Original Article

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Can Sepsis-induced Coagulopathy Scores and Routine Blood Tests Indicate Prognosis in Patients with COVID-19?

Sepsise Bağlı Koagülopati Skoru ve Rutin Kan Testleri COVID-19'lu Hastalarda Prognozu Öngörebilir mi?

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ABSTRACT

Objective: Coronavirus disease-19 (COVID-19) is a multisystemic disease and prognostic factors should be well defined to assess its severity. Sepsis-induced coagulopathy (SIC) score is calculated using parameters related to cardiac, renal, gastrointestinal, and central nervous systems, and coagulation. In this study, we investigated the prognostic effectiveness of the SIC score during the follow-up of patients with COVID-19.

Methods: The study was conducted retrospectively by evaluating 123 patients diagnosed as having COVID-19 and hospitalized in the intensive care unit. Patients were divided into two groups, low-risk and high-risk, according to their calculated SIC scores. Patients in these groups were compared in terms of laboratory parameters and outcome patterns.

Results: The rate of in-hospital deaths was higher in the group with positive SIC scores compared to the group with negative scores. In the positive-SIC (high-risk) group, albumin level was 2.6±0.6 g/dL, the neutrophil-lymphocyte ratio was 13.6±13.8%, and prothrombin time (PT) was 18.2±2.8. The difference between the values obtained in the comparison between the groups was found to be statistically significant.

Conclusion: The SIC score can be used to predict in-hospital mortality in patients wi the COVID-19. Serum albumin level was shown to have a significant association with poor prognosis in our study. An increase in the neutrophil-lymphocyte ratio, which is a cheap, easily measured, and reproducible parameter, can be used as an indicator of poor prognosis. PT was prolonged by 4 seconds over

ÖZ

Amaç: Koronavirüs hastalığı-19 (COVID-19) multisitemik bir hastalıktır ve hastalığın ciddiyetini değerlendirmek için prognostik faktörler iyi tanımlanmalıdır. Sepsise bağlı koagülopati (SIC) skoru; kardiyak, renal, gastrointestinal, merkezi sinir sistemi ve pıhtılaşma ile ilgili parametreler kullanılarak hesaplanır. Bu çalışmada, COVID-19'lu hastaların takibi sırasında SIC skorunun prognostik etkinliğini araştırdık.

Yöntemler: Çalışma COVID-19 tanısı konup yoğun bakıma yatırılan 123 hasta değerlendirilerek retrospektif olarak yapıldı. Hesaplanan SIC skoruna göre hastalar düşük riskli ve yüksek riskli olmak üzere iki gruba ayrıldı. Her iki gruptaki hastalar laboratuvar parametreleri ve sonlanım şekilleri (ölen, taburcu) açısından karşılaştırıldı.

Bulgular: Hastane içi ölümlerin oranı SIC skoru pozitif olan grupta negatif olan grup ile karşılaştırıldığında daha yüksek bulundu (p<0,001). SIC skoru pozitif hasta grubunda albümin düzeyi 2,6±0,6 g/dL, nötrofil lenfosit oranı %13,6±13,8 ve protrombin zamanı (PZ) 18,2±2,8 idi. Gruplar arası karşılaştırmada elde edilen değerler arasındaki fark istatistiksel olarak anlamlı bulundu.

Sonuç: SIC skoru, COVID-19'lu hastalarda hastane içi mortaliteyi tahmin etmek için kullanılabilir. Çalışmamızda serum albümin düzeyinin kötü prognoz ile anlamlı bir ilişkisi olduğu gösterildi. Ucuz, kolay ölçülebilir ve tekrarlanabilir bir parametre olan nötrofil-lenfosit oranındaki artış kötü prognoz göstergesi olarak kullanılabilir. Çalışmamızda PZ normal değerin (10-14 saniye) üzerinde 4 saniye (18,2±2,8 saniye) uzadı. PZ uzaması mortalite ile

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ABSTRACT

the normal value in our study. PT prolongation may be associated with mortality. SIC score can serve as a marker of disease severity.

Keywords: COVID-19, sepsis-induced coagulopathy score, prognosis

ÖZ

ilişkili olabilir. SIC skoru, hastalığın şiddetini gösteren bir belirteç olarak kullanılabilir.

Anahtar Sözcükler: COVID-19, sepsise bağlı koagülopati skoru, prognoz

Introduction

The coronavirus disease-19 (COVID-19), a worldwide pandemic, is a cause of high mortality and morbidity (1). It is a multisystemic disease (2). Since the clinical course of the disease is variable, it is important to evaluate its prognosis (3). The parameters to be used should be inexpensive, easily measurable, and repeatable. Complete blood count, urea, creatinine, lactate dehydrogenase (LDH), creatine kinase (CK), D-dimer, ferritin, troponin, C-reactive protein (CRP), coagulation parameters, and ferritin are routine parameters that are measured in emergency rooms for COVID-19 (4). The Sequential Organ Failure Assessment (SOFA) score evaluates the patients' saturation, blood pressure, consciousness, liver and kidney functions. Sepsis-induced coagulopathy (SIC) score is calculated by adding coagulation and platelet count to the SOFA score. It is important for the feasibility of the study that COVID-19 has a multisystemic effect (5) and that the SIC score includes parameters that will respond to this diversity. SIC is a scoring system that considers coagulation abnormalities in sepsis. It is used for possible sepsis-induced coagulopathy (6). Therefore, we decided to use the SIC score in this study.

In this study, we investigated the prognostic effectiveness of the SIC score during the follow-up of patients with COVID-19. The SIC score and some laboratory markers (albumin, PT, NLR) can serve as early markers of severe disease and can be used to develop prognostic scores.

Methods

The study was carried out retrospectively in the emergency department between 01.03.2020 and 31.05.2020. It was carried out in accordance with all the criteria set in the Declaration of Helsinki. Data were obtained from hospital records using ICD-10 code U07.3 (COVID-19). Patients over the age of 18 who were diagnosed as having COVID-19 (confirmed by polymerase chain reaction) and hospitalized in the intensive care unit (ICU) were included in the study. Patients excluded from the study are shown in Figure 1. Those whose SIC score could not be calculated due to missing laboratory data were excluded from the study (Figure 1).

The patients were first evaluated in the emergency room and then sent to the ICU. The criteria used for the indication of ICU hospitalization were: dyspnea and severe respiratory distress, respiratory rate ≥30/min, PaO_2/FiO_2<300, SpO_2<90% or PaO_2<70 mmHg despite oxygen therapy, mean arterial pressure <65 mmHg, tachycardia >100/min.

Using these criteria, 123 of 723 patients were included in the study over a three-month period. The SIC score was used to assess the severity of the disease. SIC score was calculated from the blood sample and vital signs taken at the time of first admission to the emergency department. The parameters of this score were platelet count, prothrombin time (PT) and SOFA score. SIC score can be calculated using platelet count, PT or

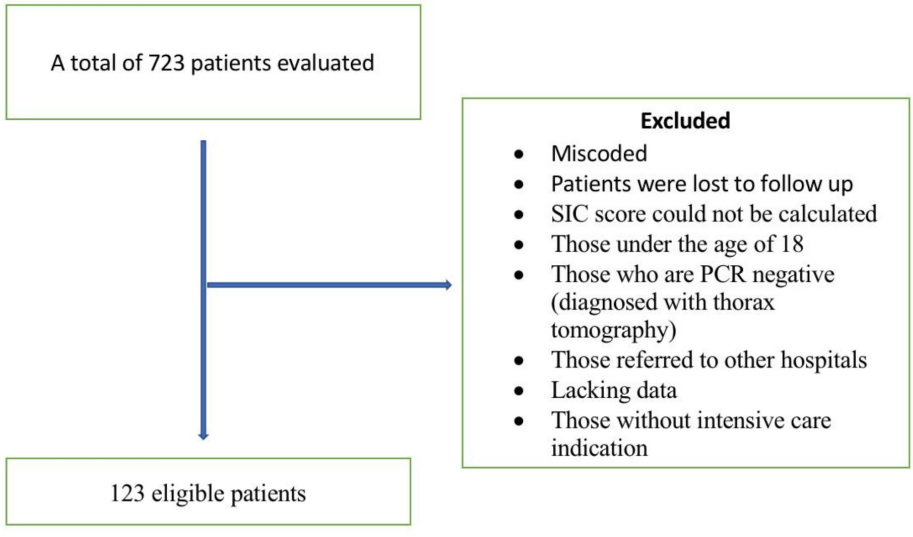

Figure 1. Flowchart of patient selection
PCR: Polymerase chain reaction

INR value, SOFA score. Many studies have shown that PT levels present at admission in patients with COVID-19 may be used as early prognostic markers of severe pneumonia requiring transfer to the ICU. So, we used PT instead of INR to calculate SIC score (7). A calculated score of four or more is considered high risk (Table 1). From the results of blood samples taken when the patients presented to the emergency department; complete blood count, urea, creatinine, albumin, LDH, CK, D-dimer, ferritin, troponin, CRP and coagulation parameters were recorded. We divided the patients into two groups: low risk (negative SIC score) and high risk (positive SIC score). Routine blood parameters were compared between the groups. The relationship between SIC score and patient outcomes (death or discharge) was investigated.

Population and Sample

The research population consisted of patients over the age of 18 who were admitted to the emergency department of our hospital and were diagnosed as having COVID-19. The study was carried out between 01.03.2020 and 31.05.2020. As a result of the power analysis, the values were determined as α=0.05, β=0.20, (1-β)=0.80, and it was decided to include 123 patients in the sample. The power of the test was evaluated as p=0.89904.

Ethics committee approval with the date 22.12.2020 and decision number 21/407 was obtained from the ethics committee of our university.

Statistical Analysis

Behaviors of quantitative variables were expressed using centralization and measures of variance: mean ± standard deviation. The chi-square test was used to identify differences in ratios or relationships between categorical variables. To show the behavioral differences of the group averages, the ANOVA and T-test were used in cases where the assumptions of normality and equivalence were met, and the Mann-Whitney U test method was used when the assumption of normality was not met. Statistical significance was determined as being p≤0.05 for all analyses. Statistical analyses were provided with the IBM SPSS (Statistics Package for Social Sciences for Windows, Version 21.0, Armonk, NY, IBM Corp) program package.

Results

Of the 123 patients evaluated, 72 were male (58.5%) and 51 were female (41.5%). The numbers of female/men with SIC score negative/positive are given in Table 2. The mean age was 70.6±13.8 years. The mean age of those with negative SIC score was 69.5±12.2 years, and of those with positive SIC score was 72±15.9 years (Table 2). The most common chronic diseases were hypertension (69 patients, 56.1%), diabetes mellitus (45 patients, 36.6%), and coronary artery disease (45 patients, 36.6%). There was a statistically significant difference in the numbers of those with heart failure and chronic kidney failure between the high-risk and low-risk groups (Table 2). The most common complaints were shortness of breath (48 patients, 39%) and fever (33 patients, 26.8%). There were 69 patients (56.1%) with a Glasgow Coma score of 14 or less. There were 71 patients (57.7%) with a negative SIC score and 52 patients (42.3%) with a positive score. The compared vital signs of patients with negative and positive SIC scores are given in Table 3. Six of the 20 parameters examined showed a statistically significant difference between the groups. The difference in the values of decrease in albumin level (p=0.003), increase in NLR (p<0.001), and prolongation in PT (p<0.001) between the groups was found to be statistically significant. All checked parameters are shown in Table 4. Six patients (8.5%) with negative SIC score died, and 65 patients (91.5%) were discharged. Twenty five patients (48.1%) with positive SIC score died, and 27 patients (51.9%) were discharged (p<0.001) (Table 5).

Discussion

In this study, we found that the SIC score is effective in predicting in-hospital mortality in patients with COVID-19. It has been

Table 1. Scoring for the diagnosis of SIC and SOFA

The Sepsis-Induced coagulopathy (SIC) score				
Category	**Parameter**	**0 point**	**1 point**	**2 points**
Prothrombin time	PT-INR	≦1.2	1.2-1.4	>1.4
Coagulation	Platelets 10^9/L	≧150	100-150	<100
Total SOFA	SOFA four items	0	1	≧2
The Sequential Organ Failure Assessment (SOFA) score				
Category	**1 point**	**2 points**	**3 points**	**4 points**
SaO_2/FIO_2 ratio	221-301	142-220	67-141	<67
Platelets 10^3/L	<150	<100	<50	<20
Creatinine mg/dL	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Bilirubin mg/dL	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or NE ≤0.1	Dopamine >15 or NE >0.1
GCS score	13-14	10-12	6-9	<6

INR: International normalisation ratio, PT: Prothrombin time, SOFA: Sequential Organ Failure Assessment, NE: Norepinephrin, GCS: Glasgow coma score

shown that COVID-19 has serious effects on many systems such as the respiratory, cardiac, renal, gastrointestinal, and central nervous systems (8,9). The reason for this finding may be that COVID-19 is a multisystemic disease and the SIC score contains parameters to evaluate many systems.

Coagulation disorder plays an important role in the clinical process of COVID-19. In particular, a prolongation of PT for more than 3 seconds has been shown to be a strong prognostic factor (10). In our study, PT prolongation was over 4 seconds in the SIC-positive group. Recognition of prolonged PT is essential for early diagnosis of disseminated intravascular coagulability (DIC). It is important to reduce the risk of DIC and predict the need for intensive care in patients with COVID-19.

Low serum albumin level is an important indicator of morbidity and mortality. The condition that causes hypoalbuminemiain COVID-19 is severe inflammation, rather than hepatocellular damage (liver function tests are normal) (11,12). In this study, we found that low albumin level at admission might be associated with mortality. In our study, albumin level was below normal values in both groups, but it was lower in the SIC-positive group (2.6±0.6 g/dL). This difference was statistically significant (p=0.003).

While neutrophil count increases in bacterial infections, lymphocyte count decreases during viremia. Examining these two parameters can greatly aid in the assessment of COVID-19 infection. NLR can be used as an easy-to-calculate, inexpensive, and effective parameter, giving early warning for COVID-19 infection. Such markers are important for early diagnosis and management of the disease. NLR was reported as a prognostic marker in patients with COVID-19 in many previous studies (13,14). In our study, NLR was evaluated and it was found to be 6.5% in SIC-negative patients and 13.6% in SIC-positive patients (p<0.001).

High red cell distribution width (RDW) has been associated with increased mortality in many diseases (such as chronic obstructive pulmonary disease, pneumonia, sepsis, and viral hepatitis) (15,16). In addition, a RDW of over 14% is considered a strong inflammatory marker (17). A high RDW level in viral infections may be due to deregulation of erythrocyte homeostasis and impaired production. Inflammation and oxidative conditions can cause insufficient erythropoiesis deformation. Hyperinflammatory response and cytokine storm determine the clinical process in COVID-19 (18).

In our study, while the RDW was within the normal range in patients with negative SIC score, it increased to 14% in patients with positive SIC score (p=0.035). Therefore, RDW should be part of routine laboratory assessment and monitoring of COVID-19.

Table 2. SIC score and chronic disease

	n (%)	SIC negative n (%)	SIC positive n (%)	p-value (p)
Gender	Female 51 (41.5)	26 (36.6)	25 (48.1)	0.27
	Male 72 (58.5)	45 (63.4)	27 (51.9)	
Age	Mean ± SD	69.5±12.2	72±15.9	0.12
Chronic disease	Diabetes mellitus	24 (33.8)	21 (40.4)	0.57
	Hypertension	36 (50.7)	33 (63.5)	0.22
	Heart failure	11 (15.5)	19 (36.5)	0.01
	Hepatic disease	8 (11.3)	4 (7.7)	0.72
	Chronic renal failure	9 (12.7)	18 (34.6)	0.00
	Coronary heart disease	23 (32.4)	22 (42.3)	0.34
	Chronic pulmonary	21 (29.6)	12 (23.1)	0.55
	Malignancy	8 (11.3)	7 (13.5)	0.93
	Cerebrovascular accident	10 (14.1)	8 (15.4)	1.00

SIC: Sepsis-induced coagulopathy, SD: Standard deviation

Table 3. SIC score and vital signs

Parameters	SIC negative (n=71) Mean ± SD	SIC positive (n=52) Mean ± SD	p-value (m)
Body temperature °C	37.1±0.8	37.2±0.7	0.13
Respiratory rate/minute	22.3±3.2	21.2±2.5	0.14
Systolic blood pressure mmHg	141.9±35.3	135.4±34.8	0.44
Heart rate/minute	105.6±29.3	94.8±11.8	0.11

m: Mann-Whitney U test, n: Number, SD: Standard deviation

Table 4. SIC score and blood parameters

Parameters	Unit	SIC negative (mean ± SD)	SIC positive (mean ± SD)	p-value
Urea	mg/dL	69±48.2	103.8±62.2	0.002*
Creatinine	mg/dL	1.4±0.8	1.5±0.9	0.888*
LDH	U/L	533.1±791.9	701.1±927.1	0.052*
PT	sec	16.57±3.3	18.2±2.8	<0.001*
PTT	sec	38.9±11.1	41.1±10.2	0.29*
INR	Ratio	1.5±0.5	1.5±0.6	0.184*
WBC	10^9/L	9.8±5.5	9.8±5.0	0.66*
Hemoglobin	g/dL	12.1±2.2	11.6±2.1	0.194*
NLR	%	6.5±3.9	13.6±13.8	<0.001*
Albumin	g/dL	3.0±0.6	2.6±0.6	0.003**
AST	IU/L	43.8±9.1	59.9±10.5	0,166
ALT	IU/L	34.9±3.3	43,8±2.5	0,826
RDW	%	13.1±1.6	14.0±2.2	0.035*
Troponin	ng/dL	83.5±148.1	127.2±246.8	0.838*
D-Dimer	ng/mL	950±1318.2	1103.5±1026.3	0.073*
Creatine kinase	U/L	144.8±124.6	196.8±182.2	0.154*
C-reactive protein	mg/L	110.23±76.5	128.3±71.9	0.063*
Ferritin	ng/mL	885.9±885.7	1352.2±1435.1	0.068*

LDH: Lactate dehydrogenase, PTT: Partial thromboplastin time, INR: Internationel normalized ratio, WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, RDW: Red cell distribution width, PT: Prothrombin time, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase. **: Anova T-test, *: Mann-Whitney U test

Table 5. Comparison of the patients that died in hospital and those that were discharged

		SIC negative n (%)	SIC positive n (%)	p-value
Outcomes	Died in hospital	6 (8.5%)	25 (48.1%)	<0.001
	Discharged	65 (91.5%)	27 (51.9%)	

p: Pearson chi-squared test, n: Number, %: Percent, SIC: Sepsis-induced coagulopathy

Changes in urea level and platelet count were statistically significant (p=0.002, p=0.014). In addition, the increase in LDH, D-Dimer, CRP and ferritin levels should be monitored more closely (Table 5).

Study Limitations

One of the most important limitations of our study was that patient data were obtained retrospectively. Another important limitation was that data belonging to only one center were included in the study.

Conclusion

The SIC score can be used to predict in-hospital mortality in patients with COVID-19. Decrease in albumin level may be associated with poor prognosis. NLR, which is a cheap, easily measured, and reproducible parameter, is an indicator of a prognosis. Caution should be exercised in critically ill patients with a PT prolongation of four seconds or more (18.2±2.8 seconds) from the normal value. SIC score and some laboratory values (albumin, RDW, PT, NLR) can serve as early markers of severe disease and can be used to develop prognostic scores.

Ethics

Ethics Committee Approval: Bezmialem Vakıf University Non-Interventional Research Board (number: E-54022451-050.01.04-1928/date: 22.12.2020).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.T., Concept: B.T., Design: E.S., Data Collection or Processing: B.T., E.S., Analysis or Interpretation: A.C., Literature Search: B.T., E.S., Writing: E.S.

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