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Clinical and Laboratory Predictors of Mortality in Septic Patients on ICU Admission

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Abstract

Sepsis is one of the leading causes of death for patients in the Intensive Care Unit (ICU). In the case of suspected or proven infection, sepsis is defined with increasing severity as (uncomplicated) sepsis, severe sepsis and septic shock. The present review aimed to present and discuss the literature about the prognostic value for survival or death of clinical and laboratory parameters in septic patients on ICU admission. Among laboratory parameters special attention was paid for the various disorders of the blood coagulation system and the immune and inflammatory response (i.e., levels of pro- and anti-inflammatory cytokines and other biomarkers of sepsis). We concluded that in patients admitted to the ICU with a suspected or confirmed diagnosis of infection and sepsis, the various clinico-laboratory scores and measurements [i.e., Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, Lung Injury Score (LIS), and PaO2/FiO2) seem to have a significant predictive value in terms of survival or death in almost all three groups of septic patients. Ant thrombin III and Protein C activity, as well as lactate level, have prognostic value in patients with severe sepsis or septic shock. Coagulation factors' activity, as well as cytokine, procalcitonin and thrombopoietin levels have some predictive value only in distinct groups of septic patients.

Keywords: Sepsis; Septic shock; Coagulation; Coagulation inhibitors; Procalcitonin; Thrombopoietin; Cytokines; Antithrombin III; Protein C

Abbreviations

ICU: Intensive Care Unit; SIRS: Systemic Inflammatory Response Syndrome; PCT: Procalcitonin; TPO: Thrombopoietin; TNF-a: Tumor Necrosis Factor a;IL-6: Interleukin 6; IL-1b : Interleukin 1β; IL-10:Interleukin 10; ATIII: Antithrombin III; PrC: Protein C;Dds: D-dimmers; PT: Prothrombin time; Lactate: Lactic acid; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; LIS: Lung Injury Score; ARDS :Acute Respiratory Distress Syndrome; ROC: Receiver Operating Characteristic; AUROC: Area Under The ROC

Introduction

Sepsis is one of the leading causes of death for patients in the Intensive Care Unit (ICU) and a major contributor to the growing financial burden of medical care worldwide [1,2]. As a series of inflammatory and homeostatic changes that occur as a reaction to systemic infection, sepsis is defined as the suspected or proven infection and coexisting Systemic Inflammatory Response Syndrome (SIRS: fever, tachycardia, tachypnea, leukocytosis, etc.) [3-6]. Severe sepsis is defined as sepsis in combination with organic dysfunction (hypotension, hypoxemia, metabolic acidosis, thrombocytopenia, etc) [3-6]. Septic shock is defined as severe sepsis in combination with hypotension despite the adequate recovery of body fluids [3-6].

In 2016, a new definition of sepsis was created (Sepsis-3), according to which sepsis is defined as an infection that causes organic dysfunction, with the abolition of the term SIRS when referring to sepsis and the term severe sepsis [7-9]. However, there are conflicting views in the literature as to the necessity of the new definition and objections, in particular to the abolition of the term SIRS [10]. Nevertheless, we will use the old definitions in this review.

Septic shock and multiorgan dysfunction are the most common causes of death in patients with sepsis [3-6]. Several systemic factors that interact to promote organic deficiency have been evaluated in many studies, suggesting that coagulation disorders occur even before the onset of clinical symptoms of severe sepsis or septic shock, are associated with the severity of the disease, and are likely to predict mortality [2,5,6,11]. Also, pro-inflammatory cytokines and other molecules, like the hormone thrombopoietin (TPO), have been systematically screened, considered biomarkers of severity, and possibly able to predict the final outcome in the sense of survival or death of the septic syndrome [12,13].

The present review aimed to present and discuss the literature about the prognostic value for survival or death of clinical and laboratory parameters in septic patients on ICU admission. Among laboratory parameters special attention was paid for the various disorders of the blood coagulation system and the immune and inflammatory response (i.e., levels of pro-

and anti-inflammatory cytokines and other biomarkers of sepsis).

Literature Review

Severity scores and usual laboratory parameters

SOFA score: The Sequential Organ Failure Assessment (SOFA) (range 0-24, with higher scores indicating more severe illness) rating index is a simple but effective method to describe organ dysfunction in severely ill patients. It was originally designed to evaluate/describe and not to predict the survival expectancy of seriously ill patients [14,15]. It includes the evaluation of 6 organ-systems with a score of 0-4 for each organ-system. Systematic and repetitive scoring helps to better monitor and understand the clinical picture of patients [15]. SOFA score does not work only for septic patients, and the European-North American Study of Severity System database showed a satisfactory correlation of the SOFA score with survival [14,16]. Indeed, in a study by Vincent et al, data were collected from 1449 critically ill patients in 40 ICUs and the SOFA score was found to be satisfactorily related to survival [14]. Respiratory failure was more common than other organ dysfunctions and was a very sensitive parameter.

Thus, patients with respiratory failure had a higher SOFA score in a shorter period of time than patients with hepatic impairment. This has been attributed to the fact that the increase in bilirubin takes time and may therefore lead to liver failure being recognized later [14]. Another study evaluated the mean and highest value of the SOFA score as prognostic indicators of survival; regardless of the initial value, an increase in the SOFA score in the first 48 hours after admission to the ICU is a predictor of mortality of at least 50% [15]. In our study, SOFA score also had a very significant predictive value in all groups of septic patients on ICU admission [Area under the Receiver Operating Characteristic (AUROC) curves 0.72-0.82] [17].

APACHE II score: Acute Physiology and Chronic Health Evaluation (APACHE) II score (range 0-71, with higher scores indicating more severe disease and a higher risk of death) is widely used in ICUs as a system for assessing the severity of the general condition of the patients [18]. An earlier study comparing the initial APACHE II values of patients entering the ICU with the worst values of the first 24 hours showed that the two scores in critically ill non-injured patients did not differ in their predictive capacity [19].

In patients with ventilator-associated pneumonia, APACHE II appeared to be the most reliable tool for predicting mortality compared to other suggested scores [20]. In a relatively recent study, the ability of APACHE II to predict in-hospital mortality in critically ill patients declines over the years, leading authors to suggest a possible renewal of some of its parameters [21]. In contrast, other researchers argue that it remains useful to differentiate patients by their severity using APACHE II [22]. In our study, the APACHE II score had a significant predictive value on ICU admission in all three groups of septic patients (AUROCs 0.76-0.84).

PaO_2/FiO_2 ratio and lung injury score: On ICU admission, both PaO_2/FiO_2 ratio and Lung Injury Score (LIS) [with 0 indicating the absence of acute lung injury, 0.1-2.5 indicating the presence of mild-to-moderate acute lung injury, and >2.5 indicating the presence of Acute Respiratory Distress Syndrome (ARDS) could predict the need for mechanical respiratory support, but PaO_2/FiO_2 ratio was a better prognostic indicator for the length of stay in the ICU compared to the LIS [23,24]. LIS has also been used as a predictor of mortality with higher values associated with increased mortality [23,25]. Generally, patients with septic shock have usually a more severe degree of respiratory failure than patients in the other septic groups (higher LIS and lower PaO_2/FiO_2 ratio) [17]. LIS also had a significant predictive value in all three groups of septic patients (AUROCs 0.78-0.82) [17]. Furthermore, PaO_2/FiO_2 ratio had a significant predictive value for the groups of patients with severe sepsis and septic shock (AUROCs 0.90 and 0.79, respectively) [17].

Lactic acid: The relationship between elevated blood lactic acid levels and tissue hypoxia has been noted since 1927 in patients with shock [25]. Several experimental and clinical studies have shown that lactate levels increase in tissue hypoxia [26]. Moreover, elevated lactate levels are sufficient to diagnose shock regardless of hypotension, and lactate levels are indicators of mortality rate in patients with trauma and sepsis [27,28]. Sepsis with lactate levels ≥ 4mmol/l is associated with high mortality and is an indication for initiation of treatment protocols [29].

Meregalli et al showed that in postoperative patients with similar hemodynamic parameters blood lactate levels in the first 12 hours after ICU admission are those that will predict survival. Changes in lactate levels over time can be a predictor of survival and show a response to treatment [30]. Vincent et al described changes in lactate levels over time after resuscitation in patients with circulatory shock and showed that those patients who died did not present a decrease in baseline lactate levels after resuscitation [31].

Other authors, studying only patients with multiple injuries, showed that the improvement of hemodynamic parameters, i.e., cardiac output, oxygen consumption, and oxygen supply, are not predictive indicators of survival, whereas the optimization of blood lactate levels is a prognostic indicator of survival [32]. In our study, at the time of ICU admission, patients with septic shock had higher blood lactate levels than patients in the other septic groups, and lactate levels had a significant predictive value for this group of patients with septic shock (AUROC 0.87).

Coagulation system

Coagulation disorders are strongly linked to the process of sepsis. For example, fibrinolysis which involves a complex system of activation and inhibition mechanisms is affected during sepsis so that the result is reduced fibrinolysis, deposition of microthrombi in the vascular bed, and multiorgan failure [33].

Platelets: Platelets play an important role in the normal formation of thrombus-hemostasis. After activation, they change shape to increase their ability to adhere by activating

glycoprotein receptors on their surface [34]. Activated platelets secrete various proteins including oxidizing agents, platelet-activating agents, complement proteins, cytokines, and other enzymes that modulate their action but also affect the action of the cells to which they attach (endothelium and neutrophils) [34]. However, platelet activation also has potentially detrimental effects.

Platelet aggregation in the area of inflammation may be responsible for microcirculation disorders, thus contributing to organ dysfunction and insufficiency in patients with sepsis [35,36]. Of course, their primary role is to activate the defense mechanisms that will contribute to healing in the area of the lesion and vascular remodeling [36,37].

An acute decrease in platelet count occurs in the early stages of many diseases. It is due to various causes such as reduced production, increased consumption, or pathological fragmentation [38]. Their reduced production may be due to suppression of the bone marrow by infectious agents, toxic drugs or mediators of inflammation. Their increased destruction is often a side effect of drugs, such as heparin which through immunostimulation can reduce the half-life of platelets [39]. Injured or postoperative patients lose circulating platelets, thus showing thrombocytopenia in severe cases. Patients, especially after cardiac surgery, have platelet dysfunction after the extracorporeal circulation which they undergo [40].

Thrombocytopenia is common in severely ill patients and has been associated with a worse prognosis in several studies [36, 37]. Patients with ARDS may have reduced platelet counts due to their entrapment in the lungs, while patients with diffuse intravascular coagulation have a high consumption of platelets and coagulation factors from the micro vascular network of many organs [41]. Thrombocytopenia in patients admitted to the ICU is an indicator of poor prognosis and is associated with a longer stay in the ICU [38]. Akca et al., reported that thrombocytopenia in septic patients had a relative risk for death of 1.66 while Brun–Buisson et al., found a relative risk of 1.5 in patients with platelet counts<50.000/ml [42].

Although thrombocytopenia in an ICU has been associated with worse survival expectancy, the exact correlation between the change in platelet count over time and the mortality rate has not been established [40,42]. Akca et al., showed changes in platelet counts in severely ill patients with a biphasic pattern that differed in those who survived from those who died. Late thrombocytopenia was associated with increased mortality compared to early; although thrombocytopenia was more common on the 4th day of hospitalization than on the 14th, the mortality rate was higher in late thrombocytopenic patients [40].

Moreover, in thrombocytopenic patients, an increase in platelet count occurred in surviving patients but was not observed in those who died [40]. In this study, individual platelet counts were of little value in predicting life expectancy, but changes in their number over time correlated with patient life expectancy [40]. Similar biphasic changes in platelet counts have been reported in postoperative patients and myocardial infarction, as well as healthy donors after plasmapheresis[43-45].

Smith-Erichsen showed this biphasic distribution in a small study of 18 surgical patients with severe sepsis [46]. Patients who died had persistent thrombocytopenia while survival was associated with the degree of thrombocytopenia over two weeks [46]. In another study, a large number of ICU patients were evaluated and no correlation was found between platelet count on admission and survival [47]. However, patients who eventually died appeared to have a smaller increase in platelet count between days 2 and 10 than those who survived [47]. In our study, the predictive value of platelet counts was negligible.

Prothrombin time: Prothrombin time (PT) is often prolonged in septic patients [46]. In the study by Dhainaut et al, changes in PT overtime alone were almost equally capable of predicting mortality at 28 days compared with a combined assessment of D-dimmers and Antithrombin III (ATIII) but had a lower value for the prognosis of multiorgan failure [47]. In our study, the predictive value of PT was nil in all septic groups.

Antithrombin III: The activity of the coagulation inhibitor ATIII is frequently low in severely ill patients. This decrease in the activity of ATIII, as well as that of the other coagulation inhibitor Protein C (PrC), is caused by the combined action of various processes, such as: (a) overconsumption due to increased thrombin production, (b) degradation by plasma elastases, which are released by activated neutrophils, and (c) insufficient synthesis [48, 49, 48-54].

Indeed, thrombin is produced and competes with ATIII, resulting in low levels of ATIII in the blood of most patients with severe inflammation [48,49,51-54]. In general, a hepatic impairment that patients with sepsis may experience affects the coagulation mechanism by reducing the synthesis of coagulation proteins (including coagulation inhibitors) and by reducing the clearance of activated enzymes and complexes of enzymes-inhibitors [48,51,52]. In our study, on ICU admission, ATIII had lower activity in patients with severe sepsis or septic shock than in those with sepsis, and ATIII activity had sufficient predictive value in the group of patients with severe sepsis (AUROC 0.74) **(Figure 1)**.

Protein C: Besides its action as a coagulation inhibitor, PrC contributes to fibrinolysis, as follows: The conversion of plasminogen to plasmin is activated by tissue-type plasminogen activator (t-PA) and urokinase-like plasminogen activator (uPA). Endothelial cells are the main source of t-PA but t-PA can also be isolated in other tissues [55]. The fibrinolytic process has two levels: initially, these activators can be inhibited by the plasminogen activator inhibitor type 1 (PAI-1) produced by the endothelium and form complexes with them so that they cannot activate the plasminogen [55,56]. The action of PAI-1 is also inhibited by activated PrC which binds and inactivates PAI-1, thus increasing fibrinolysis. In most patients with sepsis or septic shock, PrC activity decreases and is associated with an increased risk of death [11,57,58].

Bernard et al showed reduced PrC activity (by approximately 50%) in patients with severe sepsis, whereas Lavranou et al demonstrated similar reduction of PrC activity in patients with

septic shock [59]. In this latter study, PrC had sufficient predictive value in both patients with severe sepsis and septic shock (AUROCs 0.75 and 0.78, respectively) [17] **(Figure 1)**.

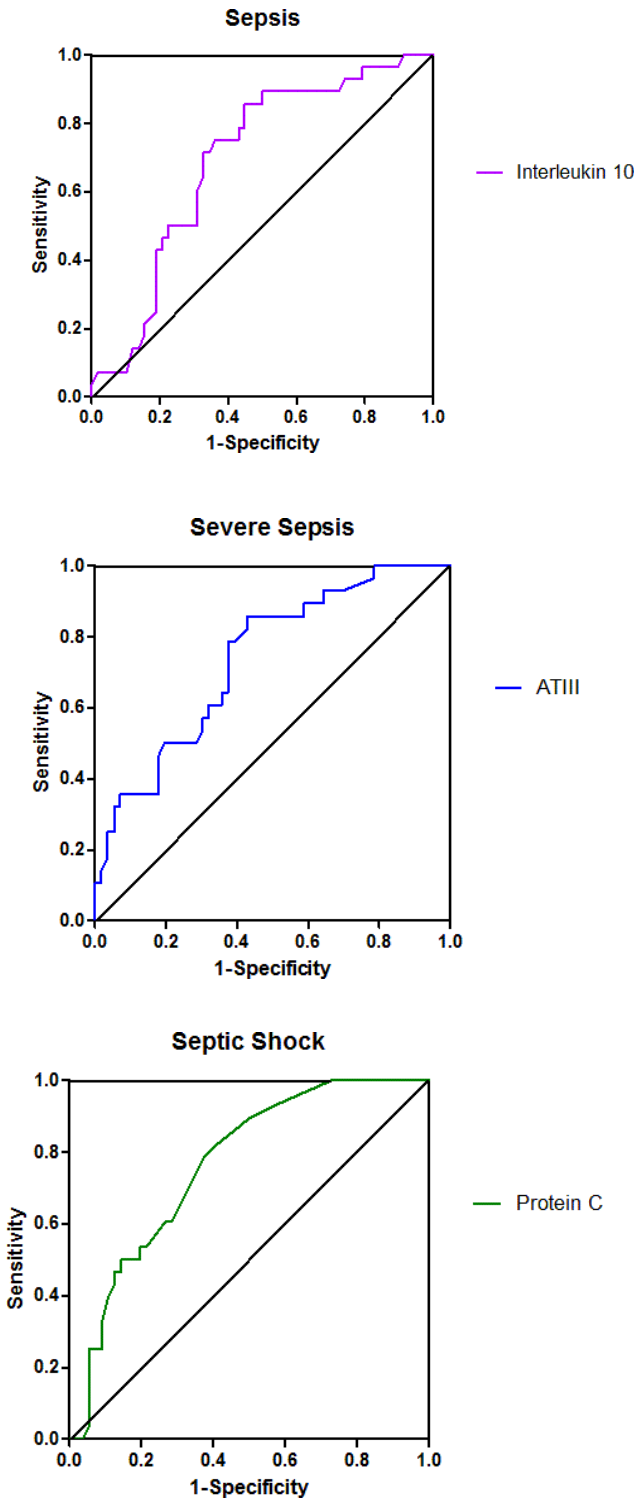

Figure 1: Receiver operating characteristic curves for Inteleukin 10, Antithrombin III (ATIII) and Protein C in sepsis, severe sepsis and septic shock, respectively; the areas under the curves, indicating the predictive value of each variable in terms of patient deterioration or improvement, were 0,72 ([95% confidence interval], 0,51-0,87), 0,74 (0,62-0,86) and 0,78 (0,62-0,88), respectively [17].

Coagulation factors: It has been found that the activity of all coagulation factors is gradually reduced in severe sepsis and primarily in septic shock, mainly due to depletion of homeostatic mechanisms [11,58]. Among many coagulation factors measured on ICU admission, only the reduced activity of FVII and FIX showed sufficient (AUROC 0.72) and poor (AUROC 0.67) predictive value of death, respectively [17].

Cytokines

Interleukin 1b, 6 and 10: Many studies have been performed to evaluate interleukins (ILs) as prognostic markers of death/ survival. In the study of Bozza et al., IL-1b and IL-6 appeared to be the best prognostic markers compared to other cytokines and their prognostic value was much better than the initial evaluation of patients based on the APACHE II score [60]. Several other studies have shown that the majority of patients with sepsis have elevated IL-6 levels and these levels have been associated with severity and survival expectancy [61-63]. Constantly elevated IL-6 levels have been associated with multiple organ failure and death.

Il-1b is not normally identified in the serum but is detected in the serum of patients with sepsis. McAllister et al,. Detected IL-1b in the serum of patients who developed sepsis after being transfused with concentrated red blood cells infected with Gram negative bacteria [64]. These patients had detectable IL-1b that peaked 4 hours later and returned to normal in two surviving patients while remained elevated for 22 hours in the patient who eventually died. IL-1b is not detected in all septic patients but is an indicator of sepsis severity [65]. Endo et al., found elevated serum IL-1b levels in only 2 of 40 patients with sepsis, but in 15 of 22 patients with septic shock [66].

The findings of Lavranou et al., are consistent with those of Endo et al., because IL-1b levels in patients with septic shock were significantly higher than those in patients with sepsis when patients were admitted to the ICU. Goldie et al. detected plasma IL-1b in 29% of 146 patients with sepsis but found no association with mortality [67]. Generally, studies to date show that IL-1b is elevated in the serum of some patients with sepsis and that initial concentrations may be associated with disease severity but not with mortality [65-67].

IL-10 was originally described as an inhibitor of cytokine production by activated macrophages. Gerard et al., showed that administering IL-10 to mice before endotoxin infusion protects against endotoxin-induced mortality and reduces TNF-α production, while other authors showed that administering anti-IL-10 mice antibodies increase TNF-α production and mortality [68]. Several studies have shown that IL-10 is detected in the serum of patients with sepsis.

Van Deuren et al., found higher concentrations in patients with septic shock than in septic patients without shock and other authors reported higher concentrations in patients with septic shock than in patients with uncomplicated sepsis; however, these results were not confirmed by findings of septic patients on ICU admission [17,69]. Nevertheless, in the study by Lavranou et al., IL-1b and IL-10 levels had significant predictive value only in the group of patients with uncomplicated sepsis,

because IL-1b and IL-10 levels were higher in patients who died compared to those who survived with sufficient predictive value (AUROCs 0.71 and 0.72, respectively) **(Figure 1)**.

TNF-a is a precursor of inflammation in a large number of inflammatory diseases, infectious and non-infectious [67]. TNF-a can be detected in the serum of many patients with sepsis and its concentrations are correlated with both severity and prognosis. Endo et al., showed that the serum concentrations of TNF-a, IL-1b, and IL-6 in patients with septic shock were higher than those in patients with uncomplicated sepsis, or with shock from other causes. The findings of Lavranou et al., were consistent with those of Endo et al., because TNF-a levels of patients with septic shock were significantly higher than those of patients with sepsis upon admission to the ICU.

Casey et al., showed that TNF-a, IL-1b, and IL-6 levels in patients with sepsis may have been higher compared to those in non-sepsis ICU patients, but TNF-a levels alone had no predictive value in terms of mortality [70]. In other studies, elevated TNF-a concentrations were associated with a worse prognosis in patients with sepsis [62,71]. Martin et al., repeatedly measured TNF-a and IL-6 in patients with septic shock and showed that non-surviving patients had consistently higher TNF-a levels compared with those in survivors.

Other authors reported that TNF-a concentrations were higher in patients with septic shock compared to non-septic shock and that constantly increased serum TNF-a concentrations predict a worse outcome in patients with shock. Overall, persistently increased concentrations of TNF-a appear to have a better predictive value for survival than individual measurements. In the study by Lavranou et al.,TNF-a levels were higher in patients who died compared to those who survived only in the group of patients with uncomplicated sepsis, however with poor predictive value (AUROC 0.66).

Inflammatory markers

Procalcitonin (PCT) in the blood of healthy individuals has values <0.1 ng/ml. In bacterial as well as fungal infections, PCT levels are found to be elevated to some degree, depending on the severity of the infection. Thus, in septic patients, PCT levels may increase 5.000–10.000-fold, while calcitonin levels remain within normal limits [72]. In SIRS due to serious and dangerous infections, such as severe sepsis or septic shock, serum PCT levels are particularly high, in contrast to SIRS due to non-infectious causes where PCT levels are usually low.

A significant number of studies confirm that PCT is an indicator of serious infection and sepsis. Patients with PCT levels ≤ 0.5 ng/ml are unlikely to have severe sepsis or septic shock, while levels >2 ng/ml are found in patients at high risk for sepsis or septic shock [73,74]. These findings agree with those of the recent study by Lavranou et al., where, at the time of admission to the ICU, PCT levels of patients with septic shock or severe sepsis were significantly higher than those of patients with uncomplicated sepsis.

TPO is a glycoprotein hormone that regulates the number of circulating platelets by stimulating the growth and maturation of megakaryocytes [75,76]. It is also involved in the later stages of erythropoiesis and induces the proliferation of CD34+ progenitor cells [76]. TPO is produced mainly in the liver and secondarily in the kidney by non-hematopoietic cells. Elevated TPO levels have been detected in septic patients with or without diffuse intravascular coagulation; TPO levels may not be inversely related to platelet counts, which reinforces the view that inflammatory cytokines are involved in TPO regulatory mechanisms [13].

Moreover, the correlation of TPO levels with the severity of sepsis has already been reported [13]. These findings are consistent with those of the study by Lavranou et al., since TPO levels in patients with septic shock or severe sepsis were significantly higher than that of patients with uncomplicated sepsis. Nonetheless, both PCT and TPO upon admission to the ICU were higher in patients who died compared to those who survived only in the group of patients with severe sepsis with sufficient predictive value (AUROCs 0.73-0.75) [17].

Conclusion

In patients admitted to the ICU with a suspected or confirmed diagnosis of infection and sepsis, the various clinico-laboratory scores and measurements (i.e., APACHE II, SOFA, LIS, and PaO2/FiO2) seem to have a significant predictive value in terms of survival or death in almost all three groups of septic patients. ATIII and PrC activity, as well as lactate level, have prognostic value in patients with severe sepsis or septic shock. Coagulation factors' activity, as well as cytokine, PCT and TPO levels have some predictive value only in distinct groups of septic patients.

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