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Biomarkers in infection and sepsis: Can they really indicate final outcome?

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ABSTRACT

Infectious diseases are among the most common reasons for admission to hospital and can easily lead to sepsis. Sepsis is globally associated with increased mortality, and although biomarkers could help clinicians in the early diagnosis of sepsis and immediate onset of antibiotics, there are always questions to be answered about their usefulness in the prognosis of infectious diseases. This article reviews some of the available biomarkers used in infectious diseases and sepsis in order to evaluate their utility to predict mortality and unfavourable outcome. Several studies present the pros and cons of each compound, but it is obvious that the ideal biomarker, with high sensitivity and specificity, cost effectiveness and with definite cut-off ranges and time of blood sampling, is yet to be found.

1. Introduction

Q2 Infectious diseases are very common in hospitalised patients. Most of them can lead to sepsis, especially in the intensive care unit (ICU) [1]. Sepsis is one of the main causes of death globally [2]. The main reason behind this remains the delay in diagnosis and treatment. Diagnosis of infectious diseases and sepsis may be difficult for clinicians for many reasons, such as previous antibiotic therapy [3]. It is difficult to predict unfavourable outcome, despite great efforts that have been made towards early diagnosis and prognosis, mainly with the use of biomarkers [4].

Biomarkers can help in the early diagnosis of infectious diseases, predict prognosis and help the clinician in antibiotic stewardship. A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' [2]. In the literature, 178 biomarkers have been described but only a few of them are really useful in clinical practice because most of them lack sensitivity and specificity [2]. In addition, an ideal biomarker should be easily measurable in body fluids and the results should be available in a short period of time [5]. Moreover, for most of them there is a lack of studies confirming their usefulness, mainly due to the related cost.

This article reviews several of the available biomarkers used in infectious diseases (Table 1), focusing on the 'classic' and promising. The question addressed is whether or not we need these biomarkers in the prognosis of sepsis and infectious diseases.

2. Acute-phase proteins

2.1. C-reactive protein (CRP)

CRP is a short pentraxin, synthesised in the liver, mostly in response to stimulation with interleukin-6 (IL-6) [6]. It was first described by Tillet and Francis in 1930 when they isolated it from patients with pneumonia caused by *Streptococcus pneumoniae* [7]. Normal concentrations are <0.8 mg/L [2]. It is used to confirm inflammation, mainly in the acute phase of an infection. However, it carries a low specificity, making its use as a biomarker in sepsis controversial [8].

Use of CRP as a prognostic biomarker does not appear to be helpful in infectious diseases. Vassiliou et al. studied 89 critically ill patients admitted to a general ICU who did not meet any sepsis criteria at the time of their admission [9]. Within the first 24 h after admission, blood samples were drawn and CRP was measured. Of the 89 patients, 45 eventually became septic and 44 did not. The analysis showed no relationship between CRP and sepsis development over time [9].

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Table 1
Biomarkers reviewed in this paper.

Biomarker	Comment
C-reactive protein	Acute-phase protein biomarker
Procalcitonin	Acute-phase protein biomarker
Serum soluble urokinase-type plasminogen activator receptor (suPAR)	Receptor biomarker expressed on neutrophils, lymphocytes, monocytes/macrophages, endothelial and tumour cells
Soluble triggering receptor expressed on myeloid cells (sTREM)-1	Receptor biomarker expressed on monocytes, neutrophils, granulocytes, dendritic cells and natural killer cells
E- and P-selectin	Adhesion molecules; biomarkers related to vascular endothelial injury
Angiopoietin-2	Biomarker related to vascular endothelial injury

In several other studies, CRP levels had no correlation with severity scores such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores in patients with sepsis [10,11]. In one study, 201 septic patients were enrolled and the values of CRP among groups with different APACHE II scores and SOFA scores were compared. CRP was not significantly different between non-survivors and survivors ($P = 0.665$) and was not significantly correlated with APACHE II and SOFA scores [10]. The second study to confirm these results was by Luzzani et al. [11]. In that study, 800 patients participated and serum procalcitonin (PCT) and CRP were measured daily. The enrolled patients were separated into three groups by their SOFA score: (i) 1–6; (ii) 7–12; and (iii) 13–18. CRP did not differ between the three groups [11].

In a study of 48 patients with acute pancreatitis, the study endpoint was identification of factors that can predict early necrosis infection [12]. CRP, PCT, IL-6 and tumour necrosis factor-alpha (TNFα) were measured on the first 3 days post admission. Although PCT and IL-6 levels were increased in those who eventually developed infection of necrosis, CRP and TNFα were not significantly different between the patient group that developed infection of necrosis and those who did not [12].

In another study of 194 patients with burns and sepsis, the receiver operating characteristic (ROC) curve analysis showed that serum levels of PCT and CRP had poor predictive value for sepsis prognosis ($P > 0.05$) [13].

2.2. Procalcitonin

PCT, the prohormone of calcitonin, is produced by C-cells of the thyroid gland [2]. In the past it was considered as a hormone produced only by the latter. However, in microbial infections and inflammatory processes its levels rise and it is a useful biomarker for the severity of infection and antibiotic administration [14]. Normal levels in serum are <0.1 ng/mL, whilst PCT starts to rise ca. 4 h after infection onset [15]. The main advantages of PCT in comparison with other biomarkers are that it increases early in the event of infection, it can be used even under immunosuppressive medication and it has better negative prognostic value. Finally, it appears to have a better correlation with outcome, although it has its own limitations [16].

A prospective study by Frasquet et al. enrolled 51 patients with acute pancreatitis [17]. Blood samples were drawn within the first day of admission. Of the 51 patients, 15 suffered from severe acute pancreatitis and 36 from mild acute pancreatitis. The PCT strip test showed a sensitivity of 26.7%, a specificity of 77.7%, a positive predictive value (PPV) of 33.3% and a negative predictive value of 71.4% for the development of an infection [17].

In a promising study, Giamarellos-Bourboulis et al. found that PCT levels on Day 1 could predict the types of organ dysfunction in patients who eventually progressed to multiple organ dysfunction syndrome (MODS) [18]. Although some promising studies encourage the use PCT as a marker of unfavourable outcome, more studies are needed in order to confirm this feature.

3. Receptor biomarkers

3.1. Serum soluble urokinase-type plasminogen activator receptor (suPAR)

suPAR is the soluble form of urokinase-type plasminogen activator receptor (uPAR), which is expressed on neutrophils, lymphocytes, monocytes/macrophages, endothelial cells and tumour cells. suPAR participates in several processes, such as chemotaxis, migration and invasion [19]. Normal values range between 1.2 ng/mL and 4.0 ng/mL [20,21]. Although suPAR may not be useful as a diagnostic marker in patients with infections [19], it appears to be a good prognostic marker, especially when combined with other markers or scores. In a study from the Hellenic Sepsis Study Group on 1914 patients, prediction of outcome could be done by suPAR combined with APACHE II score [22]. More precisely, four risk groups were developed: (i) APACHE II <17 and suPAR <12 ng/mL with mortality 5.5%; (ii) APACHE II <17 and suPAR ≥12 ng/mL with mortality 17.4%; (iii) APACHE II ≥17 and suPAR <12 ng/mL with mortality 37.4%; and (iv) APACHE II ≥17 and suPAR ≥12 ng/mL with mortality 51.7% [22].

Koch et al. prospectively studied 273 patients (197 with sepsis and 76 without sepsis) [23]. The study showed that increased suPAR levels at admission and on Day 3 were connected with ICU and long-term mortality. More specifically, suPAR >8 ng/mL on admission or >13 ng/mL on Day 3 was associated with unfavourable outcome [23]. Another study by Savva et al. showed that suPAR is an independent predictor of mortality in patients with sepsis and ventilator-associated pneumonia; levels of >12.9 ng/mL showed 80% specificity and 76.1% PPV for unfavourable outcome [24].

3.2. Monocytic surface and soluble triggering receptor expressed on myeloid cells (TREM)-1

TREM-1 is a member of a large family of TREM protein receptors, expressed in phagocytes. Although many functions of TREM-1 are not well investigated, it is known that it plays a role in the regulation of T-cell proliferation and activation of antigen-presenting cells [25].

Xie et al. examined the value of soluble (s) TREM-1 to predict the outcome of early-onset stroke-associated pneumonia (EOP) [26]. Among 207 patients with stroke, 91 developed EOP, 52 of whom survived and 39 who did not within the first 28 days. Interestingly, serum sTREM-1 levels were slightly elevated on Days 1, 3 and 5 in the patients who died and were decreased in the patients who survived; sTREM-1 levels were significantly higher in non-survivors than in survivors. The sensitivity and specificity of sTREM-1 to predict unfavourable outcome were 71.8% and 92.3% respectively [26].

Bopp et al. studied 65 patients with different stages of sepsis and 21 healthy controls. The results showed no significant difference in sTREM-1 concentrations between survivors and non-survivors on any day of measurement [27].

4. Biomarkers related to vascular endothelial injury

4.1. E- and P-selectin

E- and P-selectin are endothelium-related molecules expressed on activated endothelial cells promoting leucocyte adhesion [28]. They have been studied as biomarkers not only for diagnosis

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