# Correlation between Hemostasis Profile and Sepsis Outcome

*by* Lima Susi

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# Correlation between Hemostasis Profile and Sepsis Outcome

**Sisi Melansi[1], Eny Rahmawati[2], Susilawati[2]**

[1]Medical Student, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine, Sriwijaya University/Dr. Mohammad Hoesin Hospital, Palembang, Indonesia. E-mail: enyrahma14@gmail.com

## ABSTRACT

Sepsis is an organ dysfunction caused by infection. Excessive cytokine activation, which causes hemostasis disorder is rated by Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), fibrinogen, and D-dimer tests. Hemostasis disorder can affect several sepsis outcomes (mortality and duration of treatment period). This study aimed to determine the correlation between hemostasis profile and sepsis outcome. This research was an analytical-observational with retrospective cohort study design with subjects consisting of 76 sepsis patients at Dr. Mohammad Hoesin Hospital, Palembang. The data were obtained by medical record observation and analyzed by Chi-Square and Spearman tests. From 76 sepsis patients, 76.7% of subjects had normal PT; 88.2% had normal aPTT; 71.1% had elevated fibrinogen, and 100% had elevated D-dimer. The patients' sepsis outcomes showed that 67.1% survived, and 32.9% has died, and the duration of the treatment period without much differences is as long as ≤ 12 days and > 12 days. The statistical analysis showed that there was no significant relationship between PT, mortality, duration of the treatment period (p=1.000; p=0.418), between aPTT, mortality, duration of the treatment period (p=0.709; p=0.480), between fibrinogen, mortality, duration of the treatment period (p=0.350; p=1.000), and there was a weak negative correlation between D-dimer mortality and duration of the treatment period (p=0.459; p=0.939). It could be concluded that there was no significant correlation between hemostasis profile and sepsis outcome.

**Keywords**: Sepsis, prothrombin time, aPTT, fibrinogen, D-dimer

## INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulation of the inflammatory cytokine response. Along with developing the understanding of sepsis pathophysiology, the manifestations that arise in sepsis patients are not limited to pro and anti-inflammatory cytokines reactions, but also the role of non-immunological pathways (cardiovascular, neurological, hormonal, metabolic, and coagulation).[1]

The Centers of Disease Control (CDC) report showed that sepsis incidence always increases from year to year (± 8.7% per year).[2] In the United States, there were 750,000 sepsis incidents with a mortality rate of 215,000.[2] Data obtained from Dr. Mohammad Hoesin Hospital, Palembang, showed that in 2017 and 2018, there were 173 and 136 adult patients diagnosed with sepsis, respectively. If calculated as a whole from 2016-2018, there were 459 adult patients, and 349 pediatric patients and neonates were diagnosed with sepsis at Dr. Mohammad Hoesin Hospital, Palembang.

The etiology of sepsis in Indonesia is Gram-negative bacteria (60-70%), and Gram-positive bacteria cause 20-40%. Research in Singapore in 2011 showed 58.5% of sepsis patients with positive blood cultures and 41.5% with negative culture results. The most commonly found Gram-positive and Gram-negative bacteria in many culture results are *Staphylococcus aureus* and *Klebsiella pneumonia*.[3]

The diagnosis of sepsis developed by the European Society of Intensive Care Medicine is a Sequential Organ Failure Assessment score (SOFA score) by assessing the organ systems (kidney, liver, cardiovascular, hematological, respiratory, and nervous systems) to determine the degree of organ dysfunction. In 2016, the SOFA score was developed into qSOFA (quick SOFA), which simplified the sepsis into three criteria: Glasgow Coma Scale (GCS) ≤ 13, systolic blood pressure ≤100 mmHg, and respiratory rate ≥ 22x/minute.[1]

The outcome in sepsis patients is quite diverse. The complications due to organ system failure (such as failure of the coagulation system that manifests in DIC), duration of treatment, transfer of care (such as transfer to ICU), amount of blood transfusion, blood culture results, and the last outcomes of survival or death.[4]

The pathophysiology of sepsis involves dysregulation of proinflammatory cytokines, a vital role for hemostasis, especially the activation of the coagulation and fibrinolysis activation. The abnormalities profile of hemostasis in sepsis is measured with conventional hemostasis tests. Traditional tests that are routinely performed to assess the activation of coagulation are Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), and fibrinogen test, whereas routine, conventional hemostasis test to assess fibrinolysis activation is D-dimer.[5]

Previous studies have shown the correlation between hemostasis profiles and DIC outcomes, the association of length of stay with sepsis outcomes, the relationship between qSOFA, sepsis mortality, and sepsis patients' hemostasis profile. This study needs to be carried out to develop previous research to determine the correlation between hemostasis profiles (PT, aPTT, fibrinogen, and D-dimers) and other sepsis outcomes (life or death and duration of treatment period), especially in sepsis patients in Indonesia.

## METHODS

The method used in this study was an observational analytic retrospective cohort design performed at Dr. Mohammad Hoesin Hospital, Palembang, from August to November 2019. The research subjects were sepsis patients who met the inclusion and exclusion criteria. The inclusion criteria were adult sepsis patients (aged 18-70 years) who underwent hemostasis tests (PT, aPTT, fibrinogen, and D-dimers). Exclusion criteria were patients who received anticoagulant therapy, had liver problems and bleeding disorders (such as hemophilia or von Willebrand Disease). The study used medical records of sepsis patients as secondary data, which were then analyzed using The Chi-Square and The Spearman tests.

Research permission was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Sriwijaya University/Dr. Mohammad Hoesin Hospital, with number 379/ kepkrsmhfkunsri/2019.

## RESULT AND DISCUSSION

This research was carried out on 76 sepsis patients at Dr. Mohammad Hoesin Hospital, Palembang, in January 2018-July 2019. Data taken were based on age, gender, comorbid diseases (diabetes mellitus and hypertension), and hemostasis profile (PT, aPTT, fibrinogen, and D-dimer). The results of this study indicated that there was no significant difference between the number of sepsis incidents in males (53.9%) and females (46.1%), the highest incidence of sepsis was found in the age of 61-67 years (32.9%). The lowest incidence was found in the age range of 26-32 years (5.3%). Comorbid diseases found in sepsis patients were as follows: 19.7% Diabetes Mellitus (DM), 17.1% hypertension, and most subjects did not have these two comorbid diseases. Table 1 shows the distribution of sepsis patients' characteristics by age, gender and comorbid illness .

Hemostasis test results in this study showed that most sepsis patients had normal PT and aPTT (76.3% and 88.2%), increased fibrinogen, and D-dimers (71.1% and 100%). Distribution of hemostasis profile test results in sepsis patients can be seen in Table 2.

**Table 1.** The characteristics of subjects

| Characteristics | n=76 | % |
|---|---|---|
| **Gender** | | |
| Male | 41 | 53.9 |
| Female | 35 | 46.1 |
| **Age** | | |
| 26-32 | 4 | 5.3 |
| 33-39 | 5 | 6.6 |
| 40-46 | 8 | 10.5 |
| 54-60 | 9 | 11.8 |
| 61-67 | 25 | 32.9 |
| 68-70 | 10 | 13.2 |
| **Comorbid disease** | | |
| DM | 15 | 19.7 |
| Hypertension | 13 | 17.1 |
| (-) DM & hypertension | 41 | 53.9 |

**Table 2.** Hemostasis profile of subjects

| Hemostasis Profile | n=76 | % |
|---|---|---|
| **PT** | | |
| Normal | 58 | 76.3 |
| Prolonged | 18 | 23.7 |
| **aPTT** | | |
| Normal | 67 | 88.2 |
| Prolonged | 9 | 11.8 |
| **Fibrinogen** | | |
| Normal | 22 | 28.9 |
| Elevated | 54 | 71.1 |
| **D-dimer** | | |
| Elevated | 76 | 100 |

Sepsis patients in this study mostly survived (67.1%), and the number of subjects with the duration of treatment ≤ 12 days and > 12 days was equal. The distribution of sepsis patient outcomes can be seen in Table 3.

**Table 3.** Sepsis outcome of subjects

| Outcome | n=76 | % |
|---|---|---|
| **Mortality** | | |
| Survived | 51 | 67.1 |
| Not survived | 25 | 32.9 |
| **Duration of treatment** | | |
| ≤ 12 days | 38 | 50 |
| > 12 days | 38 | 50 |

The correlation of PT, aPTT, and fibrinogen examinations with sepsis outcomes was determined using the Chi-Square test. The correlation between D-dimers and sepsis outcomes was analyzed using the Spearman test. All analysis results showed p-values > 0.05, indicating no significant relationship between the hemostasis profile and sepsis outcomes (Table 4, Table 5 & Table 6).

**Table 6.** Correlation between D-dimer and sepsis outcome

| Outcome n=76 | r-value | p-value |
|---|---|---|
| Mortality | -0.086 | 0.459 |
| Duration of treatment | -0.009 | 0.939 |

Gender did not show a significant difference in the number of sepsis patients.[6] Females mortality due to sepsis is not as high as mortality in males because there is a role of sex steroid hormones in females as immunoprotective processes of trauma or bleeding. High estrogen levels in females can maintain a balance of cytokine production and expression of major histocompatibility complex class II (MHC-II) and maintain splenocyte proliferation.[7-9]

Most sepsis patients aged > 65 years. This phenomenon is because, at this age, there is a decrease in the body's physiological functions, including immunity against infection, making it more susceptible to develop into sepsis.[6,10]

**Table 4.** Correlation between hemostasis profile and sepsis outcome (mortality)

| Hemostasis Profile | Outcome of Subjects | | n=76 | p-value*) |
|---|---|---|---|---|
| | Survived | Not survived | | |
| | 51 (67.1%) | 25 (32.9%) | | |
| **PT** | | | | |
| Prolonged | 12 (16%) | 6 (7.8%) | 18 (23.7%) | 1 |
| Normal | 39 (51.1%) | 19 (25.1%) | 58 (76.3%) | |
| **aPTT** | | | | |
| Prolonged | 7 (9.2%) | 2 (2.6%) | 9 (11.8%) | 0.709 |
| Normal | 44 (57.9%) | 23 (30.2%) | 67 (88.2%) | |
| **Fibrinogen** | | | | |
| Elevated | 34 (44.8%) | 20 (26.3%) | 54 (71.1%) | 0.350 |
| Normal | 17 (22.3%) | 5 (6.6%) | 22 (28.9%) | |

**Table 5.** Correlation between hemostasis profile and sepsis outcome (duration of treatment)

| Hemostasis Profile | Duration of Treatment | | n=76 | p*) |
|---|---|---|---|---|
| | ≤ 12 days | > 12 days | | |
| | 38 (50%) | 38 (50%) | | |
| **PT** | | | | |
| Prolonged | 11 (14.5%) | 7 (9.2%) | 18 (23.7%) | 0.418 |
| Normal | 27 (35.5%) | 31 (40.8%) | 58 (76.3%) | |
| **aPTT** | | | | |
| Prolonged | 6 (7.9%) | 3 (4%) | 9 (11,8%) | 0.480 |
| Normal | 32 (42.1%%) | 35 (46%) | 67 (88.2%) | |
| **Fibrinogen** | | | | |
| Elevated | 27 (35.5%) | 27 (35.5%) | 54 (71.1%) | 1 |
| Normal | 11 (14.5%) | 11 (14.5%) | 22 (28.9%) | |

Comorbid diseases of sepsis patients in this study were highly diverse and were different among patients that it might affect the results of hemostasis profile and sepsis outcome. Research at the ICU of Adam Malik Hospital, Medan, showed that 64.6% of sepsis patients had comorbid diseases. From these data, as much as 19.2% were hypertension, and 5.1% were DM.[11] Both of these diseases are chronic diseases, which basically can affect the body's immunity.[12] The risk of sepsis also increases along with the number of comorbidities (comorbidities) in a person.[13]

Conventional hemostasis profiles of PT and aPTT in this study were mostly normal in sepsis patients. The research by Fenny *et al.* showed that 85% of sepsis patients had normal or elevated PT value and outcome of non-decompensated DIC.[5] Another study performed at Dr. Hasan Sadikin Hospital, Bandung showed that 80% of study subjects had normal aPTT. Also, from the results of conventional examinations, it was known that 83.33% of subjects showed changes in Clot Waveform Analysis (CWA), which were very significant in forming a biphasic wave. This examination is a thorough hemostasis test to assess the coagulation disturbance from the beginning of the formation process until the clots.[14] According to the theory, in the early sepsis hypercoagulation phase, it will shorten the aPTT value. Activation of the coagulation system in sepsis occurs from mild to severe degrees (DIC). If this process lasts in a long time or there is slow coagulation activation, the coagulation factors will decrease, leading to a normal or prolonged PT and aPTT. This process can also occur if there is an increase in coagulation factors due to the compensatory mechanism by the liver in maintaining the balance of coagulation in the body.[5]

The research by Moore *et al.* also showed increased levels of fibrinogen in sepsis patients. Fibrinogen is an acute-phase reactant when the infection level remains high for a long time. Therefore, increased fibrinogen levels are mostly increased in sepsis patients.[5] Research by Kim *et al.* showed a similar result that 100% of sepsis patients had positive or increased D-dimers.[15] D-dimer will increase if fibrinolysis is activated. In sepsis, this can occur due to activated hypercoagulation via the intrinsic and extrinsic pathways to form thrombin. Excessive formation of thrombin will cause the release of tissue plasminogen activator (tPA) by the endothelium, which plays a role in forming plasminogen into plasmin. Cleavage of plasmin into cross-linked fibrin causes the formation of D-dimers. Therefore, excessive cleavage will increase D-dimer levels.[5]

Deaths of sepsis patients are relatively high (one-third of the total cases). Research by Martin & Wheeler suggested that sepsis's mortality rate was 20% and might increase along with the development of the severity of the disease.[16] Most of the age of sepsis patients in this study were above the age of 60, indicating that sepsis commonly occurs at a vulnerable age due to decreased immune response to infection.[17]

The mortality rate in sepsis patients was lower compared to patients who received treatment (survived). A study by Lorente *et al.* showed that the coagulation system's severity is associated with poor prognosis and is a factor causing organ dysfunction or failure in sepsis patients. However, hemostasis parameters must be serially measured to determine the diagnosis, prognosis, and therapy success.[18] The PT and aPTT tests in this study were principal to assess the time needed from the start of reagent insertion to the formation of fibrin clots. Results came out and were stated with seconds. This test does not describe the process that occurs during fibrin formation. Therefore, normal test results do not necessarily describe the good function of coagulation factors in sepsis. According to theory, excessive coagulation activation can increase fibrinolysis and prolong PT and aPTT.[5]

Research conducted at ICU Prof. Dr. R. D. Kandau Hospital, Manado, showed that 48.6% of sepsis patients had a length of stay of 1-5 days, and there were 5.7% of sepsis patients who had a treatment period of more than 20 days.[10] treatment period of sepsis patients who get good treatment at the ICU will produce a good outcome, indicating that patients will show improvement with an average of 7-14 days of care. Age, site of infection, or disease that underlies and accompanies sepsis patients can be important factors in patient improvement after treatment.[19]

A prospective observational study by Davies *et al.* showed that sepsis patients who had prolonged PT values and decreased fibrinogen concentrations were closely related to poor prognosis. There are microstructural changes from clots made by platelets and fibrin and are at risk for thromboembolism.[20] The research by Garnacho *et al.* and Williams *et al.* showed that the length of stay and death of sepsis patients are not directly related. In sepsis patients, the risk of nosocomial infection is

quite high if the patient is treated in ICU > 10 days, uses the long-term drug, hospital costs, and the risk of having a pressure ulcer.[21]

The results of this study do not statistically show a significant correlation between hemostasis profiles and sepsis outcomes. The bias factors that might influence this study's results were comorbid diseases, etiology, and risk factors that are diverse and are different among research subjects, age, and gender. While the parameter factors that might play a role in this research were a time of hemostasis profile test, which was different among the research subjects. The data used in this study were the first test data after the patient was diagnosed with sepsis. This result was different among patients, indicating that not all data used in this study were test results on the first day or the same day among research subjects after being diagnosed with sepsis.

## CONCLUSION AND SUGGESTION

The hemostasis profile test of sepsis patients in this study showed that patients mostly had normal PT and aPTT, but elevated fibrinogen and D-dimers. Sepsis patients in this study mostly survived, and the duration of treatment was less and more 12 days equally. There was no significant correlation between the hemostasis profile (PT, aPTT, fibrinogen) and the outcome of sepsis (life-death and length of treatment). D-dimers and sepsis outcomes also showed negative correlations with very weak correlation strengths.

Research with a larger sample and primary data can be performed to determine the relationship between hemostasis profiles and other sepsis outcomes such as culture results and the amount of blood transfusion. Examinations with advanced technology of hemostasis profile test such as global coagulation test or comprehensive coagulation examination {such as Thromboelastography (TEG), Thrombin Generation Test (TGT), Clot Waveform Analysis or CWA}, can be developed to determine hemostasis damage in patients with sepsis that are not detected through a conventional test.

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