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Biomarkers of Sepsis

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Sepsis remains a leading cause of death in critically ill patients, despite efforts to improve patient outcome. Thus far, no magic drugs exist for severe sepsis and septic shock. Instead, early diagnosis and prompt initial management such as early goal-directed therapy are key to improve sepsis outcome. For early detection of sepsis, biological markers (biomarkers) can help clinicians to distinguish infection from host response to inflammation. Ideally, biomarkers can be used for risk stratification, diagnosis, monitoring of treatment responses, and outcome prediction. More than 170 biomarkers have been identified as useful for evaluating sepsis, including C-reactive protein, procalcitonin, various cytokines, and cell surface markers. Recently, studies have reported on the usefulness of biomarker-guided antibiotic stewardships. However, the other side of these numerous biomarkers is that no novel single laboratory marker can diagnose, predict, and track the treatment of sepsis. The purpose of this review is to summarize several key biomarkers from recent sepsis studies.

Key Words: Biomarkers; Cytokines; Diagnosis; Outcome; Prognosis; Sepsis

Introduction

1. Sepsis: Where are we now?

Severe sepsis and septic shock are leading causes of death, representing 30–50% of hospital-reported mortality [1]. Sepsis treatment outcomes are disappointing, despite a long history of interventions, such as numerous antibiotics including penicillin, efforts to follow guidelines from the Surviving Sepsis Campaign (SSC), and development of supportive modalities for organ dysfunctions accompanying sepsis (e.g., dialysis, ventilators, extracorporeal membrane oxygenation). We have seen the rise and fall of recombinant human activated protein C (drotrecogin alfa) for the treatment of severe sepsis, while the disappointing results might be explained by statistical insignificance stemming from the relatively lower mortality rate (25%) in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study [2, 3]. In addition to activated protein C, treatments with agents such as toll-like receptor (TLR) 4-blocker (eritoran) and human recombinant lactoferrin (talactoferrin) are also viewed with skepticism [4-6]. Failure of these treatments in clinical trials might be predictable for several reasons. Sepsis is the result of a complex chain of events composed of innate and adaptive immune responses, including activation of the complement system, coagulation cas-

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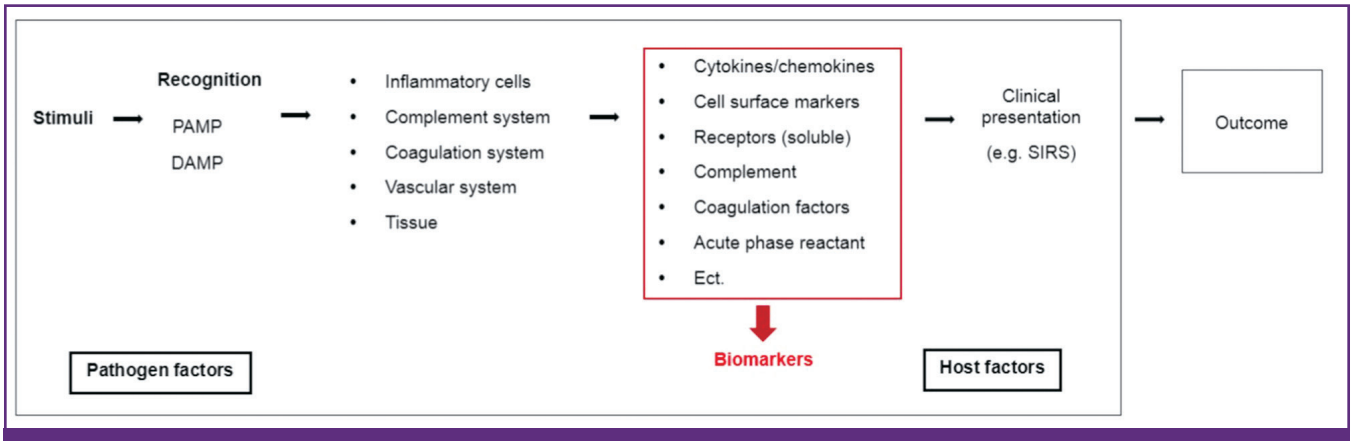

Figure 1. Systemic responses to sepsis and possible biomarkers. Systemic response to sepsis results from multiple changes to the inflammatory, coagulatory, and vascular systems. Candidate biomarkers include proteins such as cytokines, soluble receptors, and acute phase reactants.
DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; SIRS, systemic inflammatory response syndrome.

cades, and the vascular endothelial system (Fig. 1). Such complexity makes it difficult for new drugs targeting a single immunological event to improve sepsis outcome. In addition, immune responses are based on individual patient factors including age, underlying diseases, nutritional state, and even genetic variability. For this reason, treatments, especially immunotherapy, have to be individualized. Furthermore, pathogen factors also vary by patient. Given that adjunctive therapy for sepsis has shown disappointing results, conventional management is of immediate importance in the real world. Practically, "bundled care" for sepsis, with early administration of appropriate antibiotics and supportive care based on SSC guidelines, improves outcome [7, 8]. This emphasizes the necessity for early and accurate detection of sepsis. However, a definite microbiological diagnosis cannot be made in approximately one-third of patients with clinical manifestations of sepsis [9, 10]. For this reason, good biomarkers can guide the early diagnosis and management of sepsis. Here, we discuss sepsis biomarkers and directions for future research.

2. Pathophysiology of sepsis

Sepsis is the result of host response to infection by microbial pathogens, meaning that antimicrobial agents are insufficient for treatment of this infectious disease. In 1904, William Osler noted, "It appears that patients are dying not from their infections but rather their reaction to them." Sepsis has traditionally been considered as a result of uncontrolled inflammatory response, a "cytokine storm" that results in shock or organ dysfunction [11]. More than 30 clinical trials have focused on blocking these inflammatory cascades, such as steroids, tumor necrosis factor (TNF)-α antagonist, and anti-endotoxin. However, the paradigm of sepsis understanding and treatment has shifted toward its immunosuppressive effects [12]. For example, elderly patients with sepsis are lack of fever and other immune responses, that are associated with poor prognosis. Such immunosuppression is now considered a key pathogenesis associated with sepsis mortality. Immunosuppressed conditions lead to secondary infections due to nosocomial pathogens such as *Acinetobacter, Enterococcus, Stenotrophomonas*, or *Candida* species, which could worsen outcome. In addition, several clinical trials have shown that immune-enhancing therapies such as recombinant human interleukin (IL)-7 and granulocyte-macrophage colony-stimulating factor may have beneficial effects [13, 14]. Immunosuppression in sepsis has been also identified in post-mortem studies of patients who died of sepsis [11, 15]. There was a marked decrease in lipopolysaccharide (LPS)-stimulated cy-

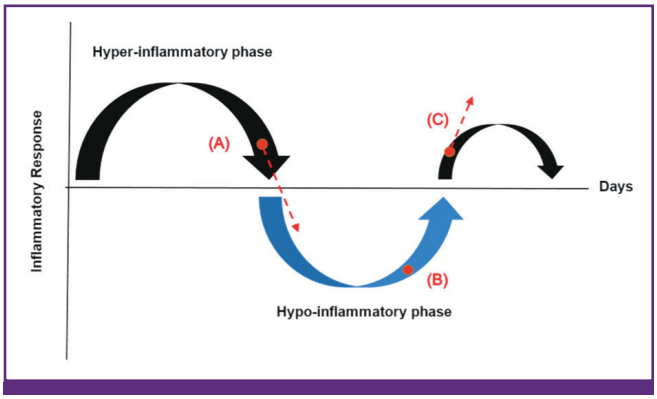

Figure 2. Inflammatory response to sepsis. Immune response to sepsis is both proinflammatory and anti-inflammatory. An initial hyper-inflammatory phase is followed by a hypo-inflammatory (immunosuppressive) phase. Immunosuppression in sepsis contributes to increased mortality in elderly patients. Ideally, good biomarkers can reflect the hyper- (A) or hypo-inflammatory (B) status and the direction of inflammatory response (A or C).

tokine secretion of mediators including TNF, interferon-γ, IL-6, and IL-10 in splenocytes from patients diagnosed with sepsis. In addition, immune effector cells, including clusters of differentiation (CD) 4, CD8 cells, and human leukocyte antigen-DR were significantly decreased in splenic tissue of patients dying of sepsis compared to control patients [15]. Early hyper-inflammatory and late compensatory anti-inflammatory response syndromes are included in current immunological models of sepsis (Fig. 2). However, this is not a simple biphasic model in many cases. The degree and duration of immune response differs from patient to patient according to age, underlying physical state, comorbidities, pathogen virulence, pathogen burden, and genetic factors. These cycles may repeat, with waxing and waning of clinical symptoms. During the course of sepsis, the duration and degree of immunosuppression could affect the outcome, which leads us to consider tailored immunomodulatory therapy.

Biomarkers of sepsis

An ideal biomarker can be objectively measured and reflects normal biological and pathogenic processes as well as responses to therapeutic interventions [16]. Many trials have identified potential biomarkers. More than 170 biomarkers have been studied for use in evaluation of sepsis [17]. Development of sepsis changes the expression and activity of thousands of endogenous mediators of inflammation, coagulation, and intermediary metabolism [18, 19]. Even when biomarkers start at equal values, the effect of inflammatory responses can cause these values to change in opposite directions (Fig. 2). While early diagnosis is helpful, biphasic or repeated biphasic models of sepsis make it difficult to predict mortality and prognosis based on initial biomarker levels. Nevertheless, the ideal biomarkers could play a role in sepsis screening, early diagnosis, risk stratification, critical assessment, and prognosis prediction [19, 20], which can improve outcomes (Table 1). This review will discuss the major measurable sepsis biomarkers that have been proposed for clinical use.

Table 1. Characteristics of ideal sepsis biomarkers

Role of biomarkers
Screening patients at risk of sepsis
Establish early diagnosis that helps the initial management of sepsis
Risk stratification to identify patients at risk of poor outcome
Monitoring the response of intervention
Predict outcomes
Requisites for useful biomarkers
Objectively measured
Have reference standard
Reproducibility of test
Have well-known kinetics
Cost-effectiveness
Reflect normal biologic process, pathologic process or pharmacologic response to therapy

1. Markers for early response to sepsis

The traditional sepsis model is the immune response activated when TLR expressed on the macrophage recognizes LPS in cell walls of gram-negative bacteria. This is an example of pattern recognition receptors (PRR) and pathogen-associated molecular patterns (PAMP). This recognition stimulates secretion of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6. Various inflammatory cytokines and LPS have therefore been studied as sepsis biomarkers.

1) Cytokines and chemokines

TNF-α, IL-1β, and IL-6 are cytokines responsible for mediation of the initial innate immune system response to injury or infection. These proinflammatory cytokines contribute to fever, activate endothelial cells, attract circulating polymorphonuclear cells (PMNs), and enter the circulatory system. Studies have demonstrated increased blood cytokine levels in patients with sepsis. However, levels of these cytokines also increase after trauma, surgery, stroke, or with autoimmune diseases. Use of these inflammatory cytokines to diagnosis sepsis is difficult because they are nonspecific and unable to differentiate infection from inflammation. TNF-α and IL-6 levels have been reported to be related to organ damage and mortality, making them potentially useful prognosis predictors [21-23]. However, a clinical trial of pretreatment with polyclonal ovine anti-TNF fragment antigen binding fragments (CytoFab) showed no difference in 28-day mortality [24, 25]. The conflicting reports could be explained by the short half-life (the half-life of TNF, for example, is 17 minutes) and earlier peak concentration of proinflammatory cytokines than other biomarkers. IL-1β levels are not elevated to the same degree as TNF. Therefore, neither TNF nor IL-1β has proven to be useful as major biomarkers of sepsis. It is difficult to translate certain clinical condition into particular cytokine profile [26], which could be caused by and is the result of complex inflammatory responses. Recent studies have proposed that measurement of multiple cytokines correlates well with disease severity and prognosis [26-28]. Combined biomarkers will be addressed later.

2) Lipopolysaccharide-binding protein

LPS-binding protein (LBP), mainly synthesized in the liver, is a polypeptide that binds LPS. The LPS-LBP complex initiates signal transduction according to LBP level. This complex complex has a dual action, enhancing and inhibiting LPS signaling at low and higher levels, respectively [29]. Serum LBP level increases several-fold in sepsis, making it useful for diagnosis [30, 31]. It may also be effective as a predictive marker for disease severity and outcome [32, 33]. However, LPS and LBP levels are affected by administration of antibiotics and generally do not correlate to the clinical course of sepsis [34]. Therefore, it is of limited use as a sepsis biomarker.

2. Markers for late response to sepsis

TNF-α and IL-1β are released within minutes of exposure to LPS. In the late 1990s, investigators found that LPS-treated mice died after serum TNF-α and IL-1β returned to basal levels, suggesting that mediators other than TNF-α might contribute to death. There are two well-known inflammatory mediators, high-mobility group box 1 (HMGB1) protein and macrophage migration inhibitory factor (MIF), which are important in late phase of severe infections.

1) High-mobility group box 1 protein

HMGB1 is a cytoplasmic and nuclear protein that is undetectable in healthy subjects. It is released by activated monocytes or necrotic tissues during infection or injury. This proinflammatory cytokine reaches detectable levels after 8–12 hours and plateaus after 18–32 hours. Plasma HMGB1 concentration has been shown to increase in patients with severe sepsis and septic shock and is correlated with the degree of organ failure [35, 36]. In a prospective study, HMGB1 measurements on day 3 discriminated survivors from non-survivors with a sensitivity and specificity of 66% and 67%, respectively. HMGB1 levels greater than 4 ng/mL on day 3 were associated with a 5.5-fold increased risk of death (95% confidence interval [CI]: 1.3–23.6) [37].

2) Macrophage migration inhibitory factor

The other "late" proinflammatory molecule, MIF normally circulates at low levels of 2–10 ng/mL [38]. Plasma MIF concentration increases during infection and very high levels have been found in cases with severe sepsis and septic shock [39]. A recent study concluded that high MIF levels serve as an early indicator of poor outcome in sepsis [40]. These results imply that late mediators such as HMGB1 and MIF could predict sepsis prognosis.

3. C-reactive protein

Tillet & Francis first discovered C-reactive protein (CRP) in a patient with lobar pneumonia in 1930. It was identified as a protein responsible for precipitating C polysaccharide during the acute phase of *Streptococcus pneumonia* infection [41]. CRP was also found in patients with endocarditis or rheumatic fever. Its response is stronger in acutely ill patients; levels decrease as patients recover. These characteristics make CRP a member of the class of acute-phase reactants. CRP is an old biomarker used most commonly in clinical settings. It is a nonspecific marker of inflammation that also increases after surgery, burns, myocardial infarctions, and rheumatic diseases [42]. The sensitivity and specificity of CRP as a marker for bacterial infections are 68–92% and 40–67%, respectively [43-46]. Its low specificity and inability to differentiate bacterial infections from noninfectious causes of inflammation makes CRP of limited diagnostic value. However, CRP shows promise for evaluating sepsis severity and prognosis. CRP plasma levels have been shown to correlate with the severity of infection [47]. A rapid decrease in CRP levels has been reported to correlate with good response to initial antimicrobial therapy in septic patients [48]. CRP is a useful biomarker to monitor treatment response. However, hasty interpretation or antibiotic guidance within 1–2 days after starting empirical antibiotic treatment is problematic in many clinical situations. Clinicians cannot interpret changes in CRP levels without considering the kinetics of this marker.

4. Procalcitonin

Procalcitonin (PCT) is a precursor of calcitonin, a calcium regulatory hormone secreted from thyroid tissue in healthy individuals. In infectious conditions, PCT is released from nearly all tissues including lung, liver, kidney, pancreas, spleen, colon, and adipose tissues. In 1993, PCT was first described as a marker elevated in bacterial infections [49]. In 2008, PCT was proposed as an adjunctive diagnostic marker to differentiate acute bacterial infection from other inflammatory states by the American College of Critical Care Medicine and the Infectious Diseases Society of America [50]. In a systematic review and meta-analysis, PCT was found to be more specific (specificity 81% [95% CI: 67–90%]) than CRP (67% [95% CI: 56–77%]) for differentiating bacterial infection among hospitalized patients [46]. The cutoff median PCT value in this meta-analysis was 1.1 ng/mL (interquartile range: 0.5–2.0 ng/mL). PCT cutoffs for diagnosis of sepsis or guidance of antibiotic choice have not yet been fully determined; the sensitivity and specificity of this marker for diagnosis of sepsis are affect-

ed by different cutoff values. PCT values need to be further evaluated according to different sites of infection, hosts, and pathogens. Another recent meta-analysis showed that PCT is a useful marker for early diagnosis of sepsis in critically ill patients, with sensitivity and specificity of 77% (95% CI: 72–81%) and 79% (95% CI: 74–84%), respectively [51]. PCT levels are also elevated after surgery, cardiogenic shock, heat shock, acute graft-versus-host disease, and immunotherapy such as granulocyte transfusion, which could limit its usefulness as a sepsis biomarker [52, 53]. PCT has also drawn attention because it can be used for guidance of antibiotic stewardship to reduce inappropriate use of antibiotics [54]. However, many experts recommend that PCT-guided decision-making should be an adjunctive method based on consideration of the patient's clinical course.

5. Lactate

Serum lactate levels can reflect tissue hypoperfusion and anaerobic metabolism in severe sepsis and septic shock. At a cellular level, energy production depends on glucose and oxygen metabolism. Glycolysis converts glucose to pyruvate and yields 2 adenosine triphosphates (ATPs). Pyruvate then enters the Krebs cycle, which produces more ATPs. However, in hypoxic circumstances, pyruvate is instead converted to lactate. Elevated lactate levels and lactate-to-pyruvate ratios result mostly from increased glycolysis and lactate production as well as limited tissue oxygenation. Elevated levels are also related to impaired hepatic lactate clearance and mitochondrial dysfunction [20]. Several studies have demonstrated that elevated lactate levels are related to mortality in patients with sepsis [55-58]. In a retrospective study of critically ill patients, serum lactate levels greater than 2 mmol/L on admission were associated with a 1.94–10.89-fold increased mortality compared to levels below 2 mmol/L [59]. In a large study of 1,278 patients with infections, those with lactate levels above 4 mmol/L had higher in-hospital mortality rates than patients with lactate levels less than 2.5 mmol/L (28.4% vs. 4.9%) [57]. Another study has reported that sustained hyperlactatemia is predictive of in-hospital mortality [60]. In contrast, however, early lactate clearance was associated with improved outcomes in patients with severe sepsis and septic shock [61]. A recent systematic review further confirmed the utility of monitoring serial blood lactate and its value as a predictive marker of in-hospital mortality [58]. Recently, data from a retrospective study by the Vasopressin Septic Shock Trial and a single-center septic shock cohort (St. Paul's Hospital cohort) have suggested that even minimal increases in arterial lactate concentration within the reference range (1.4–2.3 mmol/L) may predict 28-day mortality (sensitivity and specificity of 86% and 27%, respectively). Furthermore, the data suggested that patients with lactate levels below 1.4 mmol/L might benefit from vasopressin infusion [56]. Therefore, lactate screening and monitoring may be a valuable tool for risk stratification and to predict sepsis outcome.

6. Mid-regional proadrenomedullin

Like PCT, proadrenomedullin (proADM) is a kind of "hormokine" that encompasses the cytokine-like behavior of hormones during inflammation and infections. Adrenomedullin (ADM) is a 52-amino-acid peptide produced by the adrenal medulla. ADM is produced during physiological stress and has various functions including vasodilation and anti-inflammatory and antimicrobial effects [62]. Plasma ADM concentration and ADM gene expression increases in patients with sepsis [63]. However, ADM is rapidly cleared from the circulation, making measurements unreliable. Therefore, instead of ADM, serum quantification of the mid-regional fragment of proADM has been studied. Recent clinical data have shown that circulating mid-regional proADM levels are significantly higher in patients with sepsis than in patients with systemic inflammatory response syndrome (SIRS) [64]. A recent study of febrile patients with hematologic malignancies reported that proADM could predict localized bacterial infections and differentiate sepsis from SIRS [65]. In addition, proADM is responsible for hypotension associated with severe sepsis, which has been proposed as a good marker for risk assessment and predicting sepsis prognosis [64, 66]. If further data support these findings on the predictive value of proADM, it could be useful as both a prognostic marker and a diagnostic marker for early stages of localized infections.

7. Cell surface markers and soluble receptors

1) CD64

CD64 is a membrane glycoprotein with increased expression in patients with bacterial infections. CD64 expression increases hours after activation of innate immunity; it is not expressed by PMN in healthy individuals. Therefore, CD64 expression can reflect very early stages of infection and help to both make early diagnosis and predict prognosis. The CD64 index has been suggested to be predictive of positive bacterial cultures and a useful test for management of sepsis and other significant bacterial infections [67]. Another study demonstrated that the CD64 index is higher in febrile adult patients

with bacterial infections, with a sensitivity of 87% (95% CI: 79–92%), and that high CD64 expression is related to survival [68]. In contrast, it has been reported that CD64 indices greater than 2.2 are specific (89% specificity [95% CI: 83–94%]) but less sensitive (63% sensitivity [95% CI: 55–71%]) to predict bacterial infections in critically ill patients [69]. A systematic review and meta-analysis concluded that CD64 could be a marker for bacterial infection with a pooled sensitivity and specificity of 79% (95% CI: 70–86%) and 91% (95% CI: 85–95%), respectively. However, because published studies have low methodological quality, further studies are needed to verify these findings [70].

2) Soluble triggering receptor expressed on myeloid cells 1

Soluble triggering receptor expressed on myeloid cell 1 (sTREM-1) is a soluble form of TREM-1, a glycopeptide receptor expressed on the surface of myeloid cells such as PMNs, mature monocytes, and macrophages. TREM-1 expression increases in bacterial or fungal infections [71-73]. A prospective study by Gibot et al. suggested that the sensitivity and specificity of sTREM-1 for diagnosis of sepsis are comparable to that of CRP and PCT [74, 75]. A meta-analysis reported that the sensitivity and specificity of sTREM-1 to diagnose bacterial infections were 82% (95% CI: 68–90%) and 86% (95% CI: 77–91%), respectively [76]. Another recent meta-analysis showed that plasma sTREM-1 had only moderate diagnostic performance to differentiate sepsis from SIRS [77]. A prospective study at a single center in Korea reported that sTREM-1 levels on admission were independently significant for survival in patients with severe sepsis [78]. In addition, rapid decrease of sTREM-1 is correlated with better outcome [72]. Therefore, sTREM-1 may be useful for sepsis diagnosis or predicting sepsis prognosis. The usefulness of sTREM-1 as a biomarker requires further evaluation in clinical settings either measured alone or combined with other biomarkers.

3) Soluble urokinase plasminogen activator receptor

First described in 1990, urokinase plasminogen activator receptor (uPAR) is a surface signaling receptor expressed on most leukocytes [79]. uPAR was originally thought to assist directional invasion of migrating cells, but is now known to be involved in multiple immunological functions including cellular adhesion, differentiation, proliferation and angiogenesis, as well as migration [80]. During inflammatory processes, uPAR is cleaved from the cell surface by proteases and released as soluble uPAR (suPAR). It is measurable in blood and body fluids including urine, cerebrospinal fluid, bronchial washing fluid, and saliva. suPAR plasma levels reflect immune activation in response to bacterial or viral infection, cancer, burns, and rheumatic diseases. suPAR levels are significantly higher in patients with sepsis than those without and also higher in critically ill patients than control patients [81]. However, recent studies have demonstrated that suPAR has a lower diagnostic value for sepsis (areas under receiver operating characteristic curves [AUC-ROC] of 0.62) than CRP or PCT [82-84]. Several studies have suggested suPAR to be an informative marker for severity of sepsis [81, 84-87]. In a prospective study of 543 acutely-ill patients, baseline suPAR levels were significantly associated with 30 day- and 90 day-mortality after adjusting for age, CRP, and Charlson's comorbidity index [86]. In a recent systematic review, suPAR was superior to other biomarkers, including CRP, PCT, and sTREM-1 for predicting prognosis [84]. Overall, suPAR might have better prognostic value to predict mortality instead of diagnosing sepsis.

8. Angiopoietin

Angiopoietin (Ang)-1 and -2 are endothelial-derived vascular growth factors that play opposing roles during sepsis. Ang-1 stabilizes the endothelium, whereas Ang-2 facilitates loss of endothelial integrity and vascular leakage. Ang-1 or Ang-2 activates the transmembrane endothelial tyrosine kinase Tie2, which mediates the quiescent, healthy state of blood vessels [88]. Ang-2 plays a crucial role in induction of inflammation [88, 89]. Elevated levels of circulating Ang-2 are associated with sepsis with multi-organ dysfunction, which is indicative of impaired vascular endothelial integrity. A cohort study revealed that elevated Ang-1 and lower Ang-2 levels were observed in sepsis survivors [90]. The endothelium and Ang-Tie2 receptor ligand system have been the recent focus of ongoing sepsis studies.

9. Combined biomarkers and sepsis scoring systems

We have discussed several sepsis biomarkers. Numerous biomarkers have been evaluated for clinical use in sepsis, with moderate to good sensitivity and specificity for diagnosis and prognosis. However, the results of measuring a single biomarker are inconclusive in clinical settings. Owing to this limitation, combination approaches measuring multiple biomarkers have recently been introduced. "Scoring systems" have also been developed, which use both clinical and laboratory markers [28, 91, 92]. In 2003, the infection probability score (IPS) was introduced to assess the probability of infection in critically ill patients. The IPS ranges from 0 to 26 points, and includes patient body temperature (0–2 points), heart rate

Table 2. Several clinical examples of combined sepsis biomarkers

Authors [references]	Markers	Outcome	Results
Bozza et al. [27]	MCP-1, APACHE-II	Predict 28-day mortality	AUC-ROC of 0.89
Selberg et al. [44]	PCT, C3a	Differentiate sepsis from SIRS	AUC-ROC of 0.93[a]
Kofoed et al. [82]	suPAR, sTREM-1, MIF, CRP, PCT, WBC	Differentiate bacterial infection from SIRS	AUC-ROC of 0.88
Gibot et al. [91]	sTREM, PCT, CD64	Diagnose sepsis	AUC-ROC of 0.95[b]
Shapiro et al. [92]	NGAL, protein C, IL-1ra	Predict severe sepsis, septic shock, and death	AUC-ROC of 0.80, 0.77, and 0.79[c]
Kofoed et al. [94]	suPAR, sTREM-1, MIF, age	30-day and 180-day mortality	AUC-ROC of 0.93 and 0.87
Harbarth et al. [95]	Temperature, HR, BP, WBC, PCT	Differentiate sepsis from SIRS	AUC-ROC of 0.94

[a] $p\ (\text{sepsis}) = e^{(-28.6106 + 0.8912 \times \ln(\text{PCT}) + 4.3571 \times \ln(\text{C3a}))}/[1 + e^{(-28.6106 + 0.8912 \times \ln(\text{PCT}) + 4.3571 \times \ln(\text{C3a}))}]$.
[b] "bioscore" was calculated by scoring as 0 or 1 values below or above each threshold value for sTREM, PCT, and CD64 index.
[c] Sepsis Score = probability of severe sepsis = $[e^{(\text{raw score})}/1 + e^{(\text{raw score})}] \times 100$; Raw Score = −8.7 + 0.63 (NGAL quartile) + 0.41 (IL-1ra quartile) + 0.50 (protein C quartile)
APACHE-II, acute physiology and chronic health evaluation II; AUC-ROC, areas under receiver operating characteristic curves; BP, blood pressure; CD, cluster of differentiation; CRP, C-reactive protein; C3a, complement 3a; HR, heart rate; IL-1ra, interleukin-1 receptor antagonist; MCP, monocyte chemoattractant protein; MIF, macrophage migration inhibitory factor; NGAL, neutrophil gelatinase-associated lipocalin; PCT, procalcitonin; sTREM-1, soluble triggering receptor expressed on myeloid cell-1, suPAR; soluble form of urokinase-type plasminogen activator receptor, WBC; white blood cell.

(0–1 points), respiratory rate (0–1 points), white blood cell counts (0–3 points), CRP (0–6 points), and sepsis-related organ failure assessment score (0–2 points). The AUC-ROC of IPS was 0.82 for predicting the probability of infection. Patients with <14 points have only a 10% risk of infection [93]. Several clinical examples of combinations of biomarkers and scoring for sepsis are shown in Table 2 [27, 31, 44, 82, 91, 92, 94, 95].

Combined biomarkers and inclusion of sepsis scoring systems showed better AUC-ROC values than single biomarkers. Theoretically, combining multiple markers can improve diagnostic and prognostic values, because sepsis is composed of multiple immune responses with various changes in cytokines and biomarkers. However, which and how many combinations of biomarkers are most informative have not yet been investigated for use as a high-throughput technology. Cost-effectiveness and comprehensive clinical interpretation must also be evaluated.

Conclusions

Biomarkers are useful for early diagnosis of sepsis, to predict outcome, and to guide choice of antibiotic therapy. In these modern times, clinicians encounter the laboratory results on a daily basis. Therefore, proper interpretation and wise use of biomarkers are necessary. Combination approaches of biomarkers with new techniques needs to be further evaluated.

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