International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Description of the Mortality Rate of Hypercoagulation, Hypocoagulation, and Normocoagulation Patients in the ICU of Hasan Sadikin Bandung, Hospital

Dewi Yuliana Fithri[1], Tinni Trihartini Maskoen[2], Ezra Oktaliansah[3]

Department of Anesthesiology and Intensive Therapy Faculty of Medicine Padjajaran University, Dr. Hasan Sadikin Bandung

Abstract: ***Introduction: Coagulopathy is a complication of sepsis that is often associated with increased mortality. Examination of conventional coagulation tests is considered unable to assess the function of the coagulation cascade as a whole, but thromboelastography is. Thromboelastography can differentiate septic coagulopathy into hypercoagulation, normocoagulation, and hypocoagulation, but this examination is rarely performed. For this reason, the aim of this study was to describe the mortality features of sepsis patients with hypercoagulation, hypocoagulation, and normcoagulation. Materials &Methods: Descriptive study with research locations in the ICU, Dr. Hasan Sadikin Bandung. The sample for this study was sepsis patients with consecutive sampling. Sample collection begins in September–November 2022. The sample size for this study is total sampling. Data analysis using IBM SPSS Statistics for Windows, version 21 The analysis was carried out univariately, and categorical data will be assessed in the form of a percentage, while numerical data will use the mean or standard deviation if the data is normally distributed. If the data is not normally distributed, use the median or interquartile range. Results: About 86 sepsis patients were analyzed in this study. In terms of coagulation disorders, the most common in this study were 73.2% hypercoagulation, 17.4% normcoagulation, and 19% hypocoagulation. The highest mortality of sepsis patients was in the hypocoagulation group at 50%, normcoagulation at 40%, and hypercoagulation at 34.9%. However, the highest mortality was in the 50% hypocoagulation group compared to the other groups. Discussion: Coagulopathy is an organ failure with high mortality rates. The overall cascade of coagulopathic disorders cannot be established by conventional hemostatic examination, but thromboelastography can assess the overall coagulopathy. Hypocoagulation in sepsis has a higher mortality rate than hypercoagulation and normcoagulation disorders.***

Keywords: Coagulation disorders in sepsis, Mortality, Thromboelastography

1. Introduction

Sepsis is a systemic inflammation with a high mortality rate. Organ failure contributes cumulatively to death in patients with sepsis.[1] Globally, 31.5 million cases of sepsis are estimated to occur each year, with 5.3 million deaths.[2] It is estimated that there are more than 30 million cases of sepsis worldwide per year. The incidence of sepsis increases by 9–13% every year, with an incidence of 33–35% mortality.[3]

Coagulation disorders are one of the organ failures that often occur in patients with sepsis. They are common in patients with sepsis and are usually associated with mortality. In an observational study in Japan of 1, 895 sepsis patients treated in the ICU, approximately 29% had coagulation in septic patients.[4] Coagulation mechanisms arise as a result of being triggered by a combination of upregulation of procoagulants, downregulation of endogenous anticoagulants, and impaired fibrinolytics. Dysregulation of this hemostatic system can lead to disseminated intravascular coagulation (DIC) and result in microvascular thrombosis, hypoperfusion, major organ dysfunction, and ultimately death.[4, 5] Coagulation disorders that can occur in patients with sepsis include hypercoagulation, normcoagulation, and hypocoagulation. Conventional coagulation tests such as activated partial thromboplastine time, prothrombin time, and international normalized ratio cannot explain the coagulation process that occurs in patients with sepsis. One examination that can explain the whole thing is a thromboelastography examination.[4]

In a 6 - month prospective cohort study of septic patients admitted to the ICU, of 247 septic patients, 106 (42%) were hypocoagulable, 35 (14%) hypercoagulable, and 106 (42%) normcoagulable. From this analysis, hypocoagulation evaluated by Transient elastography (TEG) was significantly associated with a higher 30 - day mortality (42% vs.13%, P < 0.0001) compared to patients with normcoagulation.[5] This study is to describe the mortality rate in sepsis patients who experience hypercoagulation, hypocoagulation, and normcoagulation in the ICU. Dr. Hasan Sadikin Bandung

2. Materials and Methods

This research is a descriptive study conducted in the ICU by RSUP Dr. Hasan Sadikin Bandung. The time frame of this research begins in September and ends in December 2022. The sample selection in this study uses a consecutive sampling technique if it meets the inclusion and exclusion criteria. The inclusion criteria in this study were age ≥ 18 years, and sepsis criteria were enforced based on SOFA Score criteria ≥ 2. The study exclusion criteria were patients with pregnancy, patients with a history of antiplatelet use, anticoagulants, or antifibrinolytics before sepsis was established, and patients with one or a combination of comorbidities such as blood coagulation disorders, coronary heart disease, and ischemic stroke.

The examination of septic coagulopathy in this study used thromboelastography. Coagulation disorders in sepsis patients are divided into hypercoagulation, normcoagulation,

and hypercoagulation. Hypocoagulation on thromboelasotography is indicated by prolonged R and K times and/ or decreased Maximum amplitudo (MA) and alpha angles, while hypercoagulability is characterized by short R times and increased clotting as indicated by increased alpha and MA angles.

This study was analyzed univariately to get the characteristics of the research subjects. Categorical data will be assessed in the form of a percentage (%), while numerical data will use the mean or standard deviation if the data is normally distributed. If the data is not normally distributed, use the median and interquartile range. The data were analyzed using IBM SPSS 26 for Windows.

3. Results

Eighty - six sepsis patients in the ICU who met the inclusion and exclusion criteria were analyzed. Based on the coagulation status of the TEG examination, the most common coagulation disorders in sepsis patients were 63 people experiencing hypercoagulation (73.2%), 15 people experiencing normcoagulation (17.4%), and 8 people experiencing hypocoagulation (9%).

Characteristically, the average age of the study subjects was around 47 years. The average age of the three groups was not much different, with the lowest average age being hypocoagulation, with an average age of 39. Based on sex characteristics, the most common sufferers of sepsis were about 50 men (58.1%) and 36 women (41%). In the hypercoagulable group, men also suffer from sepsis the most (78%) compared to women (38%). However, in the normocoagulation and hypocoagulation groups, women were more dominant than men, as can be seen in Table 4.1.

The average length of stay for sepsis patients in the ICU is around 1520.9 days. Based on the length of stay in the hypercoagulation group, the mean length of stay was 15 days longer compared to the average length of stay in normcoagulation, 13 days, and 11 days for hypocoagulation.

In Table 4.1, it can be seen that the most common comorbidities suffered by sepsis patients in this study were diabetes mellitus (39.5%), followed by Chronic Kidney Disease (CKD) (12.8%), and Hypertension (8.1%). Judging from the status of coagulation disorders, the most comorbid in the hypercoagulation group had comorbid hypertension (39.7%), while the most comorbid in normcoagulation and hypocoagulation had diabetes mellitus.

Based on the characteristics of the source of infection in septic patients, pneumonia is the most common cause as a source of sepsis infection, at around 86%, followed by UTI at 8.1% and peritonitis at 5.8%. In the hypercoagulation group, normcoagulation and hypocoagulation pneumonia are sources of infection that cause sepsis, which can be seen in detail in Table 4.1.

Based on the characteristics of the SOFA score, the average SOFA score was around 11. The hypercoagulable group had a higher mean SOFA score of about 11 and the hypocoagulable group had a 10 compared to the normocoagulated group 9. Based on the results of the TEG examination, the average R time in this study was 9. In the hypocoagulation group, the average R time was 28 days longer than normcoagulation 6 and hypercoagulation 7. Based on the average K time, which was 2, the hypocoagulation group also had a longer K time.9. The average alpha angle in this study was 56, and the hypercoagulation group had a greater average alpha angle of 65. The average maximum amplitude (MA) in this study was 63, and the highest average Maximum Amplitude was found in the hypercoagulation group at around 69.

An overview of the mortality rate for sepsis patients in this study found that around 54 people survived (62.8%) and 32 people died (37.2%). Of the sexes, more died in the male group—78.4% for men and 60% for women. Based on comorbidities, many sepsis patients died if they had comorbidities—around 94.5%—and multiple comorbidities had a higher mortality rate of 93.3%, compared to 60% for single comorbidities. Based on the coagulation status of septic patients, the TEG examination showed that the highest mortality was in the hypocoagulation group, around 50%, followed by normcoagulation, 40%, and hypercoagulation, 34.9%, which can be seen in detail in Table 4.2.

4. Discussion

TF - mediated thrombin formation is expressed on the surfaces of endothelial cells, monocytes, and platelets when these cells are stimulated by toxins, cytokines, or other mediators. The presence of endotoxin causes an increase in several proinflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin (IL) - 6. The IL - 6 cytokine is a proinflammatory cytokine that is most associated with clinical sepsis and complications. TF - mediated thrombin formation is an important step in the pathogenesis of sepsis. Physiologically, this formation is immediately inhibited by antithrombin; however, with very fast thrombin formation, this inhibitory pathway can become fatigued, resulting in thrombinemia. Once thrombin is formed then fibrinogen. Coagulation abnormalities in septic patients result from subclinical activation of coagulation leading to widespread microvascular thrombosis and subsequent consumption of platelets, leading to disseminated intravascular coagulation and severe bleeding.[6, 7]

From the results of thromboelastography, 9.3% of septic patients were found to be hypocoagulable and 73.2% hypercoagulable, while only 17.5% were normcoagulable. In this study, the most common coagulation disorder found in sepsis patients was hypercoagulation, which was around 73.2%. The results of this study indicate that coagulation disorders are common in septic patients, which often lead to organ failure.[8]

Hematologic dysfunction (as in DIC) that occurs within the first 24 hours of sepsis treatment is associated with high rates of organ failure and death. In the early stages, only PT and aPTT prolongations can be seen. Finally, due to the consumption of coagulation factors, septic coagulopathy will occur and often cannot be detected by conventional examinations, so it is very important to perform

thromboelastography for early detection.[7] This study shows that the majority of patients with hypercoagulation experienced coagulation disorders (around 73.2%). This study is consistent with a study conducted by Sang Min Kim et al. based on a prospective cohort study in which 889 sepsis patients with thrombocytopenia had 18% hypercoagulability and 15.4% hypocoagulation. In general, the prevalence of hypercoagulability in sepsis has been reported to range from 14% to 30%, which varies depending on the definition of hypercoagulability.9 The occurrence of coagulopathy in sepsis has a variety of features, ranging from mild activation of the coagulation system to more severe forms such as disseminated intravascular coagulation (DIC). The initial coagulation process in septic patients is increased coagulant activity (hypercoagulation),) where the initial pathophysiological mechanism underlying coagulation is for the development of organ failure by inhibiting microcirculation.[9] The occurrence of coagulopathy in sepsis has a variety of presentations, ranging from mild activation of the coagulation system to more severe forms such as disseminated intravascular coagulation (DIC). The initial coagulation process in septic patients is increased coagulant activity (hypercoagulation),) where the initial pathophysiological mechanism underlying coagulation is for the development of organ failure by inhibiting microcirculation.8, [9] The occurrence of coagulopathy in sepsis has a variety of presentations, ranging from mild activation of the coagulation system to more severe forms such as disseminated intravascular coagulation (DIC). The initial coagulation process in septic patients is increased coagulant activity (hypercoagulation), where the initial pathophysiological mechanism underlying coagulation is for the development of organ failure by inhibiting microcirculation.[9, 10, 11]

Based on sepsis mortality with coagulation disorders, hypercoagulation has a lower mortality rate of around 34.9%, and hypocoagulation has a higher mortality rate of around 50%. This study is in accordance with a study conducted by Sang Min Kim et al., where septic patients with hypercoagulability had a lower mortality of around 7.1% compared to hypocoagulable 36.8%, and in their study, patients who had sepsis with hypercoagulability reduced mortality with an OR of 0.38. Based on Ostrowski's study, S et al. found that in 28 - day mortality for patients with sepsis, hypocoagulation had a higher mortality rate of 55%, hypercoagulation was 20%, and normocoagulation was 13%.

Characteristically, the average age of sepsis patients in this study was around 47 years. The results of this study are in accordance with a cohort study conducted by Fibi NK et al. in India on 87 patients who underwent thromboelastography examination, where the average age was 50 years and the age range of the subjects of this study was 40–60 years. This study, which was carried out at Prof. Dr. Kandao Manado, was found to be the largest group in the age range of 40–59 years, around 30%.11 With increasing age, the incidence of sepsis and sepsis - related deaths substantially increases. People aged 65 and over account for about 65% of sepsis cases in the United States. Age - related co - morbidities may partially explain this increase in incidence and mortality. However, Significant studies have shown that the immunosenescence of age - related changes in the immune system may be a further crucial contributor. Aging is associated with low - grade systemic inflammation, often referred to as "spoilage" in the non - infectious state. One study reported an association between increasing age and an increased coagulation response in patients with CAP. Host response pathways involved in the pathogenesis of sepsis, such as endothelial cell activation and dysfunction and activation of the coagulation system, have not been described in the context of sepsis and aging.[12]However, there ise no data showing a correlation between age and coagulation status in septic patients. Aging is associated with low - grade systemic inflammation, often referred to as "spoilage" in the non - infectious state. One study reported an association between increasing age and an increased coagulation response in patients with CAP. Host response pathways involved in the pathogenesis of sepsis, – such as endothelial cell activation and dysfunction and activation of the coagulation system, m have not been described in the context of sepsis and aging.1[2] However, there ise no data showing a correlation between age and coagulation status in septic patients. Aging is associated with low - grade systemic inflammation, often referred to as "spoilage" in the non - infectious state. One study reported an association between increasing age and an increased coagulation response in patients with CAP. Host response pathways involved in the pathogenesis of sepsis, – such as endothelial cell activation and dysfunction and activation of the coagulation system, m have not been described in the context of sepsis and aging.[13, 14] However, there is no data showing a correlation between age and coagulation status in septic patients.

Based on gender, men suffered the most in this study, at around 58.1%. The results of this study are in accordance with a prospective study on 28 - day mortality conducted by Ostrowski, S. et al. The majority of sexes were males, around 60%.[13] The findings of this study were no different from a retrospective study conducted by Driessen RG et al in the Netherlands in 2020 of which males usually suffer the most from sepsis, at around 65% compared to 35% of females.[14] There is no correlation between gender and the incidence of sepsis, according to a prospective cohort study conducted by N. Nasir et al. in Pakistan in 97 sepsis patients, where the sexes were predominately male (54%) and female (46%) in their study.[15]

Based on the length of stay in the ICU, the sepsis patients in this study had an average length of stay of 15 days. In a retrospective cohort study by Ren C et al., the median ICU stay in patients with sepsis - induced coagulopathy was around 12.5 days, whereas in sepsis without coagulation disorders, the number of days of stay was lower with a median value of 10 days, although there was no correlation between length of stay and coagulation events in septic patients.[16]

Several common conditions have been linked to chronic inflammation, including obesity, diabetes, heart disease, and smoking. Inflammation plays a central role in the pathophysiology of sepsis, and chronic inflammation can increase the risk of developing sepsis when exposed to bacteria. Chronic inflammation may also indicate individuals who tend to develop dysfunctional or

exaggerated responses to microbial infections. There is a relationship between vascular disease and sepsis.[17] In this study, sepsis patients without comorbidities were around 8.1%, and more had comorbidities, with the most comorbidity being diabetes mellitus at 39.5%. This study is also in accordance with research conducted in China by Xie J. et al., who found comorbid diabetes mellitus in 459 patients (19.8%).[18]

The results of this study show that the source of infection that causes sepsis in the ICU in this study is pneumonia, which is around 86%. The results in this study were supported by research by Xie, J., et al. in China, who came from 2322 sepsis patients, where the most common source of infection was pneumonia (68%), followed by intra - abdominal infection (26.6%), and urinary tract infection (7.2%). conducted by Rob G et al. found that the most common source of infection was pneumonia (39%), followed by intra - abdominal infection (33%), and urinary tract infection (7%).1[8, 19]

5. Limitations

This study has several limitations, such as the small number of samples, which cannot represent the entire population. This study is a descriptive study that only displays a description of events in the study, so it cannot measure significant bias in influencing a study. This assessment only focuses on coagulation status and does not examine other coagulation factors. Samples were taken when sepsis was established based on the SOFA score when the patient entered the ICU; the previous condition was not assessed, so the initial status was not uniform.

6. Conclusion

From the results of this study, it was shown that the highest mortality rate is in sepsis patients with hypercoagulation of 50%, followed by normcoagulation of 34.9% and hypocoagulation of 34.9%.

References

[1] Zhao H, Cai X, Liu N, Zhang Z. Thromboelastography as a tool for monitoring blood coagulation dysfunction after adequate fluid resuscitation can predict poor outcomes in patients with septic shock. Journal of the Chinese Medical Association.2020 Jul 1; 83 (7): 674 - 7

[2] Huerta LE & Rice TW. Pathologic difference between sepsis and bloodstream infections. The journal of applied laboratory medicine.2019 Jan 1; 3 (4): 654 - 63.

[3] Singer M, Deutschman CS, Seymour CW, Shankar - Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS. The third international consensus definitions for sepsis and septic shock (Sepsis - 3). Jama.2016 Feb 23; 315 (8): 801 - 10.

[4] Hotchkiss, R., Moldawer, L. & Opal, SM Sepsis & Septic Shock. HHS Public Access, 2016 (16045), p: 1 – 47.

[5] Johansson PI, Stensballe J, Vindeløv N, Perner A, Espersen K. Hypocoagulability, as evaluated by thrombelastography, at admission to the ICU is associated with increased 30 - day mortality. Blood coagulation & fibrinolysis.2010 Mar 1; 21 (2): 168 - 74.

[6] Simmons J, Pittet JF. The coagulopathy of acute sepsis. Current opinion in anaesthesiology.2015 Apr; 28 (2): 227.

[7] Kilic Y, Topcu I, Bambal H, Civi M. Thromboelastography in the evaluation of coagulation disorders in patients with sepsis. Turkish Journal of Medical Sciences.2014; 44 (2): 267 - 72.

[8] Luo C, Hu H, & Gong J, et al. The Value of Thromboelastography in the Diagnosis of Sepsis - Induced Coagulopathy. SAGE.2016. (26), p: 1 – 6.

[9] Kim SM, Kim SI, Yu G, Kim JS, Hong SI, Kim WY. Hypercoagulability in Septic Shock Patients With Thrombocytopenia. Journal of Intensive Care Medicine.2022 Jun; 37 (6): 721 - 7.

[10] Nina KF, Varghese JK, Geevar T, Nair SC, Yadav B, Carey RA, et al. Thromboelastograph: a prognostic marker in sepsis with organ dysfunction without overt bleeding. Journal of Critical Care.2021 Oct 1; 65: 177 - 8

[11] Tambajong RN, Lalenoh DC, Kumaat L. Profile of sepsis sufferers in the ICU of Prof. Dr. RD Kandou Manado for the period December 2014–November 2015. e - CliniC.2016; 4 (1).

[12] Michels EH, Butler JM, Reijnders TD, Cremer OL, Scicluna BP, Uhel F, Peters - Sengers H, Schultz MJ, Knight JC, van Vught LA, van der Poll T. Association between age and the host response in critically ill patients with sepsis. CriticalCare.2022 Dec; 26 (1): 1 - 6

[13] Ostrowski SR, Windeløv NA, Ibsen M, Haase N, Perner A, Johansson PI. Consecutive thrombelastography clot strength profiles in patients with severe sepsis and their association with 28 - day mortality: a prospective study. Journal of critical care.2013 Jun 1; 28 (3): 317 - e1.

[14] Driessen RG, Heijnen NF, Hulsewe RP, Holtkamp JW, Winkens B, van de Poll MC, van der Horst IC, Bergmans DC, Schnabel RM. Early ICU - mortality in sepsis–causes, influencing factors and variability in clinical judgment: a retrospective cohort study. Infectious Diseases.2021 Jan 8; 53 (1): 61 - 8.

[15] Nasir N, Jamil B, Siddiqui S, Talat N, Khan FA, Hussain R. Mortality in sepsis and its relationship with gender. Pakistan journal of medical sciences.2015 Sep; 31 (5): 1201

[16] Ren C, Li YX, Xia DM, Zhao PY, Zhu SY, Zheng LY, Liang LP, Yao RQ, Du XH. Sepsis - Associated Coagulopathy Predicts Hospital Mortality in Critically Ill Patients With Postoperative Sepsis. Frontiers in medicine.2022; 9.

[17] Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S, Howard G. Chronic medical conditions and risk of sepsis. PlS one.2012 Oct 31; 7 (10): e48307.

[18] Xie J, Wang H, Kang Y, Zhou L, Liu Z, Qin B, Ma X, Cao X, Chen D, Lu W, Yao C. The epidemiology of sepsis in Chinese ICUs: a national cross - sectional

survey. Critical Care Medicine.2020 Mar 1; 48 (3): e209 - 18.

[19] Sakr Y, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys - Silva SA, Martin - Loeches I, Leone M, Lupu MN, Vincent JL, ICON Investigators. Sepsis in intensive care unit patients: worldwide data from the intensive care over nations audit. InOpen forum infectious diseases 2018 Dec (Vol.5, No.12, p. ofy313). US: Oxford University Press.

Table 1: Characteristics Subjects

Variable	Sepsis			
	All Participants (n = 86)	Hypocoagulation (n=8)	Normocoagulation (n=15)	Hypercoagulation (n=63)
Age, median	47	39	47	49
Gender, n (%)				
Man	50 (58.1)	4 (8)	7 (14)	39 (78)
Woman	36 (41.9)	4 (11, 1)	8 (22, 2)	24 (66.7)
LOS, median	15	13	13, 8	15, 7
Comorbid, n (%)				
No comorbid	7 (8.1%)	2 (28.6)	1 (14, 3)	4 (57.1)
Chronic Kidney Disease	11 (12, 8)	1 (9, 1)	2 (18, 2)	8 (72.7)
Congestive heart failure	2 (2, 3)	1 (50)	-	1 (50)
Diabetes mellitus	34 (39.5)	4 (11, 8)	6 (17, 6)	24 (70.6)
HIV	1 (1, 2)	-	-	1 (100)
Hypertension	31 (36.1)	-	6 (19.4)	25 (80.6)
Surgical	66 (76.7)	5 (7, 6)	21 (31.8)	40 (60.6)
Abdomen	41 (62.1)	3 (7, 3)	12 (29.3)	26 (63.4)
Thorax	17 (25.8)	1 (5, 9)	7 (41.2)	9 (52.9)
Other	8 (12, 1)	1 (12.5)	3 (37.5)	4 (50)
Non Surgical	20 (23, 3)	5 (25)	8 (40)	7 (35)
Source of Infection, n (%)				
Pneumonia	74 (86)	8 (10, 8)	13 (17, 6)	53 (71.6)
UTI	7 (8, 1)	-	2 (28.6)	5 (71.4)
Peritonitis	5 (5, 8)	-	-	5 (100)
Score SOFA, median	11	10	9	11
TEGS Examination, median				
R time (minutes)	9	28	6	7
Time K (minutes)	2, 8	9	3	1
Alpha angle (degrees)	56	20	40	65
Maximum Amplitude (MA)	63	40	52	69

Table 2: Description of the Mortality Rate on the Coagulation Status of Patients

Coagulation Status	N (%)	outcomes		Mortality (%)
		Survive (n =54)	Non Survive (n=32)	
Gender	86	25	61	70, 9
Male	51	11	40	78.4
Female	35	14	21	60
Comorbid	55	3	52	94.5
Single Comorbid	10	4	6	60
Multiple Comorbid	45	3	42	93, 3
Hypocoagulation	8 (9, 3)	4	4	50
Normocoagulation	15 (17.5)	9	6	40
Hypercoagulation	63 (73.2)	41	22	34, 9
Total	86	54	32	