two studies have shown that *EPCR* mutations and polymorphisms influence the risk of severe sepsis in children and adults [218, 219]. More specifically, the rare 23-bp insertion is significantly more common among patients with severe sepsis [218], while simultaneous carriers of minor alleles belonging to both the H1 and H3 haplotypes may be at reduced risk of developing severe sepsis and/or septic shock among critically ill patients [219].

Table 1 lists the role of major circulating biomarkers and genetic polymorphisms in the prognosis and diagnosis of sepsis.

Biomarker	Diagnostic significance	Prognostic significance
C-reactive protein (CRP)	<ul style="list-style-type: none"> - Discriminates bacterial and viral infections [14] - Measurement of CRP is an indicator of sepsis [15–19] 	<ul style="list-style-type: none"> - CRP is a valuable marker for the disease severity [15, 20] - Elevated concentrations of serum CRP on admission have been associated with increased risk of organ failure and mortality [21, 22]
Procalcitonin (PCT)	<ul style="list-style-type: none"> - PCT is important in the detection and differential diagnosis of inflammatory states [26]. The highest levels of PCT are achieved in acute bacterial infections and sepsis - PCT is a good biological diagnostic marker for sepsis, severe sepsis, or septic shock [34] - PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients [36] - Serial PCT concentrations may have value in monitoring sepsis outcomes [28, 29] 	<ul style="list-style-type: none"> - PCT nonclearance is a prognostic factor of death in patients with sepsis [33] - Significant difference between PCT levels as early as day 1 between survivors and nonsurvivors among septic patients [37]
Tumor necrosis factor- α (TNF- α)	<ul style="list-style-type: none"> - Levels of TNF-α are frequently increased in sepsis [49, 56] 	<ul style="list-style-type: none"> - High concentrations of TNF-α are predictive of organ failure and increased mortality in septic patients [55]
Interleukin-1 β (IL-1 β)	<ul style="list-style-type: none"> - Levels of IL-1β are frequently increased in sepsis [56] 	
Interleukin-6 (IL-6)	<ul style="list-style-type: none"> - Levels of IL-6 are frequently increased in sepsis [50, 54, 56] - IL-6 levels are increased in patients with infectious complications and have been used to differentiate systemic inflammatory response syndrome (SIRS) from sepsis [58] 	<ul style="list-style-type: none"> - High concentrations of IL-6 are predictive of organ failure and increased mortality in septic patients [57, 59]

Biomarker	Diagnostic significance	Prognostic significance
Interleukin-8 (IL-8)	- Levels of IL-8 are frequently increased in sepsis [50, 56]	- IL-8 has been used to predict the severity of sepsis in pediatric patients, although the use of IL-8 has not been confirmed in adults [60, 61]
Interleukin-27 (IL-27)	- Useful biomarker in estimating risk of bacterial infection among critically ill pediatric and adult patients [67–70] - In combination with PCT, IL-27 may improve classification of critically ill adults with sepsis [68, 71]	
Interleukin-10 (IL-10)		- Poor patient outcome has been associated with increased blood levels of the anti-inflammatory cytokine IL-10 [74]
Angiopietin-1 (Ang-1)	- Decreased levels in critically ill septic or nonseptic patients compared to healthy controls [94]	- Decreased levels of Ang-1 at ICU admission are correlated with higher mortality [97]
Angiopietin-2 (Ang-2)	- Ang-2 levels are higher in patients with severe sepsis compared to patients with or without SIRS or sepsis [89–91]	- Increased Ang-2 plasma levels have been associated with worst clinical outcome in patients with major trauma and severe sepsis or shock [92–94] - Increased Ang-2 plasma in nonsurvivors compared to survivors [95, 96]
Selectins	- Soluble E-selectin concentration increases in various inflammatory pathologies [99–102]	- Higher sE-selectin levels in nonsurvivors than survivors [103, 104] - sE-selectin levels may be used as predictor of fatal outcome in patients with SIRS [105] - sE-selectin has also been proposed as a predictor of bacteremia in severe sepsis patients [106] High levels of sE- and sP-selectin at ICU admission, are associated with sepsis development in time [109]
Soluble intercellular adhesion molecule-1 (sICAM-1)	- sICAM-1 production has been shown to be related to increased sepsis severity [102, 111] - sICAM-1 appears to be a reliable biomarker for classifying patients with infectious SIRS, i.e., sepsis, from those with noninfectious SIRS [105]	- sICAM-1 concentration has been shown to be related to increased mortality [111, 112]
Soluble platelet/endothelial cell adhesion molecule-1 (sPECAM-1)	- sPECAM-1 is higher at admission in septic patients compared with nonseptic patients and healthy controls [114, 115]	
Endocan	- Exhibits higher concentrations in septic patients compared to healthy volunteers [117]	- A strong and significant predictor of sepsis severity and outcome [118–122]

Biomarker	Diagnostic significance	Prognostic significance
Soluble urokinase-type plasminogen activator receptor (suPAR)	<ul style="list-style-type: none"> - Elevated suPAR in conditions of SIRS, bacteremia, sepsis, and septic shock [124–127] - Diagnostic value of suPAR for identifying sepsis is limited [128] 	<ul style="list-style-type: none"> - High circulating suPAR levels indicate an unfavorable prognosis, including organ dysfunction and mortality [124–127] - In patients with bacteremia, suPAR may be used to identify severely ill patients and predict mortality [131, 133]
Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)	<ul style="list-style-type: none"> - Moderate diagnostic performance in differentiating sepsis from SIRS [140] - sTREM-1 represents a reliable biological marker of bacterial infection [143] 	<ul style="list-style-type: none"> - Moderate prognostic significance in assessing the mortality of infection in adult patients and sTREM-1 alone is insufficient to predict mortality as a biomarker [142]
Soluble endothelial protein C receptor (sEPCR)	<ul style="list-style-type: none"> - sEPCR levels in septic patients have been found to be significantly higher [146, 147], unchanged [148], or lower [149] than in healthy volunteers 	<ul style="list-style-type: none"> - sEPCR levels correlated with worst outcomes; has been suggested that it may act as a biological marker of outcome in severe sepsis [150–152] - Levels of sEPCR at ICU admission are higher in originally nonseptic patients who subsequently become septic compared to those who will not [152]
Presepsin	<ul style="list-style-type: none"> - Discriminates between bacterial and nonbacterial infections [155] - Early diagnosis of infection in a population of patients with SIRS, sepsis, severe sepsis, and septic shock [153] - In patients with suspected severe sepsis and septic shock, presepsin reveals valuable diagnostic capacity to differentiate sepsis severity [156] - Presepsin can differentiate between septic and nonseptic patients with comparable accuracy to CRP and PCT [161, 162] 	<ul style="list-style-type: none"> - Initial values significantly correlated with in-hospital mortality of patients affected by sepsis, severe sepsis, or septic shock [156] - Presepsin reveals prognostic value with respect to 30 days and 6 months all-cause mortality throughout the first week of ICU treatment [153] - Presepsin measured on the first day in ICU in patients with severe sepsis or septic shock was higher in nonsurvivors compared to survivors [157]
Lactate	<ul style="list-style-type: none"> - Elevated serum lactate levels in sepsis [177, 178] - Early serum lactate levels can diagnose sepsis in undifferentiated patients with suspected sepsis [176, 179] 	<ul style="list-style-type: none"> - Elevated serum lactate levels are associated with poor outcomes in diverse populations of critically ill patients, such as multiple organ failure, morbidity, and mortality [172–175] - Serum lactate is a potentially useful biomarker to risk-stratify patients with severe sepsis presenting to the emergency department [170, 174, 175]

Biomarker	Diagnostic significance	Prognostic significance
		- Combining sE- and sP-selectin with serum lactate offers better prognostic value for sepsis development in initially nonseptic ICU patients [180]
Genetic polymorphisms	- Distinguish patients with sepsis from patients with sterile inflammation	- Predict long-term outcomes and identify patients who will be at risk for developing adverse clinical outcomes
Toll-like receptors (TLRs)		- D299G allele of <i>TLR4</i> gene associated with increased susceptibility to severe bacterial infections and Gram-negative sepsis [192, 193]
<i>IL-8</i>		- The 251A/T allele has been associated with survival [194], protection against sepsis [195], and also increased risk of sepsis [196]
		- The heterozygote AT genotype has been associated with increased risk of developing sepsis [197]
		- Male T allele carriers are more susceptible to sepsis [198]
<i>TNF-α</i>	- G-to-A polymorphism associated with sepsis [201]	- G-to-A polymorphism associated with adverse outcomes in patients with severe sepsis and septic shock [199, 200]
	- No association of G-to-A polymorphism and development of sepsis [202, 203]	- G-to-A polymorphism not associated with sepsis mortality [201]
<i>IL-6</i>	- 174 G/C polymorphism showed modest association with neonatal sepsis [209]	- 174 G/C polymorphism was associated with improved survival rates in patients with sepsis [207]
		- 174 G/C polymorphism was not associated with a difference in survival [208]
Angiotensin-converting enzyme (<i>ACE</i>)		- Insertion/deletion (I/D) polymorphism does not have an effect on the incidence or outcome of sepsis in ventilated low birth infants [210, 211]
		- Carriers of the I allele at increased sepsis risk [212–214]
		- I polymorphism not associated with outcome in critically ill septic patients [214–216]
		- The presence of the D allele is associated with ARDS in patients with severe sepsis [217]

Biomarker	Diagnostic significance	Prognostic significance
Endothelial protein C receptor (<i>EPCR</i>)	- The rare 23-bp insertion is significantly more common among patients with severe sepsis [218]	- Influences the risk of severe sepsis in children and adults [218, 219] - Simultaneous carriers of minor alleles belonging to both the H1 and H3 haplotypes may be at reduced risk of developing severe sepsis and/or septic shock among critically ill patients [219]

Table 1. Role of major circulating biomarkers and genetic polymorphisms in sepsis. Please note that the protein names are capitalized, whereas gene names are capitalized and italicized.

4. Conclusion

Unfortunately, a lot of work remains to find the right combination of markers to be used in clinical practice. Some have been effective in reducing mortality, but their use in diagnosis and prognosis of sepsis has been limited. It seems that a panel of diverse biomarkers rather than a group of two or three related biomarkers will be more efficient in clinical practice.

Genome-wide association studies may help confirm current findings and make them clinically applicable. Hence, developing high-throughput approaches for the analysis of alternative mechanisms by which SNPs can cause disease will be one of the remaining challenges for genomic research. Hopefully, the findings that will be generated will facilitate the successful use of modern molecular diagnostics and could enable rapid identification of particularly susceptible or less susceptible individuals, leading to tailored therapeutic approaches.

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