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Disseminated Intravascular Coagulation Score and Mortality in Adult Sepsis Patients

Yetişkin Sepsis Hastalarında Dissemine İntravasküler Koagülasyon Skoru ve Mortalite

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ABSTRACT

Aim: In the present study, we aimed to evaluate the association between disseminated intravascular coagulation (DIC) score and mortality among adult sepsis patients in intensive care unit (ICU).

Material and Methods: In this retrospective cohort study, two hundred and twenty-four patients were included. Demographic characteristics, clinical data and laboratory results were evaluated. The relationship between continuous variables was analyzed with Spearman's rank correlation coefficient. Risk factors for the development of DIC were investigated by binary logistic regression analysis using the Bakward Wald method. The sequential organ failure assessment (SOFA) score and the International Society on Thrombosis and Hemostasis DIC score were evaluated by ROC analysis to predict mortality. Youden J index was used to determine the threshold value. $p<0.05$ was considered statistically significant.

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Results: Sepsis associated overt DIC developed in 34.8% (n=78) of the patients. Mortality in patients who developed sepsis associated overt DIC (75.6%) was significantly higher than those who did not (41.1%), $p<0.001$. Albumin (r=-0.295), neutrophil (-0.282) and lymphocyte count (-0.247) were negatively correlated with DIC score, $p<0.001$ for all; whereas SOFA score (r=0.413, $p<0.001$), lactate (r=0.196, $p=0.021$) and procalcitonin levels (r=0.209, $p=0.022$) were positively correlated. Presence of hematologic malignancy, acute kidney injury and SOFA scores on admission were determined as risk factors for developing DIC. When SOFA score and DIC score were compared with each other by ROC analysis in terms of predicting mortality, no significant difference was found ($p=0.078$).

Conclusion: In conclusion, the association of high SOFA score with mortality is emphasized in guidelines in the literature. In addition, our study demonstrates the association of DIC score with mortality by comparing it with SOFA score.

Key Words: sepsis, shock, disseminated intravascular coagulation, organ failure, mortality.

ÖZET

Amaç: Bu çalışmada, yoğun bakım ünitesindeki (YBÜ) erişkin sepsis hastalarında dissemine intravasküler koagülasyon (DİK) skoru ile mortalite arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif kohort çalışmaya iki yüz yirmi dört hasta dahil edilmiştir. Demografik özellikler, klinik veriler ve laboratuvar sonuçları değerlendirilmiştir. Sürekli değişkenler arasındaki ilişki Spearman sıra korelasyon katsayısı ile analiz edildi. DİK gelişimi için risk faktörleri Bakward Wald yöntemi kullanılarak ikili lojistik regresyon analizi ile araştırıldı. Mortaliteyi öngörme açısından sıralı organ yetmezliği değerlendirme (SOFA) skoru ve Uluslararası Tromboz ve Hemostaz Derneği'nin DİK skoru ROC analizi ile değerlendirildi. Eşik değerin belirlenmesinde Youden J indeksi dikkate alndı. $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Sepsis ilişkili aşikar DİK hastaların %34.8'inde (n=78) gelişti. Bu hastalarda mortalite (%75,6), aşikar DİK gelişmeyen hastalardaki mortaliteden (%41,1) anlamlı derecede yüksekti, $p<0,001$. Albümin (r=-0.295), nötrofil (-0.282) ve lenfosit sayısı (-0.247) DİK skoru ile negatif korelasyon gösterirken (tümü için $p<0.001$); SOFA skoru (r=0.413, $p<0.001$), laktat (r=0.196, $p=0.021$) ve prokalsitonin (r=0.209, $p=0.022$) pozitif korelasyon göstermiştir. Hematolojik malignite varlığı, akut böbrek hasarı ve başvuru sırasındaki SOFA skorları aşikar DİK gelişimi için risk faktörleri olarak belirlenmiştir. Mortaliteyi öngörmede; DİK skor için kesim noktası >4 olarak belirlenmiş olup duyarlılık, özgüllük değerleri sırası ile %49,58 ve %83,65 olarak elde edilmiştir ($p<0,001$). SOFA skor için ise kesim noktası >7 olarak belirlenmiş olup duyarlılık, özgüllük değerleri sırası ile %60,50 ve %62,85 olarak elde edilmiştir ($p<0,001$). SOFA skor ve DİK skor mortaliteyi öngörme açısından ROC analizi ile birbiri ile karşılaştırıldığında anlamlı fark saptanmamıştır ($p=0.07$).

Sonuç: Sonuç olarak, yüksek SOFA skorunun mortalite ile ilişkisi literatürde kılavuzlarda vurgulanmaktadır. Buna ek olarak, çalışmamız DİK skorunun da mortalite ile ilişkisini SOFA skor ile karşılaştırarak ortaya koymaktadır.

Anahtar kelimeler: sepsis, şok, dissemine intravasküler koagülasyon, organ yetmezliği, mortalite.

INTRODUCTION

Disseminate intravascular coagulation (DIC) is defined as an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes (1) and associated with poor prognosis in intensive care unit (ICU). In sepsis associated DIC, activation of the coagulation system, downregulation of the physiological anticoagulants and the fibrinolytic system inhibition are the major pathology (2,3). Prevalence of DIC among sepsis patients varies depending on which diagnostic criteria are used but mortality in sepsis associated DIC has been reported between 7-13% and increased to 70% in septic shock, regardless of the diagnostic criteria (4-8). Overt DIC was also associated with development of multiple organ failure (9, 10). Early detection to improve outcomes is critical, however; no single laboratory test for the diagnosis of DIC is currently available. To date, several DIC criteria are used for the diagnosis of DIC. In 2001, the International society of thrombosis

and hemostasis (ISTH) published the first international diagnostic criteria for overt DIC consisting of laboratory parameters including platelet count, fibrin related markers, prothrombin time (PT) and fibrinogen (1). ISTH score has also been researched as a prognostic marker. Previous studies have suggested that the ISTH DIC score predicts fatality and is a useful tool to assess independently the risk of death in sepsis (9,11). Severity of organ dysfunction in sepsis has been assessed with Sequential Organ Failure Assessment (SOFA) score and higher SOFA score is associated poor prognosis (12). Few studies have examined the factors that correlates with ISTH DIC score (9,13).

In the present study, we aimed to investigate the association between the ISTH DIC score and mortality, to determine the factors correlated with the ISTH DIC score and to compare to SOFA score among adult sepsis patients.

MATERIALS AND METHODS

Data collection and outcome measures

This retrospective study included patients 18 years of age or above who were admitted to the intensive care unit (ICU) of Ege University Internal Medicine Department between January 2013 and April 2024 with a diagnosis of sepsis according to the Sepsis-3 definition (1). The study was performed by the permission of the Ege University Ethics Committee, number 24-6T/5 and adhered to the principles of the Declaration of Helsinki. The following data were retrospectively analyzed: patients' demographic characteristics, comorbidities, source of infection (hospital/community acquired), presence of organ failure (acute kidney injury), treatment requirements (hemodialysis, vasopressors), ICU mortality, length of ICU stay, and SOFA score on sepsis diagnosis. The results of the laboratory tests at the time of sepsis diagnosis were evaluated. ISTH DIC score on sepsis diagnosis was calculated according to the two hundred and twenty-four patients were separated into two groups with demographic, clinical and laboratory data: those who developed sepsis associated overt DIC with ISTH DIC scores ≥ 5 (n=78) and those non-overt DIC for patients with ISTH scores <5 (n=146) according to the ISTH 2001 diagnostic guideline (1).

Serum urea, creatinine, aspartate aminotransferase (AST), total bilirubin, albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin, and plasma lactate levels were determined using commercially available reagents on auto-analyzers (Roche Diagnostics GmbH, Germany, Cobas 8000 modular systems, c702).

Coagulation tests were performed on a fully automated coagulation analyzer (Sysmex CN-6000™, Sysmex Corporation, Kobe, Japan) using Siemens reagents (Siemens Healthcare Diagnostics). Prothrombin time was assessed using the clotting method (Thromborel® S, Siemens Healthcare Diagnostics). Plasma levels of fibrinogen were measured using the modified Clauss method (Dade® Thrombin; Siemens Healthcare Diagnostics), while D-Dimer levels were assessed via particle-enhanced immunoturbidimetric assay (INNOVANCE® D-Dimer; Siemens Healthcare Diagnostics).

Complete blood counts were performed using Sysmex XN-3100™ automated hematology analyzer (Sysmex Corporation, Kobe, Japan). The neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of neutrophil count to lymphocyte count from the complete blood count.

Exclusion criteria were as follows: < 18 years of age, major bleeding, pregnancy, advanced stage of malignancy, cirrhotic Child-Pugh grade C, incomplete clinical information or laboratory data.

The primary outcome was ICU mortality. Secondary outcomes were the clinical and

laboratory characteristics of the two study groups, factors correlated with the DIC score and the role of DIC score and SOFA score for predicting mortality.

Statistics

Descriptive statistics were presented as n (%) for categorical variables and median (M), interquartile range (IQR), mean±standard deviation for continuous variables by examining the normality assumption of the data. The normality of numerical variables was checked using Shapiro-Wilk test. Independent sample t test and Mann-Whitney U test were used to compare continuous variables between groups. Categorical variables were compared with Pearson chi-square test. The relationship between continuous variables was analyzed with Spearman's rank correlation coefficient. Risk factors for the development of sepsis associated DIC were investigated by binary logistic regression analysis using the Bakward Wald method. To identify the ideal cutoff level to evaluate in-hospital mortality for ISTH DIC score and SOFA score, receiver operating curve (ROC) analysis was performed, in which the Youden J index was considered in determining the threshold value. Statistical analyses were conducted using the statistical package IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) program. The significance level for all statistical tests was set at 0.05 (p-value).

RESULTS

Of the 224 participants, sepsis associated overt DIC developed in 34.8% (n=78). An analysis of clinical and demographic characteristics between patients with and without overt DIC revealed significant findings, including a younger age (p=0.006) and a higher presence of hematologic malignancy (p<0.001) in the overt DIC group. No statistically significant differences were found between the groups regarding diabetes mellitus, chronic kidney disease, cardiovascular diseases and heart failure (p>0.05 for each). Hospital acquired infections (p=0.004), vasopressor support on admission (p=0.007) and acute kidney injury (p=0.037) was significantly more frequent in the overt DIC group. Additionally, mortality, length of ICU stays and SOFA score at onset of sepsis were significantly higher in patients with overt DIC compared to those without (p<0.001 for all) (Table 1).

According to pairwise comparisons of laboratory parameters total bilirubin (p<0.001), procalcitonin (p=0.012), D-Dimer (p<0.001) levels, PT and INR p<0.001 for each, were significantly higher in patients with overt DIC. Conversely, albumin levels (p<0.001), neutrophil # (p<0.001), lymphocyte # (p<0.001), hemoglobin (p<0.001), platelet # (p<0.001) and NLR (p=0.015) were significantly lower in patients with overt DIC (Table 2).

When analyzing factors that correlates with DIC score; there was a significantly positive correlation with SOFA score at onset of sepsis, total bilirubin, lactate and procalcitonin levels (p<0.001, p<0.001, p=0.021 and p=0.022 respectively). On the other hand, albumin levels, neutrophil #, lymphocyte # and hemoglobin levels were negatively correlated with DIC score, (p<0.001 for each) (Table 3).

In a binary logistic regression analysis, hematologic malignancy, acute kidney injury on admission, and SOFA score at the onset of sepsis diagnosis were found to influence the risk of developing overt DIC. The risk of overt DIC in patients with hematologic malignancy was 16.8 times higher than in those without (OR:16.802, CI: 2.432;116.065, p=0.004). Each unit increase in SOFA score resulted in a 1.25-fold increase in overt DIC development (OR:1.258, CI: 1.041;1.520, p=0.017). Contrarily, the risk of developing overt DIC decreased in the presence of acute kidney injury (OR:0.077, CI: 0.013;0.460, p=0.005) (Table 4).

Table 1. Comparison of demographic, clinical characteristics of patients with and without overt DIC
Tablo 1. Aşikar DİK'i olan ve olmayan hastaların demografik ve klinik özelliklerinin karşılaştırılması

	Without Overt DIC (n=146)	**Overt DIC (n=78)**	***p* value**
Age	65 (23)	57 (27)	**0.006**
Gender			**0.013**
Female	72 (49.3)	52 (66.7)	
Male	74 (50.7)	26 (33.3)	
Diabetes Mellitus, present	43 (29.5)	14 (17.9)	0.060
Hypertension, present	64 (43.8)	22 (28.2)	**0.022**
Heart Failure, present	27 (18.5)	9 (11.5)	0.177
Cardiovascular Disease, present	32 (21.9)	13 (16.7)	0.350
Chronic Kidney Disease, present	15 (10.3)	7 (9)	0.756
Hematologic Malignancy, present	17 (11.6)	44 (56.4)	**<0.001**
Source of infection, hospital acquired	70 (47.9)	53 (67.9)	**0.004**
Vasopressor Support on admission, present	62 (42.8)	48 (61.5)	**0.007**
Acute Kidney Injury, present	94 (64.4)	39 (50)	**0.037**
Need for Hemodialysis, present	25 (17.1)	14 (17.9)	0.877
Mortality, yes	60 (41.1)	59 (75.6)	**<0.001**
Length of ICU Stay, days	9 (10)	6 (9)	**<0.001**
SOFA Score at Onset of Sepsis	7.1±3	10±4.6	**<0.001**

DIC: Disseminated intravascular coagulation, ICU: intensive care unit, SOFA: sequential organ failure assessment.

Table 2. Comparison of laboratory characteristics of patients with and without overt DIC
Tablo 2. Aşikar DİK'i olan ve olmayan hastaların laboratuvar özelliklerinin karşılaştırılması

	Without overt DIC (n=146)	**Overt DIC (n=78)**	***p* value**
Urea (mg/dL)	108.4±46.7	123.3±57.3	0.336
Creatinine (mg/dL)	3.7±2.1	3.3±1.6	0.088
AST (U/L)	34 (32)	31.5 (146)	0.317
Total bilirubin (mg/dL)	0.6 (1.6)	2.7 (4.5)	**<0.001**
Albumin (g/dL)	3.0±0.4	2.9±0.5	**<0.001**
CRP (mg/L)	214 (168)	226.5 (166.8)	0.808
LDH (U/L)	310 (75)	419 (310.5)	0.493
Procalcitonin (μg/L)	16.4(46.3)	42(79.2)	**0.012**
Lactate (mmoL/L)	2.6 (1.4)	4.4 (4.5)	0.055
PT (seconds)	13.8 (3.6)	18.3 (7.7)	**<0.001**
INR	1.2 (0.3)	1.6 (0.8)	**<0.001**
D-Dimer (μg/L FEU)	4281 (2704)	4404 (1070.3)	**<0.001**
Fibrinogen (mg/dL)	551.9±175.2	362±226.4	0.067
Neutrophil # (/μL)	14035.3±10735.8	8133.8±6696.1	**<0.001**
Lymphocyte # (/μL)	890 (700)	730 (662.5)	**<0.001**
Hemoglobin (g/dL)	10.9±2.3	9.4±2.3	**<0.001**
Platelet (x10^3 /μL)	181.2±73.064	93.5±59.524	**<0.001**
NLR	10.9 (20.4)	9.1 (16.8)	**0.015**

DIC: Disseminated intravascular coagulation, AST: Aspartate aminotransferase, CRP: C-Reactive protein, LDH: Lactate dehydrogenase, PT: Prothrombin time, INR: International normalized ratio, FEU:fibrinogen equivalent units, NLR: Neutrophil to lymphocyte ratio.

Table 3. Evaluation of variables that correlates with DIC score

Tablo 3. DIC skoru ile ilişkili olan değişkenlerin değerlendirilmesi

	r	p
Length of ICU Stay, days	-0.270	**<0.001**
SOFA Score at Onset of Sepsis	0.413	**<0.001**
Total bilirubin	0.263	**<0.001**
Albumin	-0.295	**<0.001**
Neutrophil #	-0.282	**<0.001**
Lymphocyte #	-0.247	**<0.001**
Hemoglobin	-0.310	**<0.001**
Lactate	0.196	**0.021**
Procalcitonin	0.209	**0.022**

DIC: Disseminated intravascular coagulation, ICU: intensive care unit

SOFA: sequential organ failure assessment.

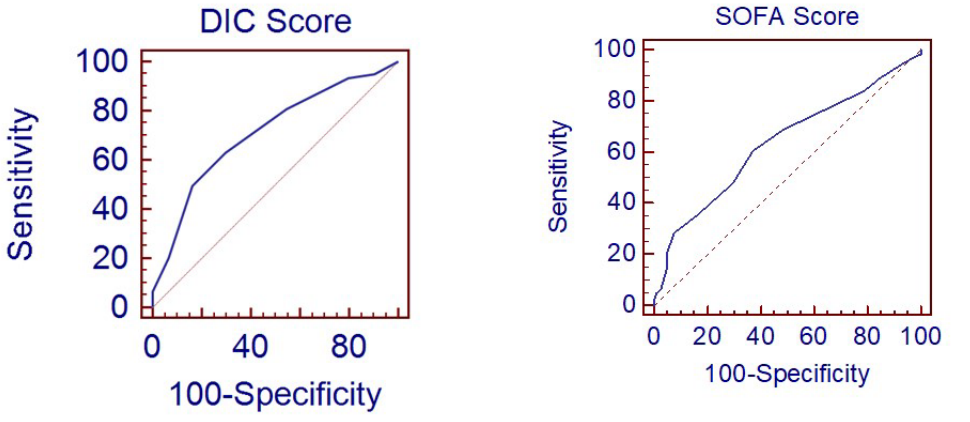
The Area Under the Curve (AUC) value for the DIC score at ICU admission, in predicting mortality, was 0.709. A cut-off value of >4 yielded a sensitivity of 49.58% and a specificity of 83.65% (95% CI: 0.644-0.767, p<0.001). The AUC for SOFA score was 0.634, with a sensitivity of 60.50% and specificity of 62.86 % at a cut-off value of >7 (95% CI: 0.568-0.697, p<0.001) (Figure 1). When comparing the DIC score and SOFA score, no significant difference was found (p=0.078). Mortality outcomes in sepsis patients according to the DIC score are shown in Figure 2; higher DIC scores were associated with increased mortality.

Table 4. Determination of risk factors affecting the development of DIC

Tablo 4. DİK gelişimini etkileyen risk faktörlerinin belirlenmesi

	OR	95 % CI	p
Hematologic Malignancy	16.802	2.432;116.065	**0.004**
Acute kidney injury on admission	0.077	0.013;0.460	**0.005**
SOFA Score at Onset of Sepsis	1.258	1.041;1.520	**0.017**

DIC: Disseminated intravascular coagulation, OR: Odds ratio, CI: Confidence interval.



	Cutoff	AUC (95 %CI)	p	Sensitivity (95% CI)	Specifity (95% CI)	+LR (95% CI)	-LR (95% CI)	PPV (95% CI)	NPV (95% CI)
DIC Score	>4	0.709 (0.644;0.767)	<0.001	49.58 (40.3;58.9)	83.65 (75.1;90.2)	3.03 (1.9;4.9)	0.60 (0.5;0.7)	77.6 (66.5;86.4)	59.2 (50.8;67.2)
SOFA Score	>7	0.634 (0.568;0.697)	<0.001	60.50 (51.1;69.3)	62.86 (52.9;72.1)	1.63 (1.2;2.2)	0.63 (0.5; 0.8)	64.9 (55.2;73.7)	58.4 (48.8;67.6)

AUC: Area under curve, CI: Confidence interval, +LR: Positive likelihood ratio, -LR: Negative likelihood ratio

PPV: Positive predictive value; NPV: Negative predictive value.

Figure 1. The Area Under the Curve (AUC) value for the DIC score at ICU admission, in predicting mortality

Şekil 1. Mortaliteyi öngörmede yoğun bakım ünitesine kabul sırasında DIC skorunun Eğri Altındaki Alan (AUC) değeri

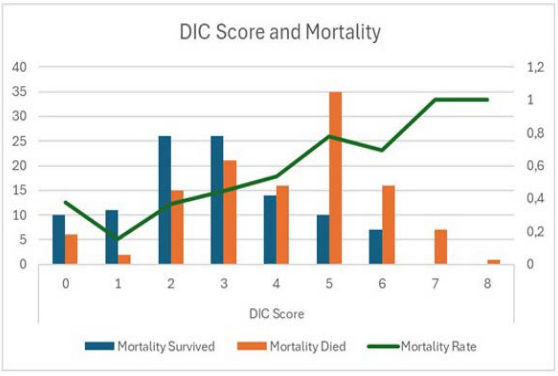


Figure 2. Mortality outcomes in sepsis patients according to the DIC score

Şekil 2. DIC skoruna göre sepsis hastalarında mortalite sonuçları

DISCUSSION

In the current study, we determined the frequency of sepsis associated overt DIC, the factors associated with the risk of overt DIC development and the association between the DIC score and mortality. Our findings revealed that the frequency of overt DIC was 34.8%. Mortality was 75.6% in the overt DIC group. The patients who developed DIC were more severely ill, as defined with the SOFA score. We concluded that presence of hematologic malignancy is a remarkable risk factor for the development of overt DIC. SOFA score (>7) and DIC score (>4) were closely related with mortality. In comparison of SOFA and DIC score we did not find significant difference.

Sepsis and septic shock can be inevitably complicated with DIC with increasing mortality. Gando et al reported overt DIC incidence and mortality as 18.1% vs 46.8% (5). Another retrospective study reported the prevalence and mortality of overt DIC 29.3% and 38.4% (14). Both studies included patients according to the sepsis-1 criteria. Wang et al examined the patients according to the Sepsis-3 criteria and prevalence and mortality of overt DIC were 22.6% and 55.2% (8). In our study, among 224 patients diagnosed with Sepsis-3 criteria, 34.8% developed overt DIC. Mortality was also determined higher than the reported in the current literature. The high mortality rate may be explained by the significantly high number of patients with hematologic malignancy in the overt DIC group.

The prognosis of critically ill patients is closely associated with laboratory parameters including procalcitonin and CRP (15,16). Additionally, hypoalbuminemia was also associated with poor prognosis in sepsis patients (17,18). In the current study the patients who developed overt DIC had lower albumin and higher procalcitonin levels consistent with the literature. Although patients who died and survived were not evaluated, since the development of DIC is a factor that increases mortality, it is not surprising that these parameters were significantly different in patients who developed overt DIC.

In our study, factors associated with DIC development were hematologic malignancy and SOFA score at the onset of sepsis, while AKI upon admission was found to be a protective factor. The presence of acute kidney injury on admission may be linked to earlier or more aggressive treatment strategies, potentially explaining its protective effect. Among sepsis studies, hematological cancer was associated with the highest odds ratio (OR:3.286) for development of DIC (19). The relationship between hematological malignancy and DIC can be as a result of prohemostatic condition caused by tumor cells (20,21). It was not possible to accurately differentiate DIC in septic patients, if the hematologic malignancy was the cause or the predisposing factor due to the design of the study. Another factor among sepsis patients for DIC development were age ≥60 years, albumin ≤2.5 g/dL, metabolic disease history and starting antibiotic therapy ≥ 1 hour (19). In addition to the existing literature, our study identified the SOFA score as a significant risk factor for the development of DIC, providing guidance for future studies.

One of the remarkable points of the present study is the evaluation of the factors that correlates with DIC score. In clinical practice, daily routine laboratory parameters can be a guide for clinician for treatment modifications.

In studies investigating the relationship between DIC score and mortality in sepsis patients, Voves et al. reported five-fold increased risk of death in patients with overt DIC and higher SOFA scores reflecting organ failure (9). In another study, presence of DIC with the ISTH DIC criteria (score ≥5) predicted mortality with a sensitivity 69.4% and a specificity 48.5% (22). Another study investigated the predictive performance of ISTH DIC score for 28-day mortality and compared to SOFA; DIC score ≥5 significantly predicted mortality whereas a high SOFA >12 also significantly predicted mortality with a greater power (23). Although it is difficult to compare this study with our study because it included intensive care unit patients other than sepsis, the prediction of mortality with increasing DIC score can be given as a common result. Among patients with sepsis associated DIC, Iba et al reported changes in SOFA score had the strongest association with the 28-day mortality in patients with sepsis and DIC (24). In the current study, we determined the cutoff value >4 for DIC score and >7 for SOFA score with no superiority over each other. The SOFA score incorporates clinical and laboratory variables, and by definition, patients with sepsis-associated DIC typically exhibit higher SOFA scores. In contrast, the ISTH DIC score offers a more specific method for evaluating DIC among patients.

This study has some limitations. First this is a single center study and have limited generalizability. Second, the group of patients is heterogeneous in terms of comorbidities including hematologic malignancy which may also a factor for development of DIC. Finally, peak DIC score and SOFA score on subsequent days was not possible to calculate because of retrospective nature.

In conclusion, the DIC score, which can be easily calculated using routine laboratory values, is associated with mortality. Our study underscores the importance of DIC screening. Additionally, we observed that more severe illnesses, such as hemodynamic instability and hematologic malignancy, were closely associated with the development of overt DIC. Neither the SOFA score nor the DIC score demonstrated superiority over each other in predicting mortality; future prospective studies are warranted.

CONFLICT OF INTERESTS

None

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