REVIEW

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Sepsis and identification of reliable biomarkers for postoperative period prognosis

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Abstract

Sepsis is currently defined as the presence of organ dysfunction occurring as the result of a disturbed host response to a serious infection. Sepsis is one of the most common diseases, which cause mortality and a considerable absorber of healthcare resources. Despite progress in technology and improving knowledge of pathophysiology, the disease mechanism is still poorly understood. At present, diagnosis is based on non-specific physiological criteria and on the late identification of the pathogen. For these reasons, the diagnosis may be uncertain, treatment delayed or an immunomodulatory therapy cannot be established. An early and reliable diagnosis is essential to achieve better outcomes on disease progression. The host response to infection involves hundreds of many mediators of which have been proposed as biomarkers. There is a need for new diagnostic approaches for sepsis, new sepsis biomarkers that can aid in diagnosis, therapeutic decision and monitoring of the response to therapy. The differentiation of sepsis from non-infectious systemic inflammatory response syndrome is difficult, and the search for a highly accurate biomarker of sepsis has become one important objective of the medicine. The goal of our review is to summarize the recent advances on the most commonly studied serum biomarkers, evaluated in clinical and experimental studies, for early diagnosis of sepsis and their informative value in diagnosis, prognosis, or response to therapy. In this context, we have tracked the clinical utility of measuring serum biomarkers, such as procalcitonin, pro- and anti-inflammatory cytokines, C-reactive protein, leptin and their combinations. Currently, has not been identified an ideal biomarker to aid in the diagnosis of sepsis. It is hoped that the discovery of new serum markers, as well as their combinations, will serve for the diagnosis and prognosis of sepsis.

***Keywords*:** sepsis, systemic inflammatory response syndrome, diagnosis, biomarkers.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by an infection [1]. Sepsis remains the leading cause of death in intensive care units (ICUs), but also in all age groups worldwide, being considered a hidden public health disaster [2]. Early recognition and diagnosis are the keys to achieving improved outcomes. The complex pathophysiology of sepsis results in a multitude of released biomarkers. By using more biomarkers, the response of the host to the infection can be better measured and could better inform clinicians treating such patients [3].

One of the most difficult tasks in differential diagnosis of patients with septic syndrome at the ICU is to differentiate between infection and non-infectious systemic inflammatory response syndrome (SIRS). SIRS can be triggered by a variety of infectious and non-infectious conditions, including ischemia, inflammation, trauma, burns, pancreatitis, autoimmune/inflammatory disorders, transplant rejection, graft-*versus*-host disease, and many others [4]. The distinction between non-infectious SIRS and sepsis is a further complicated dilemma that infectious processes are often similar in their clinical presentation and frequently predispose patients to secondary infections. For essential management decisions, such as initiation, selection and duration of antibiotic therapy, the distinction between SIRS and sepsis is very important [5].

The ability to initiate timely and specific treatment is enhanced by early diagnosis and stratification of sepsis severity [6]. Sepsis plus organ dysfunction is the definition of severe sepsis. Due to the need to quantify this dysfunction, several scoring systems have been developed [7].

Definitions

The definitions of sepsis have rapidly evolved since the early 1990s. Some of these definitions have been refined over the years, but the general gist remains the same. Schottmüller, in 1914, proposed the first scientific definition of "sepsis" as a condition caused by a microbial invasion from a local infectious source in the bloodstream, leading to signs of systemic disease in remote organs [8].

There has been a permanent, multi-special and multi-national approach to understanding the mechanism of sepsis installation and treatment. With significant morbidity and mortality, even in the modern era of critical care management, sepsis remains a critical issue [9, 10]. Researchers have tried to diagnose sepsis by combining non-specific physiological anomalies and laboratory abnormalities, as there are no gold standards in the definition of sepsis. To the international conferences that took place in 1991, 2001, and finally, in 2016, were proposed definitions of sepsis.

A 1991 consensus conference set out the concept of SIRS to describe the complex pathophysiological response to a variety of serious lesions (infectious or other). This conference was tasked with developing an easy-to-apply set of clinical parameters to help identify potential candidates to enter clinical trials to assess new treatments for sepsis [11]. In 1991, a consensus conference developed initial definitions that SIRS to infection would be called sepsis [12]. Definitions of sepsis and septic shock were revised in 2001 to incorporate the threshold values for organ damage [13, 14].

New definitions of sepsis and septic shock have changed dramatically in early 2016. Dysfunction of life-threatening organs caused by a dysfunctionally regulated host response to infection is the current definition of sepsis. The acute change in the total sequential organ failure assessment (SOFA) score higher than 2 points secondary to the cause of infection is organ dysfunction. A new bedside index, called qSOFA, was introduced by the *Sepsis-3 Task Force* to identify outpatient critical care units for patients with suspected infection that could develop sepsis. Recently updated, the consensus definitions improved specificity compared with the previous descriptions [1, 14].

Sepsis-3, the new definition of 2016 eliminates the need for SIRS to define sepsis and eliminates the definition of severe sepsis. What has been previously called severe sepsis is now the new definition of sepsis [15]. Clinical recognition and severity assessment is difficult because symptoms and signs of sepsis are extremely variable. Sepsis is a clinical syndrome that is characterized by systemic inflammation and large-scale tissue damage and complicates severe infection. There is an imperative need to further define and understand the basic pathophysiology changes to clarify targeted sepsis therapies, given the substantial morbidity and hundreds of thousands of septic deaths each year [16].

Incidence of sepsis

Sepsis has an expected 1% increase in incidence per year, affects over 18 million people worldwide and is the most common cause of death in hospitalized patients [17]. SIRS is not always related to infection. Comstedt *et al.* found a moderate relationship between SIRS and infection, increased mortality (10%) for 28 days among SIRS patients and high prevalence of SIRS (35%) among acutely hospitalized patients [18]. An incidence of SIRS of nearly 50% in ward patients has been demonstrated more recently by Churpek *et al.* [19]. Most hospitalized patients develop SIRS at some point during their stay, and these findings support the low specificity of the SIRS criteria for selecting patients at high risk of death. Angus *et al.* found that the incidence of severe SIRS associated with infection to be of three cases per 1000 population, or of 2.26 cases per 100 hospital discharges [20].

Mellhammar *et al.*, in their study, suggest a high incidence of traditional severe sepsis (687/100 000), and the incidence was even somewhat higher using the newly proposed *Sepsis-3* definitions (780/10 000) but without a significant difference [21]. In Europe, every year, 157 000 people die for this systemic multi-organs failure because of bacterial or fungal infection [6]. Several prospective and retrospective epidemiological studies have provided data on incidence, prevalence of points, time prevalence, and sepsis mortality rates for high-income countries. These reports extrapolated their results to a population level; many have suggested dramatic increases in sepsis [22].

In all areas of the world where epidemiology studies have been conducted, the incidence of sepsis is increased. The total number of people who die with sepsis each year continues to increase due to the increasing number of cases each year, despite the proportional decrease in sepsis death rates [23].

The etiology of SIRS and sepsis

SIRS is broad and includes infectious and non-infectious conditions. Although SIRS is most commonly associated with sepsis, other disease states known to cause widespread release of endogenous mediators and subsequent systemic inflammation in people include severe trauma with tissue injury, burns, major surgery, and pancreatitis, all share common inflammatory activation pathways [5]. Fungal organisms grow rapidly, although Gram-positive pathogens remain the most common cause of sepsis. Sepsis and septic shock, caused by Gram-negative and Gram-positive bacteria, fungi, viruses, and parasites, have become increasingly important in recent decades [23].

Sepsis is a complex condition characterized by the simultaneous activation of inflammation and coagulation in response to microbial insult. These events manifest as systemic inflammatory response syndrome or sepsis symptoms through the release of proinflammatory cytokines, procoagulants, and adhesion molecules from immune cells and/or damaged endothelium [24]. Patients in contemporary ICUs are more likely to have infections and increase the risk of infection with duration of ICU stay. The ICU mortality rate of infected patients was more than twice that of non-infected patients [25].

Risk factors for severe sepsis

Many well-known risk factors for infections most often accentuate severe septicemia and septic shock. Risk factors for severe sepsis are linked both to the likelihood of acute organ dysfunction if the infection develops as well as to the patient's predisposition to infection [13, 15].

Kalil & Bailey [15] synthesized risk factors for severe sepsis and septic shock, as follows: extremes of age (<10 years and >70 years), primary diseases (liver cirrhosis, alcoholism, diabetes mellitus, cardiopulmonary diseases, solid malignancy, and hematological malignancy), immunosuppressive therapy, complement deficiencies, asplenia, major surgery, trauma, burns, invasive procedures (*e.g.*, placement of catheters, intravascular devices, prosthetic devices, hemodialysis), previous antibiotic treatment, prolonged hospitalization (which is thought to induce an altered human microbiome), underlying genetic susceptibility, other factors (*e.g.*, childbirth, abortion and malnutrition).

Angus & Wax noted that risk factors for severe sepsis are linked both to the likelihood of acute organ dysfunction if the infection develops as well as to the patient's predisposition to infection [26]. The incidence of severe sepsis is influenced by age, gender, race, or ethnic group being higher in infants and elderly than in other age groups, higher in males than in females, and in blacks than in whites [15, 26].

There is considerable interest in the contribution of host genetic characteristics to the incidence and outcome of sepsis, in part because of strong evidence of inherited risk factors [27, 28]. Polymorphisms of genes encoding proteins involved in the pathogenesis of sepsis, such as cytokines and other mediators involved in innate immunity, coagulation and fibrinolysis, have been the subject of many studies [27]. During sepsis, circulating immunoglobulin (Ig) concentrations are low when immunosuppression prevails and this is associated with negative outcomes. During the progression of sepsis, it is postulated that the host is assumed to be unable to produce an adequate amount of Igs [28].

Comorbidities that depress host defense [*e.g.*, neoplasms, renal failure, hepatic failure, acquired immunodeficiency syndrome (AIDS), asplenism] and immunosuppressant medications are common among patients with sepsis, severe sepsis, or septic shock. For the treatment of gastrointestinal diseases, such as inflammatory bowel disease (IBD), autoimmune hepatitis and post-transplantation, immunosuppressive therapy is commonly used. These drugs can increase the risk of infectious complications and interfere with the immune system [29]. The relationship between sepsis and chronic health can be bidirectional; sepsis was more commonly observed in people with poor chronic health and one episode of sepsis aggravated chronic health [30].

Prognosis

Sepsis is a potentially life-threatening complication of infection, trauma or burn injury. Sepsis is a primary cause of infection-induced mortality and one of the leading causes of death worldwide. The mortality rate of sepsis is very high and increases depending on the stage and severity of the sepsis; 24% of patients with SIRS die, increasing to over 50% of patients with septic shock [31, 32].

In a study of SIRS in acutely hospitalized medical patients, Comstedt *et al.* demonstrated a 6.9 times higher 28-day mortality in SIRS patients than in non-SIRS patients [18]. SIRS patients associated with malignancy were the majority of deaths [19]. Prognosis depends on the associated comorbidities but also on the etiological source of SIRS [33].

Shapiro *et al.* [34] found the following mortality rates: suspected infection without SIRS – 2.1%, sepsis – 1.3%, severe sepsis – 9.2%, septic shock – 28%, in a study evaluating mortality in patients with suspected infection in the emergency department. Heffner *et al.* [35], in a study of patients admitted with severe sepsis from a community emergency department, found that 18% were diagnosed with non-infectious causes that were imitating sepsis (SIRS) and that 55% of patients had negative cultures; patients without an identified infection had a lower hospital mortality rate than patients with infectious etiology. Mortality for severe sepsis and septic shock has commonly been quoted as ranging from 20% to 50%. Mortality associated with septic shock ranges from 24% to 41% according to clinical trials in the last decade [36–38].

Organ dysfunction is a better predictor than SIRS criteria according to a study found that, in establishing a suspected infection, meeting SIRS criteria without evidence of organ dysfunction did not predict increased mortality [34]. A mortality rate of 56% during the ICU stays in patients with severe sepsis and 60% in those with culture-negative severe sepsis was reported in a prospective multicenter study published by Brun-Buisson [39].

The host response to sepsis

The normal host response to infection is a complex process that localizes and controls bacterial invasion, while initiating the repair of injured tissue. It involves the generation of pro-inflammatory and anti-inflammatory mediators as well as the activation of circulating and fixed phagocytic cells.

Sepsis involves normal tissues away from the site of the injury or infection and results when the response to the infection becomes generalized. Sepsis is defined as the presence of organ dysfunction occurring as the result of a dysregulated host response to an infection [1]. Sepsis is an extremely heterogeneous syndrome that is the net result of host and pathogen interactions that trigger networks of biochemical mediators and inflammatory cascades [40]. The response of the host to the infection is much more complex and prolonged, and pro-inflammatory and anti-inflammatory mechanisms can help eliminate infection and tissue recovery on the one hand and organ damage and secondary infections on the other [41]. The defense sometimes fails, usually wins, and occasionally self-destructs; such is the role of the immune system in defense against infection [42].

Bloodstream infections can produce an immune response to bacterial endotoxins. Innate immune response stimulates macrophages to produce interleukin (IL)-1β, tumor necrosis factor (TNF), and IL-6. SIRS is produced by these three proinflammatory cytokines, which is characteristic of early sepsis. Bone [43] specifically described to patients who develop severe sepsis a compensatory anti-inflammatory response syndrome (CARS) that often follows the hyperinflammatory phase. A widespread dysfunction of organs, including lung, liver, and/or kidney lesions, is present in severe sepsis. The terminal event of severe sepsis is the so-called septic shock, in which patients undergo a cardiovascular collapse that does not respond to fluid resuscitation and vasopressor therapy [44].

The septic response is an extremely complex chain of events involving circulatory abnormalities and cellular and humoral reactions [45]. Inflammatory responses are initiated by interaction between pattern recognition receptors (PRRs) expressed by host cells at the cell surface, in the endosome, or in the cytoplasm and pathogen-associated molecular patterns (PAMPs) expressed by pathogens. The consequence of exaggerated inflammation is necrotic cell death and collateral tissue damage, which results in the release of damage-associated molecular patterns (DAMPs), so-called danger molecules that perpetuate inflammation at least in part by acting on the same pattern-recognition receptors that are triggered by pathogens [41].

In the inflammatory response, an insult triggers the release of PAMPs and/or DAMPs, which are sensed by pattern recognition mechanisms, such as by PRRs of sensor cells, as well as by pattern-recognizing complex systems, such as the complement system and others. Sensors can be different types of cells, other molecules/proteins or tissues/organs, which themselves may function as effectors to modulate the immune response through various different biomarkers or pro- or anti-inflammatory mediators. As a result, organ function may be permanently or temporarily impaired and the underlying insult can be cleared or not [1, 41, 46]. In parallel with clinical development, the composition and direction of the host's response may change over time. In severe sepsis, responsible for collateral tissue damage are generally considered inflammatory responses (directed to the elimination of invading pathogens) and the secondary susceptibility to infections involves anti-inflammatory responses (important for limiting local and systemic tissue damage) [41].

Diagnosis

Due to the complexity of the disease, sepsis is difficult to diagnose. The pathophysiology of sepsis can be better understood today due to information obtained from scientific studies in the field of intensive care, immunology, biochemistry, microbiology, and other medical fields and technological advances [12]. Recently, it was suggested that sepsis develops by immune suppression [47]. Diagnosis and early treatment is required, in addition to selecting suitable patients for future clinical studies.

Clinical signs of sepsis

Diagnosis of sepsis is difficult because suggestive clinical signs are non-specific. Thus, hypotension, fever, tachycardia, tachypnea and leukocytosis are common in critically ill patients [45]. As severity worsens, signs of shock (*e.g.*, cool skin and cyanosis) and organ dysfunction develop (*e.g.*, oliguria, acute kidney injury, altered mental status). An infection can be identified from microbiology findings and clinical signs, if organ dysfunction is present, provide a diagnosis of sepsis [48].

Rapid diagnosis is important, and early treatment of sepsis is associated with improved outcomes. In critically ill patients, the diagnosis of sepsis is provocative; it can be complicated by the presence of inflammation because of other underlying disease processes and the previous use of antibiotics making negative cultures [48].

Investigation (laboratory) tests

The following are investigation (laboratory) tests to detect a clinically suspected focal infection [15, 48]:

- Complete blood count (CBC);
- Blood chemistry (*e.g.*, sodium, magnesium, chloride, lactate, calcium, glucose, phosphate);
- Coagulation studies [*e.g.*, prothrombin time (PT), fibrinogen, activated partial thromboplastin time (aPTT)];
- Renal and hepatic function tests (*e.g.*, creatinine, bilirubin, blood urea nitrogen, aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, lipase, albumin);
- Blood cultures at admission: culture of the catheter tip (for suspected central IV line sepsis);
- if suspected urinary tract source – urinalysis and urine cultures;
- Gram staining and culture of secretions, peripheral blood and tissues.

Positive blood cultures cannot be present in many patients with sepsis, and the diagnosis of culture-dependent infection is slow [48]. In the diagnosis of early sepsis and prognostic determination, some serum biomarkers may be useful [49]. For patients to have the best chance of survival, early diagnosis of sepsis is essential, so that specific therapy can be initiated promptly [50, 51].

The early diagnosis of sepsis and the identification of its origin are crucial to overcome sepsis-associated mortality [51]. The identification and validation of reliable biomarkers of sepsis is an unmet medical need; the use of new biomarkers brings clinical information that could contribute to the transformation of sepsis from a physiological syndrome into a group of distinct biochemical disorders, improves diagnosis, and makes therapeutic decisions for high-risk patients and monitors response to therapy [51]. For the best care of the patients with severe sepsis, there are many recommendations from a large group of international experts [52].

Differentiation is difficult between sepsis and non-infectious SIRS, and an important goal of medicine is the search for a very accurate sepsis biomarker [53, 54]. It is difficult to determine the frequency which sepsis is incorrectly diagnosed as a non-infectious process with significant implications for treatment and outcome [40].

The purpose of this review was to evaluate the recent advances on serum biomarkers, which are undergoing validation and may transition into clinical practice for their informative value in diagnosis, prognosis, its differentiation from non-infectious SIRS or response to therapy. We also discussed about biomarkers combination and their potential use in management of sepsis patients. In this context, we have tracked the clinical utility of measuring serum biomarkers, such as procalcitonin (PCT), pro- and anti-inflammatory cytokines, C-reactive protein (CRP), leptin and their combinations.

Sepsis biomarkers

There is an urgent need to apply reliable biomarker measurements to stratify the risk in septic patients and to easily identify those patients at highest risk of having a poor outcome, despite the use of specific antibiotics, aggressive interventions, nutritional supplements and anti-inflammatory therapies. Novel biomarkers are highly needed to better inform clinicians treating such patients [46, 49, 55]. In the past two decades, a large number of sepsis-related markers have been reported and the accuracy of diagnosis of these biomarkers remains unclear due to the lack of similar baselines among studies [56].

Ideally, the features of a sepsis biomarker are to reduce time to diagnosis, to differentiate between infectious and non-infectious SIRS, reflecting efficacy of antimicrobial therapy, highly specific and sensitive. A "perfect biomarker" should be measured accurately and results should be reproducible. Biomarkers can help determine severity, prognosis and response to intervention and can be used as a diagnostic tool [57].

Many markers of sepsis are under development and have been proposed as adjuvants to clinical evaluation because sepsis is a complicated syndrome with numerous physiological disorders. The list includes acute phase proteins, cytokines, markers of abnormal coagulation, neutrophil activation markers, and, recently, markers of suppression of both the innate and adaptive immune response. Precise identification of patients at risk for severe sepsis is a feature of the perfect biomarker; biomarkers have been investigated to do this, most of them have diminished their importance due to the low specificity of the infection [58].

Serum lactate

Lactate levels in clinical practice are often used as a surrogate to measure response to therapeutic interventions and the severity of the disease. For the first time, in 1964, Broder & Weil suggested the use of lactate as a clinical prognostic tool, when observed that an excess of lactate >4 mmol/L was associated with poor results in patients with undifferentiated shock [59].

In sepsis, serum lactate testing has become popular in recent years and is used in many centers to monitor the response to therapy and to accelerate early treatment [58]. It is a test that measures the amount of lactic acid (also called lactate) in the blood. It forms when the body turns food into energy. The body relies on this energy when its oxygen levels are low. Oxygen levels might drop in a case of an infection or disease or during an intense workout. The lactic acid level tends to return to normal once the training or recovery from the disease is complete. Lactic acidosis is a disease characterized by higher levels of lactic acid than normal.

In a study, Rhee *et al.* [60] stated that the use of serum lactate tests in patients with suspected and diagnosed sepsis has increased dramatically since 2003, and clinicians are progressively testing lactate patients without obvious signs of shock. Even in 2013, the serial lactation test rates remained suboptimal and a substantial proportion of severe sepsis patients and those with clinical markers indicating suspected septic shock did not measure plasma lactate concentrations. Risk factors for failure to attract lactate are the onset of suspected sepsis during hospitalization and admission to non-medical services. Physiologically, lactate is rapidly cleared by the liver with a small amount of additional clearance by the kidneys [61]. A useful indicator of prognosis in septic shock may be lactate concentrations in the "normal" range [62].

Elevated lactate can be caused by a number of conditions including sepsis, shock, seizure, cardiac arrest, trauma, malignancy, ischemia, diabetic ketoacidosis, thiamine deficiency, toxins, liver dysfunction, genetic disorders, and medications. In several diseases, such as sepsis, trauma and cardiac arrest, high lactate was associated with increased mortality [61]. Elevated serum lactate levels have long been known to identify patients with severe hypoperfusion and predict death [63]. Measurement of serum lactate levels has been shown to risk stratification of patients with suspected sepsis, to require early aggressive treatment and to help monitor the impact of therapy [64–66]. In a randomized trial of lactate-based goal-directed therapy in sepsis, an increase in the aggressiveness of resuscitation in response to hyperlactatemia led to improved patient survival but failed to reduce lactate concentrations effectively. This implies that while the presence and persistence of lactatemia confers a poor prognosis [66]. Implementation of lactate measurement in the emergency department was associated with decreased mortality and reduced intravenous fluid administration time in patients with suspected sepsis [67]. Studies show that lower increases in blood lactate levels are associated with an increased risk of death [62].

Procalcitonin (PCT)

In the diagnosis of bacterial sepsis, procalcitonin is a highly sensitive biomarker. C-cells of the thyroid gland synthesize primarily and to a lesser extent neuroendocrine tissue of other organs, such as intestine and the lungs, in the blood the normal levels of PCT are very low. Inflammatory cytokines stimulate production in almost all organs, causing the release of large amounts of PCT in the blood. A key tool that helps diagnose sepsis is the use of PCT levels as a biomarker of severe inflammation, infection and sepsis [68, 69].

PCT has a high negative predictive value of over 95%, and is a very sensitive biomarker for the diagnosis of bacterial sepsis [69]. Pontrelli *et al.* (2017) demonstrated that PCT is an accurate biomarker for the diagnosis of

sepsis in pediatrics [70]. The 2016 *Guidelines of the Surviving Sepsis Campaign* (SSC) recommends as a tool for the management and optimization of antibiotic therapy using of PCT [71]. Use of PCT to reduce patients' exposure to antibiotics in intensive care units is noted by Bouadma *et al.* [72]. Sager *et al.* in a recent paper, based on PCT levels, offers recommendations on antibiotic management of patients in the emergency department and urinary tract infections (UTIs) with suspected infections or sepsis [73]. Before initiating the therapy, we should wait for a blood sample to be taken for microbiological blood cultures to identify the presence of any blood-borne microorganisms. PCT levels may help the clinician in early antibiotic treatment of patients with suspected infection because the results of blood culture may take several days to be available and are associated with limited diagnostic accuracy of the infection [74]. The duration and necessity of antibiotic therapy may be better tailored to individual patient requirements if serial PCT levels are used [75].

To differentiate between sepsis and severe sepsis, PCT seems to be a useful marker [76]. PCT has superior biokinetics, characterized by earlier elevated concentrations of bacterial infections and sepsis, and declining more rapidly if the infection is controlled compared to CRP – another commonly used biomarker to help diagnose systemic inflammation and infection. Earlier diagnosis of sepsis and better monitoring of progression is permitted by this favorable kinetics [77]. PCT and CRP levels are related to the severity of organ dysfunction, but concentrations are still higher during infection. A different clinical use for both parameters is indicated by different sensitivities and kinetics [78]. Průcha *et al.* examined patients hospitalized at the ICU and compared three parameters (CRP, IL-6 and PCT) in differential diagnosis of the septic syndrome. The results of the examinations were compared to each other as well as to the diagnosis of sepsis the confirmed infection etiology. They concluded that PCT is the parameter of choice, while it may be supplemented with the examination of CRP [79].

In their study, Dahaba & Metzler determined that PCT decreased a few days before a fatal outcome and demonstrated that poor prognosis patients at some stage would show a decrease in their ability to develop an effective response to sepsis [80]. Sridharan & Chamberlain argue that PCT serum concentrations do not correlate with severity of sepsis or mortality, although higher levels of PCT suggest a systemic bacterial infection [81]. PCT level determination seems to be a reliable tool both for distinguishing between systemic inflammatory disease infections in the initial assessment of patients with acute fever and to exclude infection in patients with chronic inflammatory diseases. Diagnosis of bacteremia is accurately excluded by a serum PCT level of <0.4 ng/mL. The number of blood cultures to be processed and the number of antibiotic prescriptions could be limited by doctors using the PCT assessment [82].

The best discriminator between SIRS patients with and without bacteremia among the evaluated biomarkers was PCT. PCT was significantly elevated in SIRS patients from standard medical departments with documented bacteremia *versus* SIRS patients without documented bacteremia [83]. PCT has been evaluated as a tool to distinguish bacterial infection from other inflammatory states and infectious processes in multiple clinical settings [84–86].

Serial PCT measurements may play a role in monitoring sepsis results, even if the initial levels of PCT are not reliable as a diagnostic biomarker. It remains unclear what role the PCT can play in the management of septic patients. Even though it has limited abilities to distinguish bacterial sepsis from other inflammatory conditions, PCT is commonly used in clinical practice.

Cytokines as biomarkers

Sepsis triggers the production of a diverse array of cytokines that are pro-inflammatory and anti-inflammatory. Excessive production of proinflammatory cytokines can lead to tissue and organ damage, although proinflammatory cytokines are needed to control the infection. Anti-inflammatory cytokines are critical in establishing homeostasis and regulating the overall immune response [87, 88]. Pro-inflammatory cytokines IL-6, IL-8, IL-18 and TNF-α, and anti-inflammatory cytokines (IL-10) have been increased in patients with sepsis in response to pathogen infection. A better prognosis was associated with a decrease in IL-6 and it was found that the major predictor of severity and fatal outcome is overproduction of IL-10 [88]. In patients with sepsis, both pro-inflammatory and anti-inflammatory cytokines have been found elevated in response to pathogen infection [88, 89].

Pro-inflammatory cytokines in sepsis

Excessive production of pro-inflammatory cytokines has been associated with multiple organ dysfunctions and mortality [89]. The major pro-inflammatory cytokines that regulate early responses include IL-1α, IL-1β, IL-6, IL-8, IL-18, interferon-gamma (IFN-γ) and TNF-α. The contribution of these proinflammatory cytokines to direct mediation of septicemia mortality is unclear because in patients with sepsis, the therapies that use neutralizing antibodies or soluble receptor antagonists against TNF-α and IL-1 fail to show significant benefit [90, 91].

Interleukin-1beta (IL-1β)

IL-1β is a member of the IL-1 cytokine family and is known as catabolin. Activated macrophages produce this cytokine as a proprotein, which is proteolytically processed in its active form by caspase-1. IL-1β is involved in a variety of cellular activities, including proliferation, differentiation and apoptosis of cells and is an important mediator of the inflammatory response. In sepsis, the role of IL-1β has not been extensively studied [88]. IL-1β showed persistent increases in the first seven days after admission of sepsis patients to those who died, suggesting that IL-1β may play a role in sepsis [92].

Interleukin-6 (IL-6)

IL-6, known as interferon-β2 or LyB-stimulation factor 2 (BSF-2), is a cytokine secreted by LyT and macrophages as an immune response to various microbial

molecules, in trauma, burns and tissue damages accompanied by inflammation [88]. IL-6 has both pro-inflammatory and anti-inflammatory activity, seeing it play an important role in various pathological processes, such as autoimmune diseases or chronic proliferative inflammatory diseases [93]. IL-6 has also been shown to play an important role in sepsis, with elevated serum levels in these patients [94]. Other studies have shown that serum levels of IL-6 are higher in patients who are suffering from shock, compared to the control group, as well as an association between elevated serum levels and increased risk of death or death of patients with severe sepsis [95, 96]. Although the mechanisms by which this cytokine is implicated in regulating sepsis are not known, the results of previous studies may suggest IL-6 involvement in the septic pathophysiology [88].

Interleukin-8 (IL-8)

IL-8 is part of the cysteine X cysteine (CXC) family of chemokines and is secreted by macrophages, but also by epithelial cells and endothelial cells. It is known that IL-8 is an important mediator in the inflammatory response by inducing chemotaxis in the target cell, neutrophilic granulocytes (also called chemotactic factor of neutrophils), which will lead to the accumulation of neutrophils at the site of inflammation [23]. Studies have shown elevated levels in serum and plasma of patients with sepsis and elevated levels have been associated with the death in patients with sepsis [88, 92]. Also, elevated serum levels of IL-8 correlated with a lower prognosis in patients who experienced multiple postoperative organ failure [97]. In the studies conducted in children with septic shock who died at 28 days, plasma levels were obtained values of <220 pg/mL, which have an excellent negative predictive value (94–95%) [13, 98].

Tumor necrosis factor-alpha (TNF-α)

Tumor necrosis factor is a major cytokine involved in the acute phase reaction and participates in the cellular signaling mechanisms underlying systemic inflammation. Like other cytokines, it is produced by macrophages activated by various mechanisms, but can also be synthesized by other cells [CD4 lymphocytes, natural killer (NK) cells, neurons].

Although it is one of the most studied cytokines, it is still not fully aware of the physiological roles and mechanisms by which it intervenes in the inflammatory pathology of various human diseases [99].

For TNF-α, studies that have been performed in sepsis or in animal models have shown significantly elevated plasma levels both during early shock (manifested by hypotension, fever) and in multiple organ dysfunctions occurring in septic shock [92, 100, 101].

Interleukin-12 (IL-12)

IL-12 is known to stimulate T-lymphocytes and plays a role in stimulating the growth and function of T-lymphocytes and NK-cells. The effect of stimulating these cells is the release of IFN-γ and TNF-α, which is why they have been included in various studies, including patients who have sepsis. It was observed that serum levels of IL-12 were higher in patients with sepsis [92, 102].

Interleukin-17 (IL-17)

IL-17 is a cytokine produced by a subpopulation of T-helper cells (T-helper 17 cell) as an immune response to various pathogens. It is a powerful pro-inflammatory cytokine that plays a role in inducing and mediating pro-inflammatory responses, which can lead in various pathological conditions and excessive tissue damages [103, 104]. Although it has strong pro-inflammatory activity, there are not many studies in which has been demonstrated the role of IL-17 in sepsis. Studies have shown that IL-17 is not associated with inflammatory pathology that causes multiple organ failure in patients with fungal sepsis [105, 106]. Another study in which have been evaluated 60 patients with severe sepsis has shown, following multiplex analysis, that serum IL-17 levels were very low, even undetectable [107].

Interleukin-18 (IL-18)

Interleukin-18 (IL-18, also known as IFN-γ inducing factor) is part of the IL-1 superfamily and is synthesized by macrophages and other cells. It is known that in combination with IL-12, IL-18 can stimulate NK-cells and certain T-cells that release IFN-γ. Thus, IL-18 plays a role in inducing cell-mediated immunity because IFN-γ activates macrophages [88]. For IL-18, studies have shown that this cytokine is associated with the mechanisms involved in sepsis. Increased serum concentrations of patients were found in sepsis and association of these elevated levels with an altered clinical status of patients with severe sepsis [88, 108]. It has also been observed that elevated IL-18 concentrations may have a good diagnostic accuracy in the differential diagnosis between Gram-positive and Gram-negative septicemia [109].

Interferon-gamma (IFN-γ)

IFN-γ or type II interferon is a cytokine produced by the CD4 Th1 and CD8 cytotoxic T-lymphocytes (CTLs), NK and NK T-cells. By stimulating macrophage activity, promoting NK-cell activity, regulating the differentiation of $CD4^+$ (Th0 cells) in Th1-cells, by inducing the expression of Class II major histocompatibility complex (MHC) molecules, IFN-γ is involved in immune-directed mechanisms against viral or bacterial infections [110]. Studies have shown that severe sepsis is associated with low concentrations of IFN-γ and dependent Th1 cytokines and increased serum levels of dependent Th2 cytokines [111, 112]. A good observation is that although the profile of proinflammatory cytokines are good indicators of infection, they are also produced by sterile inflammation (SIRS), thus reducing their specificity [113].

Several types of carcinoma-associated fibroblasts, such as mesenchymal stem cells (MSCs), produce immuno-regulatory cytokines, such as TGF-β (with the pro-inflammatory roles in inflammatory responses) that block cytotoxic T-cells and NK T-cells, thus limiting the capacity of the immune system to eliminate cancer cells [114].

Anti-inflammatory cytokines in sepsis

The anti-inflammatory cytokines (IL-4, IL-6, IL-10, IL-11, and IL-13) are several proteins with a role in regulating pro-inflammatory cytokines. Together with specific cytokine inhibitors and soluble receptors, they maintain normal balance between pro- and anti-inflammatory cytokines. As with pro-inflammatory cytokines, studies have shown that anti-inflammatory cytokines exert their physiological role in inflammation and pathological roles in systemic inflammatory conditions [115]. There are no data to support the relationship of sepsis to a deficient anti-inflammatory response. On the contrary, anti-inflammatory cytokines significantly increase in the circulation of patients with sepsis [116].

Interleukin-10 (IL-10)

IL-10 is a cytokine produced by the subpopulation of $CD4^+$ T-helper 2 lymphocytes, monocytes and B-cells. IL-10 is a cytokine that inhibits the expression of Th1 cytokines, but also of IL-2 and IFN-γ [88]. It was found that the excess of this anti-inflammatory cytokine was associated with the severity of sepsis and may even be a predictor of the severity of sepsis and fatal progression [89, 95, 116]. In other situations was observed a decrease in serum levels of IL-6 and an association with a better prognosis, in contrast, overproduction of IL-10 has been associated with the severe, even fatal evolution of the situation of patients with severe sepsis, correlating the levels serum of IL-10 and sepsis score with death [88]. When was analyzed the ratio between IL-10 and TNF-α, an increased ratio of IL-10/TNF-α was associated with an increased risk of death, suggesting that sepsis patients are in deep immunosuppression [89].

The role of IL-10 in sepsis is complex, with potentially opposite effects depending on the timing of intervention and whether endogenous *versus* exogenous IL-10 is manipulated [117]. In another study the serum values of IL-10 and TNF-α in SIRS patients was found significantly higher than those of a control group, but in experimental studies on the mice, was followed the relationship between IL-10 and TNF-α after injection with lipopolysaccharide (LPS), observing that IL-10 inhibits TNF-α secretion by monocytes and thus can protect the patient with SIRS from pro-inflammatory TNF activity [118].

All of these studies indicate that the occurrence of an imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines may play a very important role in the pathogenesis of sepsis.

Analyzing these studies, we notice that increases in serum concentrations of pro-inflammatory cytokines, such as IL-6, IL-8, IL-18 and TNF-α and IL-10 anti-inflammatory cytokines, are reported in sepsis patients.

C-reactive protein (CRP)

CRP is the most widely used biomarker as an acute phase reactant to assess the presence of an infection or inflammatory process. In most studies was reported increased sensitivity and specificity for CRP in terms of diagnostic acuity in sepsis [119], which is why only CRP with PCT has entered in clinical practice [119]. Studies have shown that increases in serum patients of CRP in within 24 hours of admission, indicate sepsis and may differentiate septic patients from non-infected SIRS [120, 121].

CRP is a protein produced in the liver in response to mediators released by macrophages or adipocytes in bacterial infections and inflammatory processes. Its synthesis is mediated by three important cytokines with pro-inflammatory activity, TNF-α, IL-6 and IL-1β [122]. CRP is directly involved in the clearance of micro-organisms [123].

Some studies have shown that the CRP/albumin ratio can be used as risk factor for mortality at 90 days in septic patients and it is recommended to use this ratio as a long-term prognostic marker, because the results are more conclusive than the use of standard CRP values [124]. Tsalik *et al.* observed that PCT, IL-6 or CRP were significantly higher in patients with clinical and microbiological evidence of infection [40], results that are in contrast with those reported in several published studies [46, 79].

Leptin

Leptin is a peptide hormone, which plays an important role in regulating energy intake, including appetite and metabolism. Leptin is synthesized mainly by adipocytes. Leptin regulates body fat reserves and is also involved in cell-mediated immunity and cytokine-type diabetes. It has been demonstrated that monitoring of serum leptin in patients with critical conditions is beneficial in early diagnosis but also has significant diagnostic accuracy in distinguishing patients with sepsis from patients with non-infectious SIRS [125].

The importance of early diagnosis of sepsis, the identification of its etiology and the adaptation of the therapeutic behavior of various situations are important parameters in combating mortality associated with sepsis in a statistically significant proportion. The mechanisms through which leptin is implicated in sepsis or non-infectious SIRS are not yet fully elucidated [125].

Leptin is a hormone having multiple immune response regulation functions, including mediating macrophage effector functions and even cytokine synthesis [126]. Thus, serum leptin concentrations have been found to increase in certain infections and inflammatory processes and correlate well with serum levels of IL-6 and TNF-α [127]. Among other functions that leptin has, we can mention the mediation of cytokine production, monocyte activation, macrophage activation, role in angiogenesis and hemato-poiesis. Although there are studies in which it has been observed that serum leptin levels rise rapidly during infection and inflammation [128], the investigation of the role of leptin in the regulation of the immune response remains a challenge for the future [125, 129]. There was an association between elevated serum IL-6 levels and leptin levels, suggesting that leptin may have a host defense mechanism during sepsis [130].

In terms of leptin dynamics, it was found to have a

different early dynamics during SIRS and sepsis so that the hypothesis of leptin measurement in combination with CRP or IL-6 can be considered to make the differential and prognostic diagnosis of critical surgical diseases at different periods of time [131, 132].

At present, PCT and CRP are the only markers of sepsis routinely used in the clinical practice in most of the developed countries. A major limit of these biomarkers is their relatively low positive predictive value and specificity. Research then focused on novel tests with increased specificity, and a number of novel molecules have been identified and proposed for clinical use.

Identification of some serum biomarkers for postoperative period prognosis

A summary of the specialized literature published in 2010 by Pierrakos & Vincent [45] identified the existence of 178 different biomarkers described and analyzed in over 3000 studies. For the most part, these were clinical trials. In the last decades, a large number of serum biomarkers have been proposed for clinical applications in surgery.

Elevated lactate

Studies over time have shown several causes that may lead to lactate growth, such as shock, septicemia, cardiac arrest, trauma, seizures, ischemia, diabetic ketoacidosis, thiamine deficiency, certain neoplasias, liver disorders, affections genetic, because of the action of toxins or drugs. Also, in the surgical pathology, there have been mentioned causes that are accompanied by elevated serum levels of lactate, such as mesenteric ischemia, other diseases, bacterial peritonitis and acute pancreatitis [62]. Although sensitivity and specificity are not significant for lactate, it has been observed that this test may be useful in the clinic and may alert the clinician that there is the possibility of hypoperfusion or another cause that goes unnoticed in the initial assessment of the patient [62].

Plasma chitotriosidase (ChT) activity

Chitotriosidase is an enzyme that is synthesized and secreted by specifically activated macrophages. ChT was found to be an excellent marker for lipid-laden macrophages in Gaucher patients and in children with lysosomal storage disorders; it is now widely used to assist clinical management of patients. The last decade has witnessed the appearance of a substantial number of studies attempting to unravel its cellular functions, which have yet not been fully defined [133, 134]. Moreover, an increased ChT has been noted in atherosclerosis, hematological disorders and other conditions where activated macrophages are involved. ChT was previously proposed to quantify the severity of sepsis. In a complex surgical case, with prolonged sepsis and consistently high ChT, it was found that the least increased values occurred in stages of extreme illness, with profound hypocholesterolemia results [135].

ChT in sepsis should be better characterized, correlated to other biomarkers and to clinical events before becoming a reliable biomarker of septic evolution that could be implemented for patient management and decision process. The level of PCT was increased in patients with sepsis and severe inflammatory reactions and become an important prognostic tool. PCT test can be introduced in the daily tracking protocol for septic patients [136]. Presepsin appears to be the most promising new biomarker for early diagnosis of sepsis and a better prognostic biomarker than PCT [137].

Defined as a systemic inflammatory response to infection associated with acute organ dysfunction, severe sepsis is common among *surgical patients* and is a major cause of morbidity and mortality. Sepsis is accompanied by serum levels of several inflammatory markers (IL-6, IL-18, D-dimer) and hemostatic markers, such as protein C, protein S, antithrombin III (ATIII), aPTT and PT [138].

IL-6

IL-6 is a cytokine that has both pro-inflammatory and inflammatory action and is encoded by the IL-6 gene [139]. IL-6 is synthesized in T-lymphocytes, but also by macrophages in stimulating the immune response, as it happens during infection or after traumatic processes, especially burns or other tissue lesions that lead to inflammatory processes. Also, van der Poll *et al.* demonstrated IL-6 mice involvement in controlling infections, since defects in the gene encoding IL-6 lead to defenses of defense against *Streptococcus pneumoniae* bacteria [140].

Synthesis of IL-6 occurs, promptly and transiently because of infectious processes and after tissue damage, thus taking part in host defense mechanisms, mediates acute phase responses, regulates hematopoiesis and plays an important role in chronic inflammation and in autoimmune processes [141]. The complete elucidation of the IL-6-mediated signal transduction system has provided a molecular basis for the characteristic features of cytokines. The production of IL-6 is terminated when tissue homeostasis is restored [142]. Due to the ample effect on immune cells and the fact that it has both pro-inflammatory and anti-inflammatory action, IL-6 has been studied extensively in experimental studies to find molecules that can block the pathways by acting and thus improve disease outcomes and patient comfort [143].

There are studies that aimed to involve IL-6 in surgical pathology or in postoperative complications following various surgery interventions. Thus, in their study, Szczepanik *et al.* [144] were measured serum IL-6 on the first postoperative day (POD) in gastric cancer patients and were found an association between serum IL-6 perioperative values and postoperative morbidity. Other authors have found elevated serum levels of IL-6, IFN-γ and IL-10 in gastric cancer (GC) patients and concluded that these cytokines may be useful as diagnostic serology markers for gastric cancer. IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1) and TGF-β differentiate intestinal from diffuse GC. IFN-γ and IL-10 might be useful for diagnosis of early stage GC, and IL-1β, IL-8, and MCP-1 for late stages of the disease [145].

Other studies have shown a significant correlation of IL-6 serum values with surgical trauma, depending on the duration of the operation, the volume of blood loss during that surgery and thoracotomy. Similar findings were also observed for IL-8. These results indicate that IL-6 and IL-8 are induced and released at the operator field, and then reach the peripheral circulation [146].

IL-18

IL-18 is a protein synthesized by several types of specific cells (macrophages, monocytes, T- and B-lymphocytes, dendritic cells, epithelial cells and keratinocytes) and thus is involved in initiating and modulating various mechanisms of immune response, including autoimmunity and infectious processes [147]. This cytokine induces IFN-γ secretion from the Th1-lymphocyte subpopulation, playing an important role in differentiating Th1-cells, thus being involved in the mechanisms of host defense against intracellular bacteria, viruses and fungi. In a recent study, Esmailbeig & Ghaderi found involvement of IL-18 in differentiation of Th2-lymphocyte subpopulation, as well as IgE synthesis by B-cells, indicating that this cytokine may have dual effects on both Th1- and Th2-cells [148].

In another study, it was determined that the urine concentration of IL-18 in combination with neutrophil gelatinase-associated lipocalin (NGAL) may be a predictor of complications such as acute renal kidney injury (AKI) that may occur after cardiac surgery, complications that increase morbidity and mortality [149].

The study of biological markers in microbial aggression highlights the role of cytokines as messengers and important mediators of immunoinflammatory response [136].

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a protein synthesized in multiple tissues such as renal tubular, intestinal, hepatic and pulmonary tissue. However, in tissue lesions synthesis is especially done in the kidney [150]. Mishra *et al.* have been observed that NGAL concentrations in both urine and serum of patients are serological markers that due to their sensitivity, specificity, high predictability can diagnose early acute renal lesions following cardiac surgery [151]. NGAL level appears to be of diagnostic and prognostic value for AKI. Other outcomes predicted using NGAL were renal replacement therapy initiation and in-hospital mortality [152].

Protein C

Protein C is an important component of the coagulation system, but besides this function, it also has cytoprotective effects, such as anti-inflammatory effects, anti-apoptotic effects and protective endothelial barrier function [153].

The protein C pathway has a normal physiological role to inhibit the conversion of prothrombin to thrombin, thus preventing clotting. By activating the coagulation system and microvascular coagulation the host responds to infectious processes [154]. Also, Macias & Nelson [155] reported decreased plasma protein C levels in patients with sepsis. Furthermore, other authors have shown a strong correlation between low protein C levels and worse outcome [156]. Analysis of the dynamics of coagulopathy in the early days of severe sepsis has shown that its continuation or aggravation is associated with the development of a new organ dysfunction with unfavorable results for the patient [157]. There are studies that have shown that activation of inflammatory pathways can be induced by other conditions at the ICU, including after surgery and traumatic lesions [158]. Boldt *et al.* reported alterations in the hemostatic network in patients with severe trauma and those admitted to ICU after neurosurgical interventions [158]. They also noticed that protein C plasma levels were lower in patients with sepsis than those with severe trauma and neurosurgical interventions were, but the results of the study were limited due to the small number of patients. These studies, which analyzed the dynamics of plasma protein C levels and their relationship to morbidity and mortality, can help the clinician identify high-risk groups and possibly therapeutic targets [159].

Protein S

Protein S is a vitamin K-dependent coagulation protein whose coagulation mechanism is poorly known, and the diagnosis of protein S deficiency and the evaluation of the thrombotic risk associated with this deficit are difficult [160, 161]. Stoppelkamp *et al.* have also analyzed in their study another plasma marker observed to be present in sepsis as soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) [161].

Acute phase proteins

Acute phase proteins, such as CRP, PCT and IL-6 and IL-8 cytokines, had significantly elevated values at the end of surgery in all investigated patients. It has also been observed that these biological markers have a low predictive value in the early diagnosis of SIRS in patients who have undergone cardiovascular surgical procedures. Using the combination of normal serum levels of IL-1β and elevated plasma levels of sTREM-1 at the end of surgery may have a predictive value in SIRS diagnosis but can also be a good indicator for initiating early therapeutic interventions [161, 162].

CRP values were significantly elevated in patients with peritonitis serious complications and were correlated with multiple organic dysfunctions in deceased patients [136]. Siloşi *et al.* consider the dosage of serum matrix metalloproteinases (MMPs) as an alternative diagnostic or additional at CRP and other indicators of inflammatory disease, used in diagnosis of inflammatory bowel diseases [163].

Recent studies showed that the limitations of single biomarker could be overcome through a combination of clinical variables and laboratory traditional and novel markers, which appear more likely to be able to guide diagnosis or treatment, or assist in prognostication of sepsis [164].

Conclusions

Following investigations, several serum biomarkers available for clinical use in sepsis have been shown to have a moderate diagnostic value for sepsis, suspecting the methodological quality and size of the test sample that may affect these results. Studies analyzed, confirms the hypothesis that we do not currently have an ideal biological marker/markers to help in the diagnosis of sepsis. To be an ideal biomarker, it must also be effective and in some cases, effectiveness is limited by insignificant specificity and sensitivity in diagnosing the presence of an infection, inflammatory and immune processes and to triage and group patients according to the evolutionary stage for specific treatments.

Although a large number of markers related to sepsis have been reported in the last two decades, the diagnostic accuracy of these biomarkers remains unclear. Studies in recent decades have also shown that biomarkers have limited ability to predict results and poor diagnostic accuracy to distinguish sepsis from other inflammatory conditions. Also, previous research can provide useful information that can be used for new research and can guide the initiation of new studies.

The development of new molecular techniques and the emergence of new tools can contribute to the discovery of new serological markers that have significant efficacy, sensitivity, specificity and predictive value in the diagnosis of sepsis.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Cristian Adrian Siloşi and Lidia Boldeanu equally contributed to the manuscript.

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