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# Prognostic value of hemostasis-related parameters for prediction of organ dysfunction and mortality in sepsis

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**Background/aim:** Clinical manifestations of sepsis are not caused directly by the invading pathogens, but rather mostly by systemic inflammation that leads to activation of the coagulation system. The aim of this study was to determine whether levels of hemostasis-related parameters measured in intensive care unit admissions are associated with mortality and severity in patients with sepsis.

**Materials and methods:** Eighty-five patients who fulfilled criteria for a diagnosis of sepsis were included in our study. Platelet count, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time, D-dimer, and fibrinogen levels were determined within the first 24 h from sepsis onset. Differences between groups of septic patients were assessed by Mann–Whitney U test and Kruskal–Wallis test. Logistic regression analysis was performed to test the joint effect of different predictors.

**Results:** Prolonged aPTT and PT with higher D-dimer concentrations in patients with sepsis are associated with more severe forms of the disease. aPTT was prolonged in nonsurvivors, while platelet count and fibrinogen levels were higher in survivors. Platelet count and aPTT ratio are independent predictors of fatal outcome in our logistic regression model.

**Conclusion:** Hemostasis-related parameters have a significant impact on severity and outcome in sepsis.

**Key words:** Sepsis, hemostasis, multiple organ failure, shock, prognosis

## 1. Introduction

Sepsis is associated with high morbidity in intensive care units (ICU) and the sepsis mortality rate increased in the past decade (1). Much effort has been made to find a useful tool that could contribute to early recognition and complication development prediction in patients with sepsis, in order to ease the decision-making related to treatment (2). There are many existing clinical scores for predicting severity and organ dysfunction in critically ill patients and they also apply to patients with sepsis. However, none of them have been proven to be superior to others due to the complex pathophysiology of sepsis (3,4).

Clinical manifestations of sepsis are not caused directly by the invading pathogens, but rather mostly by systemic inflammation that leads to activation of the coagulation system and inhibition of anticoagulant mechanisms and fibrinolysis (5,6).

During sepsis, microbial products induce synthesis and the release of inflammatory mediators. Although the primary function of these mediators is to assist the host in eliminating life-threatening infections, they are also responsible for deleterious effects on the host and eventual death (5–7).

The coagulation cascade is activated with endotoxins and amplified by proinflammatory cytokines like interleukin (IL)-6, tumor necrosis factor-alpha, and IL-1. Thrombin generation intensifies the inflammatory response at sites of infection and can result in disseminated intravascular coagulation (DIC), which can be associated with high risk of death from sepsis (8,9). Not only

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does systemic inflammation lead to the activation of coagulation, but the coagulation system also modulates the inflammatory response through protease-activated cell receptors and activation of platelets (9,10).

Data from the literature indicate that clinically relevant coagulation abnormalities occur in 50%–70% of patients with sepsis, while the incidence of thrombocytopenia (platelet count of $<150 \times 10^9$/L) can be found in 35%–50% of patients and prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) occur in 14% to 28% of patients, whereas about 35% of patients meet the criteria for DIC (11).

Bearing in mind the importance of the intricate relationship between systemic inflammation and coagulation, insight into the function of hemostasis may lead to identification of new targets for therapies that can modify complications caused by this cross-talk (9,10).

Although there are simple laboratory tests that bring insight into coagulation integrity, only a few studies have researched coagulation markers that are available in the routine hospital setting for prediction of outcome in sepsis (8,12).

The primary aim of this study was to determine whether levels of hemostasis-related parameters (platelet count, aPTT, PT, thrombin time (TT), fibrinogen, D-dimer) measured within 24 h of ICU admission are associated with 28-day mortality in patients with sepsis.

The secondary aims of this study included evaluation and comparison of coagulation markers and ICU scores between different groups of septic patients according to severity upon admission and development and persistence of multiple organ dysfunction syndrome (MODS) in the first 48 h.

## 2. Material and methods

The study was approved by the relevant ethics committee of the Clinical Center of Vojvodina and the Medical Faculty of Novi Sad, and all participants gave informed consent before enrollment in the study.

### 2.1. Patients

Patients treated in the Department of Anesthesia and Reanimation at the Emergency Center of the Clinical Center of Vojvodina and in the Clinic of Infectious Disease at the Clinical Center of Vojvodina from 1 April 2012 to 1 July 2013 with a clinical diagnosis of sepsis as defined by the Consensus Conference Committee of the American College of Chest Physicians/Society of Critical Care Medicine 1992 and revised based on the International Sepsis Definitions Conference 2001 (13,14) were eligible for this study.

Exclusion criteria were applied to polytraumatized patients; patients in hemorrhagic shock and patients with malignancy, liver failure, or cardiac failure; pregnant women; and patients who were on anticoagulant therapy or treated with vitamin K antagonists. Patients with systemic inflammation caused by some other condition, like burns and pancreatitis, were also excluded from the study.

Basic laboratory tests were performed within the first hour of ICU admission (complete blood count, urea and creatinine levels, bilirubin level, and concentrations of C reactive protein and procalcitonin). The Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and Mortality Probability Model II (MPM II) were assessed upon ICU admission.

Patients were classified into 4 groups representing different forms of sepsis severity according to predefined criteria upon ICU admission (13,14).

To assess the development of complications and also the outcome of the disease, we monitored patients from the day of sepsis development to 28 days after admission to ICU.

### 2.2. Hemostasis biomarkers

Platelet count ($n \times 10^9$/L) was determined as a part of complete blood count on a CELL-DYN Sapphire ABBOT machine by flow cytometry with commercial kits from the same manufacturer. PT, TT, and aPTT (ratio (R)) were determined by coagulation method with IL reagents (Instrumentation Laboratory, Italy) on ACL 9000 machines. Fibrinogen concentration (g/L) was obtained by the Claus coagulation method with IL reagents on ACL 9000 machines. D-dimer levels (ng/mL) were determined by latex immunoassay methodology with IL reagents.

### 2.3. Statistical analysis

All data were analyzed using SPSS 20.0. Data are expressed as mean ± standard deviation (SD) or numbers (%). Since most continuous variables were skewed, nonparametric approaches were used. Differences between variables were assessed by the Mann–Whitney U test and Kruskal–Wallis test. Categorical variables were compared using the chi-square test.

To determine significant relationship between investigated data, we used Kendall's tau correlation. Logistic regression analysis was performed to test the joint effect of different predictors added to the model. All P-values were 2-sided and statistical significance was set at $P \leq 0.05$.

## 3. Results

Out of the 85 patients included in this study, 50 were male and 35 were female, all between the ages of 19 to 87 years. Patients were classified into 4 groups, simple sepsis, severe sepsis, septic shock, and MODS, upon admission to the ICU. Development of MODS in the first 48 h was noted; its persistence or resolution was noted in the groups of patients with sepsis, severe sepsis, and septic shock.

Table 1 shows clinical characteristics of the 4 groups of patients according to sepsis severity on ICU admission. The majority of patients were males, but there was no significant sex or age difference between the groups.

Among all patients with sepsis, 28.2% developed MODS in the first 48 h. Patients with MODS on admission and MODS that persisted for the first 48 h were also included. There was a significant difference between groups of septic patients for the development of MODS ($P \leq 0.05$). The more severe form of the disease upon ICU admission showed higher incidence of MODS development and persistence.

The overall mortality was 29.4%. The highest mortality was noted in the group of patients with septic shock upon admission. There was a statistically significant difference between the groups ($P \leq 0.05$).

Comparing the levels of hemostasis-related parameters, a significant difference was noticed between aPTT, PT, and D-dimer levels between the groups ($P \leq 0.05$). aPTT and PT were prolonged in groups of patients with shock or MODS present upon ICU admission, in contrast to groups of patients with simple or severe sepsis. There was no significant difference between platelet count, fibrinogen level, or TT values among groups of patients with sepsis.

Severity and outcome prediction scores upon ICU admission were also compared among the 4 groups of septic patients. There was a statistically significant difference for SOFA and MPM II scores, and both of these scores were higher in patients with more severe forms of the disease ($P \leq 0.05$). However, the APACHE II score did not differ significantly among the groups.

Since almost one-third of patients developed MODS in the first 48 h after ICU admission, the parameters were also compared between groups of patients with and without MODS in the first 48 h from ICU admission (Table 2). Results were similar to those obtained in the comparison of the 4 groups of patients with sepsis. Statistically significant differences were again noted for values of aPTT, PT, and D-dimer concentration between groups with and without MODS, as well as for values of SOFA and MPM II scores on admission ($P \leq 0.05$). Other investigated parameters (sex, age, TT value, platelet count, fibrinogen level, and APACHE II score) did not differ between groups with and without MODS. As expected, mortality was significantly higher in the group of patients with MODS in the first 48 h than in the group without MODS ($P \leq 0.05$).

Table 3 shows differences of parameters between 28-day survivors and nonsurvivors. Again, there was no significant difference between groups for age and sex. However, comparison of hemostasis-related parameters was different between 28-day survivors and nonsurvivors among groups of patients with or without MODS in

**Table 1.** Clinical characteristics of 4 groups of studied patients according to sepsis severity at admission.

| Variables | Sepsis, n = 39 | Severe sepsis, n = 19 | Septic shock, n = 18 | MODS, n = 9 (10.6%) | Value of P |
|---|---|---|---|---|---|
| Age (years) | 57.7 ± 18.2 | 66.8 ± 12.3 | 57.7 ± 12.3 | 57.7 ± 20.9 | P > 0.05 |
| Sex (F/M) | 17/22 | 10/9 | 5/13 | 2/7 | P > 0.05 |
| Platelet count ($n \times 10^9$/L) | 229.3 ± 142.5 | 185.6 ± 148.6 | 195.7 ± 128.6 | 230.1 ± 198.0 | P > 0.05 |
| aPTT (R) | 1.3 ± 0.5 | 1.3 ± 0.4 | 1.5 ± 0.8 | 2.1 ± 0.9 | P = 0.002 |
| PT (R) | 1.6 ± 0.8 | 1.5 ± 0.4 | 2.2 ± 1.2 | 2.6 ± 1.2 | P = 0.008 |
| TT (R) | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.9 ± 0.2 | 0.9 ± 0.2 | P > 0.05 |
| Fibrinogen (g/L) | 5.5 ± 1.4 | 4.8 ± 1.7 | 4.9 ± 2.2 | 4.3 ± 1.7 | P > 0.05 |
| D-dimer (ng/mL) | 1882.9 ± 1525.7 | 2304.6 ± 2129 | 1927.9 ± 1413.9 | 8162.8 ± 10077.5 | P = 0.020 |
| APACHE II | 13.2 ± 5.5 | 15.9 ± 8.1 | 14.4 ± 5.9 | 20.9 ± 9.3 | P > 0.05 |
| SOFA | 3.7 ± 3.3 | 7.4 ± 6.4 | 7.4 ± 6.6 | 12.3 ± 10.3 | P ≤ 0.001 |
| MPM II | 16.8 ± 10.6 | 30.2 ± 16.8 | 41.9 ± 13.8 | 58.8 ± 17.4 | P ≤ 0.001 |
| MODS in first 48 h (yes/no), n = 24 | 2/37 (5.4%) | 4/15 (21.1%) | 9/9 (50%) | 9/0 (100%) | P ≤ 0.001 |
| 28 day mortality (yes/no), n = 25 | 2/37 (5.1%) | 10/9 (52.6%) | 9/9 (50%) | 4/5 (44.4%) | P ≤ 0.001 |

Data are expressed as mean ± SD or numbers. SOFA: Sequential organ failure assessment. APACHE II: Acute Physiology and Chronic Health Evaluation II. MPM II: Mortality Probability Model II. MODS: Multiple organ dysfunction syndrome. R: Ratio.

**Table 2.** Studied parameters between groups of patients with and without MODS in the first 48 h from ICU admission.

| Variables | MODS absent in the first 48 h, n = 61 | MODS present in the first 48 h, n = 24 | Value of P |
|---|---|---|---|
| Age (years) | 58.6 ± 16.9 | 60.5 ± 16.9 | P > 0.05 |
| Sex (F/M) | 7/17 | 29/32 | P > 0.05 |
| Platelet count (n × $10^9$/L) | 220.8 ± 141.7 | 186.3 ± 159.1 | P > 0.05 |
| aPTT (R) | 1.4 ± 0.6 | 1.9 ± 0.8 | P = 0.006 |
| PT (R) | 1.7 ± 0.8 | 2.8 ± 1.2 | P = 0.046 |
| TT (R) | 0.9 ± 0.2 | 0.8 ± 0.1 | P > 0.05 |
| Fibrinogen (g/L) | 5.0 ± 1.7 | 5.1 ± 2.0 | P > 0.05 |
| D-dimer (ng/mL) | 2537.3 ± 4352. 9 | 4470 ± 7027. 7 | P = 0.014 |
| APACHE II | 14.6 ± 6.7 | 16.5 ± 8.6 | P > 0.05 |
| SOFA | 4.6 ± 4.0 | 10.6 ± 8.8 | P ≤ 0.001 |
| MPM II | 24.2 ± 17.4 | 46.1 ± 20.3 | P ≤ 0.001 |
| 28 day mortality (yes/no), n = 26 (30.6%) | 15/46 (24.6%) | 11/13 (45.8%) | P = 0.04 |

Data are expressed as mean ± SD or numbers. SOFA: Sequential organ failure assessment. APACHE II: Acute Physiology and Chronic Health Evaluation II. MPM II: Mortality Probability Model II. MODS: Multiple organ dysfunction syndrome. R: Ratio.

**Table 3.** Investigated parameters between 28-day survivors and nonsurvivors.

| Variables | 28-day survivors, n = 59 | 28-day nonsurvivors, n = 26 | Value of P | Logistic value of P |
|---|---|---|---|---|
| Age (years) | 57.3 ± 17.6 | 63.3 ± 14.4 | P > 0.05 | - |
| Sex (F/M) | 23/36 | 12/14 | P > 0.05 | - |
| Platelet count (n × $10^9$/L) | 240.5 ± 159.3 | 147.3 ± 89.7 | P = 0.009 | P = 0.015 |
| aPTT (R) | 1.4 ± 0. 6 | 1.9 ± 0. 6 | P = 0.007 | P = 0.02 |
| PT (R) | 1.7 ± 0.9 | 2.0 ± 1.0 | P > 0.05 | - |
| TT (R) | 0.9 ± 0.1 | 0.9 ± 0.2 | P > 0.05 | - |
| Fibrinogen (g/L) | 5.4 ± 1.6 | 4.4 ± 1.9 | P = 0.023 | - |
| D-dimer (ng/mL) | 2216.3 ± 1686.7 | 4813.4 ± 8809.2 | P > 0.05 | P > 0.05 |
| APACHE II | 14.7 ± 5.2 | 19.2 ± 9.3 | P = 0.002 | P = 0.024 |
| SOFA | 5.3 ± 6.1 | 8.6 ± 6.4 | P = 0.001 | - |
| MPM II | 25.5 ± 18.6 | 41. 5 ± 21.0 | P = 0.001 | - |

Data are expressed as mean ± SD or numbers. SOFA: Sequential organ failure assessment. APACHE II: Acute Physiology and Chronic Health Evaluation II. MPM II: Mortality Probability Model II. MODS: Multiple organ dysfunction syndrome. R: Ratio.

the first 48 h. Platelet count, aPTT ratio, and fibrinogen levels were significantly different between survivors and nonsurvivors ($P \leq 0.05$). aPTT was prolonged significantly in nonsurvivors, while platelet count and fibrinogen levels were higher in survivors. Concentrations of D-dimer, as well as PT and TT ratios, did not differ significantly between groups of 28-day survivors and nonsurvivors.

In order to establish the potential for combinations of investigated parameters to improve 28-day mortality prediction, we first used Kendall's tau correlation. aPTT was included in the logistic regression model, while MPM II, PT, TT, and fibrinogen were not included in the model of logistic regression due to positive correlations with aPTT. SOFA score significantly correlated with platelet count and MPM II, so these 2 scores were not included in the logistic regression model. We primarily wanted to investigate the predictive value of hemostasis-related parameters; hence, platelet count was a variable of interest to us more so than SOFA score. Variables that did not differ significantly between 28-day survivors and nonsurvivors also were not included in the logistic regression model.

Direct logistic regression was performed in order to assess the impact of hemostasis-related parameters (aPTT ratio, platelet count, and D-dimer concentration) and value of APACHE II score upon ICU admission on the likelihood of fatal outcome within 28 days from the onset of sepsis. The model contained 4 different variables as predictors. The full model with all the predictors was statistically significant (chi-square (4, N = 85) = 22.29, $P \leq 0.001$). The model explains between 26.6% and 37% of variance and could classify 76.4% of the cases correctly. Three variables contributed significantly to the model (platelet count, aPTT ratio, and APACHE II score), and results are shown in Table 3. According to our results, low platelet count and prolonged aPTT were slightly better predictors of dying than higher APACHE II score. Low platelet count was the strongest predictor in our model (Table 3).

## 4. Discussion

MODS occurs frequently in patients with sepsis, but the fact that sepsis may progress to MODS in certain patients, even after the restoration of adequate organ perfusion, still raises questions. Bearing in mind that dysregulation of a hemostatic system may lead to microvascular thrombosis and hypoperfusion, and that the altered fibrinolytic mechanisms might then induce tissue ischemia and tissue necrosis and consequently MODS, it is clear that endothelial damage with clotting disorders is the foundation of organ dysfunction (15,16).

ICU scoring systems are used in order to predict patients' outcomes based on physiological data available at ICU admission. The value of implementation of these scoring systems in everyday practice in order to predict severity and outcome of critically ill patients is high (3,4). However, hemostasis-related parameters are rarely included in scoring systems used for prediction of sepsis severity and outcome, except for scores that are used to diagnose DIC (4,17,18).

In our study we focused on the evaluation of hemostasis-related parameters for prediction of 28-day mortality and for identifying 48-h complication development.

Our results show that prolonged PT and aPTT and higher D-dimer concentrations upon ICU admission in patients with sepsis are associated with more severe forms of the disease and 48-h MODS development. SOFA and MPM II scores also showed significant differences in the more severe form of sepsis and complication development in the first 48 h (Tables 1 and 2). However, the APACHE II score, which is widely used for prediction of severity of critical illness, was not significantly different in patients with more severe forms of sepsis or patients with MODS development in the first 48 h. This could be explained by the fact that both SOFA and MPM II scores are mainly scores for prediction of organ failure, while the APACHE II score is more suitable for prediction of length of hospital stay and the severity of the disease (4,15). While organ failure is the basis of initial clinical manifestation and the severity of sepsis, SOFA and MPM II scores recognize more severe forms of the disease early in its development. Positive correlations of aPTT and PT with MPM II score, D-dimer with SOFA score, and platelet count with both MPM II and SOFA scores imply that these markers should be used as a part of organ dysfunction scoring systems. Our results may indicate that the combination of existing ICU scores with hemostasis-related parameters could contribute to mortality and severity prediction of sepsis.

Our results also bring evidence that lower platelet count, prolonged aPTT, and lower concentration of fibrinogen upon ICU admission in septic patients are significantly associated with 28-day mortality, which is in accordance with the fact that there is extensive cross-talk between coagulation and inflammation, whereby inflammation leads not only to activation of coagulation but coagulation also considerably affects inflammatory activity (11).

All observed ICU scores also showed significant differences with higher values in the group of nonsurvivors and this highlights the fact that the degree of organ failure is linked to the outcome, because clinical variables that are included in these scores are not specific just for the septic patients (Table 3).

Platelet count and aPTT ratio on ICU admission in patients with sepsis were proven to be independent predictors of fatal outcome with APACHE II score in our logistic regression model (Table 3).

Our results demonstrate that hemostasis-related parameters have a significant impact on severity and outcome prediction of patients with sepsis, since endothelial and coagulation dysfunction is essential in pathophysiology of sepsis (19–21).

However, these easily available laboratory parameters are not included in most commonly used ICU predictive scoring systems (3,4). Although these scoring systems have evolved over the past 25 years in an effort to increase predictive accuracy and keep pace with current critical care practice (3), we must bear in mind the fact that the new models are not superior to the originals because they have not included any new data elements, but they were modified to better fit certain populations (3).

Our study, along with a few other studies that also presented the value of hemostasis-related parameters in sepsis (8,12), implies that a revision of ICU scoring systems is needed and that coagulation markers should be part of routine monitoring of patients' clinical conditions and progression of the critical illness.

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