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Evaluation of the Modified HASBLED Score for Prediction of In-hospital Mortality in Patients with COVID-19

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Abstract

Objective: The COVID-19 outbreak continues to be the common cause of deaths worldwide in recent times. Preventing poor outcomes (death, intubation, non-invasive ventilation, need for intensive care) is the first goal for hospitalized patients. Identifying high-risk patients during hospitalization can provide more effective follow-up and treatment. The HASBLED score is highly predictive for bleeding events in atrial fibrillation patients. We used the HASBLED score to identify patients with frailty, vulnerability, and comorbid diseases, not as a bleeding score. So, we used albumin level instead of labile INR in the score because it shows both the nutritional status and inflammation. We aim to evaluate the modified HASBLED score for predicting mortality and poor outcomes in hospitalized COVID-19 patients.

Method: In total, 2850 hospitalized COVID-19 patients were screened retrospectively and, after the exclusions, 2041 patients were included in the study. The patients were divided into two groups according to the M-HASBLED score as <3 and ≥3. The demographic, laboratory, and clinical characteristics of the patients were obtained from the hospital registry system and the database of the Turkish Ministry of Health. Patients with two negative PCR tests and patients with missing data were excluded.

Results: 582 patients were included in the M-HASBLED RS ≥3 group, and 1459 patients in the M-HASBLED RS<3 group. Hypertension, diabetes mellitus, coronary artery disease, heart failure, cerebrovascular disease, and chronic renal failure were higher in the M-HASBLED RS≥3 group. In-hospital stay (7 (6-11), 9.5 (7-15) IQR), need for ICU (21.9%, 54%), NIMV (14%, 29.2%), and intubation (13%, 36.6%) were higher in the M-HASBLED RS ≥3 group compared to the other group. Death was observed in 208 (14.3%) patients in the M-HASBLED RS <3 group, and in 244 (41.9%) patients in the M-HASBLED RS ≥3 group, and it was statistically higher in the M-HASBLED RS≥3 group (p <0.001). The M-HASBLED score was found as an independent factor associated with in-hospital mortality (OR: 1.20, 95% confidence interval CI: 1.03-1.37, p=0.010).

Conclusion: M-HASBLED RS showed poor in-hospital outcomes accurately and is an independent factor associated with mortality in hospitalized COVID-19 patients.

Keywords: HASBLED score, mortality, COVID-19, hospitalization

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Modifiye HASBLED Risk Skorunun COVID-19 Hastalarında Hastane-içi Mortaliteyle İlişkisinin Değerlendirilmesi

Öz

Amaç: COVID-19 pandemisi son zamanlarda ölümlerin en sık nedeni olmaya devam etmektedir. Hastanede yatan hastalarda kötü sonlanımları (yoğun bakım ihtiyacı, entübasyon non-invazif mekanik ventilasyon, ölüm) engellemek birincil amaçtır. Yüksek riskli hastaları saptamak daha yakın takip ve daha doğru tedavi açısından son derece önemlidir. HASBLED skoru, atriyal fibrilasyon hastalarında kanama olaylarını doğru bir şekilde tahmin etmektedir. Bu çalışmamızda, HASBLED skorunu kanama skoru olarak değil, COVID-19 açısından daha kırılgan, hassas ve komorbid hastalıkları olan hastaları belirlemek için kullandık. Hem beslenme durumunu hem de inflamasyonu gösterdiği için skorda labil INR yerine albümin düzeyini kullandık. Bu çalışmada, hastanede yatan COVID-19 hastalarında mortaliteyi ve kötü sonuçları tahmin etmek için modifiye HASBLED skorunu değerlendirmeyi amaçlıyoruz.

Yöntemler: Çalışma için geriye dönük olarak 2850 hasta incelendi ancak dışlamalardan sonra 2041 hasta dahil edildi ve hastalar M-HASBLED skoruna göre <3 ve ≥3 olmak üzere iki gruba ayrıldı. Hastaların demografik, klinik ve laboratuvar verileri hastane bilgi sisteminden ve Sağlık Bakanlığı veritabanından elde edilmiştir. İki PCR testi negatif olan ve eksik verisi olan hastalar çalışmadan dışlandı.

Bulgular: M-HASBLED RS ≥3 grubuna 582 hasta ve M-HASBLED RS<3 grubuna 1459 hasta dahil edildi. Hipertansiyon, diyabetes mellitus, koroner arter hastalığı, kalp yetmezliği, serebrovasküler hastalıklar ve kronik böbrek yetmezliği M-HASBLED RS≥3 grubunda daha yüksek oranda izlendi. Hastanede kalış (7 (6-11), 9,5 (7-15) IQR), yoğun bakım ihtiyacı (%21,9, %54), non-invazif mekanik ventilasyon (%14, %29,2) ve entübasyon (%13, %36,6) M-HASBLED RS ≥3 grubunda diğer gruba göre daha yüksek oranda izlendi. M-HASBLED RS <3 grubunda 208 (%14,3) hastada ve M-HASBLED RS ≥3 grubunda 244 (%41,9) hastada ölüm izlendi ve M-HASBLED RS≥3 grubunda istatistiksel olarak anlamlı saptandı (p <0.001). M-HASBLED skoru hastane içi mortalite ile ilişkili bağımsız bir faktör olarak bulundu (OR: 1,20, %95 güven aralığı CI: 1.03-1.37, p=0.010).

Sonuç: M-HASBLED RS, hastane içi kötü sonlanımları doğru bir şekilde gösterdi ve bu skorun hastanede yatan COVID-19 hastalarında mortalite ile ilişkili bağımsız bir faktör olduğunu saptadık.

Anahtar kelimler: HASBLED skoru, ölüm, COVID-19, hastane yatışı.

INTRODUCTION

The COVID-19 outbreak continues to be the common cause of deaths worldwide in recent times[1]. Mask, social distance, and hand hygiene are the most important factors in minimizing the spread of the epidemic. Preventing poor outcomes (death, intubation, non-invasive ventilation, need for intensive care) is the first goal for hospitalized patients. The prognosis of COVID-19 disease is not the same in every patient, and it is known that patients with some risk factors show a worse prognosis[2]. Identifying high-risk patients during hospitalization can provide more effective follow-up and treatment. Studies have found that advanced age, male gender, cardiovascular diseases, hypertension (HT), renal failure, liver failure, and low albumin levels are risk factors related to the severity of disease and mortality in COVID-19 patients[3-7]. In some studies, the prognostic nutritional index (PNI), LDH, fragility index, neutrophil-lymphocyte ratio (NLR), and CHA2DS2-VASc risk score were used to predict mortality, and mortality was accurately determined by these parameters[8-13].

The HASBLED score (uncontrolled HT, abnormal hepatic/renal function, stroke (ischemic or hemorrhagic), the labile international normalized ratio [INR], bleeding history or predisposition, elderly [age ≥65 years], drugs/alcohol) is used in patients with atrial fibrillation before starting oral anticoagulant therapy and shows the bleeding risk[14]. A HASBLED score ≥3 is highly predictive of bleeding events. In other words, the HASBLED score can identify patients who are fragile, vulnerable, and with comorbid diseases. The HASBLED score includes factors which are related to mortality in COVID-19 patients (HT, cerebrovascular disease (CVD), kidney and liver failure, anemia, advanced age). Therefore, in this study, we used the HASBLED score to

identify patients with frailty, vulnerability, and comorbid diseases, not as a bleeding score. So, we used albumin level instead of labile INR in the score because it shows both the nutritional status and inflammation[15].

The present study aims to determine the predictive performance of the modified HASBLED score for predicting mortality and poor outcomes in hospitalized COVID-19 patients.

METHODS

Our study is a retrospective and observational study. Between October and December 2020, 2850 hospitalized COVID-19 patients were screened at our hospital. Thorax CT (computerized tomography) and combined oral and nasopharyngeal swab samples were analyzed for each patient. Patients having two negative PCR tests (753) and missing data (56) were eliminated from the study. Following the exclusions, the study consisted of 2041 patients, and the patients were divided into two groups according to the M-HASBLED score as <3 and ≥3.

The laboratory, clinical, and demographic features of the patients were obtained from the hospital registry system and the database of the Turkish Ministry of Health. Information about drugs and alcohol was procured from anamnesis records of the hospital database. Admission laboratory findings were used for all evaluations. In-hospital stay, need for intensive care unit (ICU), intubation, non-invasive mechanical ventilation (NIMV), death, and ARDS were evaluated as clinical features. NLR is obtained by dividing the neutrophil count by the lymphocyte count. The PNI was calculated using the formula: PNI = 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (per mm3). CHA2DS2-VASc and modified HASBLED scores were calculated by two cardiologists who were blinded to patient data. The CHA2DS2-VASc score consists of congestive heart failure (HF), HT, age≥75 years (2 points), diabetes mellitus (DM), vascular disease, age 65-74 years, female sex, and previous stroke or transient ischemic attack (2 points)[16]. M-HASBLED score consists of uncontrolled HT (systolic blood pressure (BP) >160 mmHg), abnormal hepatic and renal functions (dialysis, transplantation, serum creatinine> 200mmol / L, cirrhosis, bilirubin > 2x upper limit of normal (ULN), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) > 3X ULN), previous stroke (hemorrhagic or ischemic), a history of bleeding or predisposing conditions (anemia or thrombocytopenia), low albumin level (<35 g / L), elderly (age > 65 years), drugs (non-steroid anti-inflammatory drugs) or excessive alcohol drinking (14 unit per week)[14]. Anemia is defined as hemoglobin levels <13.0 g/dL in men and <12.0 g/dL in women[17]. Thrombocytopenia is defined as a platelet count of less than 150 × 103 per μL18.

Statistical Analysis

Statistical analysis was conducted with the IBM SPSS 24.0 program. Continuous variables were presented as a median interquartile range, and categorical variables were expressed as percentages. The Chi-square test was utilized to compare categorical variables between groups. The Mann-Whitney U test was utilized to compare the continuous variables. Univariable and multivariable regression analyses were used to identify predictors of in-hospital mortality. The accuracy of the M-HASBLED, CHA2DS2-VASc, M-CHA2DS2-VASC RS, and NLR were evaluated with ROC curves for in-hospital mortality. For the analyses, the statistical significance was fixed at p values of <0.05.

RESULTS

Patients were divided into two groups: M-HASBLED risk score (RS) <3 and ≥3. In total, 582 patients were included in the M-HASBLED RS ≥3 group, and 1459 patients in the M-HASBLED RS<3 group. The median age of all patients was 64 (54-74 IQR) and 1023 (50.1%) were male. The M-HASBLED RS ≥3 group had a median age of 74 (IQR 68-81), while the other

group had a median age of 59 (49-69), which was statistically higher in the M-HASBLED RS≥ 3 group (p <0.001).

Ferritin, C-reactive protein, D-dimer, pro-calcitonin, and LDH were higher in the M-HASBLED RS ≥3 group. Albumin, admission oxygen saturation (SaO2), and lymphocyte count were statistically lower in the M-HASBLED RS ≥ 3 group. CHA2DS2-VASc RS, M- CHA2DS2VASc RS, and NLR were higher in the M-HASBLED ≥3 group (p <0.001, p <0.001, p<0.001, respectively). PNI was lower in the M-HASBLED ≥3 group (p <0.001). Table 1 shows the results of the laboratory findings.

Table I: Laboratory parameters of groups.

Variables	HASBLED(0-2) n=1459	HASBLED(≥3) n=582	P value
Creatinin, mg/dL	0.87(0.76-1.05)	1.28(0.9-1.90)	<0.001
AST, U/L	32(23-45)	32(23-52)	0.183
ALT, U/L	25(18-39)	21(14-36)	<0.001
LDH, U/L	318(255-411)	346(268-474)	<0.001
Albumine, g/L	34(31-37)	29(26-32)	<0.001
Ferritin, ng/ml	422(217-802)	477(235-1045)	0.003
CRP, mg/dL	68(31-116)	100(53-152)	<0.001
Prokalsitonin, ng/ml	0.09(0.05-0.17)	0.21(0.10-0.73)	<0.001
D-dimer, ng/mL	231(163-362)	397(257-776)	<0.001
Troponin, ng/mL	0,1(0,1-0,1)	0,1(0,1-0,1)	0.140
WBC, 10^3/uL	6.8(5.12-9.82)	7.9(5.70-11.1)	<0.001
Hemoglobin, gr/dL	13.7(12.7-14.7)	11.9(10.9-13.5)	<0.001
Neutrophil, 10^9/L	4.97(3.53-7.52)	6.23(5.32-9.57)	<0.001
Lymphocyte, 10^9/L	1.13(0.81-1.50)	0.89(0.63-1.27)	<0.001
Platelet, 10^3/uL	207(166-258)	209(165-273)	0.222
SaO_2, %	90(85-93)	85(79-90)	<0.001
SBP, mmHg	115(110-120)	120(110-130)	<0.001
mHASBLED	1.0(0-2)	3(3-4)	<0.001
NLR	4.28(2.77-7.58)	6.83(4.30-12.3)	<0.001
CHA2DS2VASc	2(1-3)	4(3-5)	<0.001
mCHA2DS2VASc	2(1-3)	3(3-4)	<0.001
PNI	34(31-37)	29(26-32)	<0.001

Data are expressed as median interquartile range DOAC; direct oral anticoagulant, GFR; glomerular filtration rate, AST; aspartate transaminase, ALT; alanin transaminase, LDH; lactate dehydrogenase, CRP; C-reactive protein, PT; protrombin time, WBC; White blood cell, SaO2; oxygen saturation, SBP; systolic blood presure, DBP; diastolic blood pressure

HT, DM, coronary artery disease (CAD), HF, CVD, and chronic renal failure (CRF) were higher in the M-HASBLED RS≥3 group. In-hospital stay (7 (6-11), 9.5 (7-15) IQR), need for ICU (21.9%, 54%), NIMV (14%, 29.2%), and intubation (13%, 36.6%) were higher in the M-HASBLED RS ≥3 group compared to the other group. Death was observed in 208 (14.3%) patients in the M-HASBLED RS <3 group, and in 244 (41.9%) patients in the M-HASBLED RS ≥3 group, and it was higher in the M-HASBLED RS≥3 group (p <0.001). The demographic features of the groups are shown in Table 2.

Table II: Demographic and clinical characterictics of groups.

Parameters	HASBLED (0-2) n=1459	HASBLED (≥3) n=582	P value
Age, years	59(49-69)	74(68-81)	<0.001
In-hospital stay, day	7(6-11)	9.5(7-15)	<0.001
Need for ICU, n(%)	320(21.9)	314(54.1)	<0.001
Gender, male, n %	756(51.8)	267(45.9)	0.015
HT, n(%)	450(30.8)	350(60.1)	<0,001
CAD, n(%)	160(11)	185 (31.8)	<0.001
HF, n(%)	36(2.5)	49(8.4)	<0.001
DM, n(%)	343(23.5)	222)(38.1)	<0.001
COPD, n(%)	76(5.2)	56(9.6)	<0,001
CRF, n(%)	21(1.4)	56(9.5)	<0.001
CVD, n(%)	21(1.4)	78(13.4)	<0.001
Bilateral lesions, n(%)	1369(93.9)	563(96.7)	0.010
ARDS, n(%)	203(13.9)	188(32.3)	<0.001
NIMV, n(%)	204(14)	170(29.2)	<0.001
MV, n(%)	190(13)	213(36.6)	<0.001
HFNC, n(%)	117(8)	81(13.9)	<0.000
Mortality, n(%)	208(14.3)	244(41.9)	<0.001

Data are expressed as median interquartile range and percentage. ICU; Intensive care unit, HT; Hypertension, CAD; Coronary artery disease, HF; heart failure, DM; diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CVD; cerebrovascular disease, AF; atrial fibrillation, , MV: Mechanical ventilation, ARDS; Acute respiratory distress syndrome, HFNC; high flow nasal cannula

Multivariable logistic regression analysis was utilized to identify the predictors of in-hospital mortality. The M-HASBLED score (OR: 1.20, 95%

confidence interval CI: 1.03-1.37, p=0.010), NLR (OR: 1.03, CI: 1.01-1.06, p=0.001), male gender (OR: 1.80, CI: 1.32-2.50, p<0.001), age (OR: 1.04, CI: 1.02-1.06, p<0.001), admission SaO2 (OR: 0.82, CI: 0.80-0.85, p<0.001), GFR (OR: 0.98, CI: 0.97-0.99, p=0.003), and CRP (OR: 1.03, CI: 1.01-1.06, p=0.049) were found to be related to in-hospital mortality (Table 3).

Table III: Univariable and multivariable regression analysis to determine predictors of in-hospital mortality.

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
mHASBLED	1.9(1.76-2.10)	0.001	1.20(1.03-1.37)	0.010
PNI	0.85(0.83-0.87)	0.045	1.02(0.98-1.06)	0.320
CHA2DS2VASc	1.30(1.20-1.40)	0.001	1.23(0.82-1.55)	0.310
NLR	1.10(1.08-1.12	0.001	1.03(1.01-1.06)	0.001
Gender, male	2.12 (1.25-3.83)	0.007	1.80(1.32-2.50)	<0.001
Age	1.06 (1.05-1.07)	0.030	1.04(1.02-1.06)	<0.001
LDH	1.01(0.99-1.03)	0.349		
SaO_2	0.80 (0.77-0.82)	<0.001	0.82 (0.80-0.85)	<0.001
CRP	1.01(0.99-1.05	0.065	1.03(1.01-1.06)	0.049
Ferritin	1.06(0.69-1.63)	0.714		
D-dimer	1.22(0.82-1.83)	0.312		
GFR	0.97(0.94-0.98)	0.008	0.98(0.97-0.99)	0.003
HF	1.50(0.70-3.52)	0.264		
HT	1.40(0.81-2.53)	0.211		
COPD	1.03(0.59-1.75)	0.945		
DM	0.74(0.59-0.92)	0.019	0.82(0.55-1.24)	0.348
CVD	0.55(0.35-0.84)	0.037	0.58(0.22-1.52)	0.269
CAD	0.53(0.41-0.68)	0.010	0.88(0.58-1.58)	0.628)
Systolic BP	1.05(0.99-1.03)	0.190	0.99(0.98-1.03)	0.203

HT; Hypertension, CAD; Coronary artery disease, HF; heart failure, DM; diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CVD; cerebrovascular disease, AF; atrial fibrillation, SaO2; oxygen saturation

ROC analysis was performed to compare the predictive accuracy of M-HASBLED RS, M-CHA2DS2-VASc RS, CHA2DS2-VASc RS, and NLR for in-hospital mortality. The area under curve (AUC) for M-HASBLED RS, CHA2DS2-VASc RS, M-CHA2DS2-VASc RS, and NLR were 0.75, 0.69, 0.64, and 0.73, respectively (p <0.001, for all), with a 95% confidence interval. The AUC was significantly higher in the M-HASBLED risk score. The ROC analysis is shown in Figure 1.

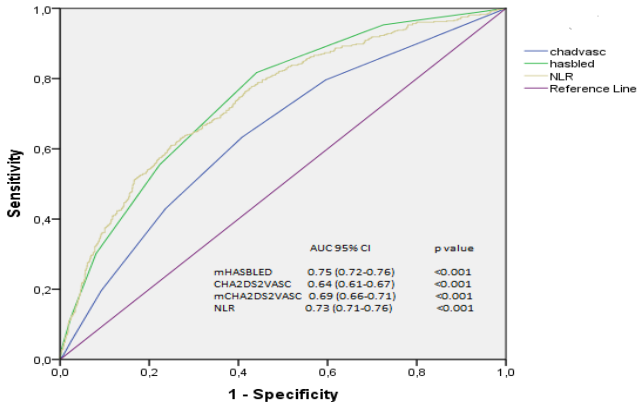

Figure 1. ROC analysis of scores.

DISCUSSION

The present study found that high M-HASBLED RS is related to in-hospital mortality in COVID-19 patients. Mortality, in-hospital stay, need for intensive care, intubation, and NIMV rate were higher in the M-HASBLED RS≥3 group compared to the other group. M-HASBLED RS, CRP, arrival SAO2, male gender, advanced age, and NLR were identified as independent risk factors related to in-hospital mortality.

COVID-19 has a different clinical spectrum. Although asymptomatic infection is common, it ranges from mild respiratory tract infection to severe pneumonia, leading to severe respiratory failure[2,4]. Due to the broad clinical spectrum of COVID-19, different parameters such as biomarkers, comorbid diseases, risk scores, age, and gender were used to predict adverse outcomes. The M-HASBLED RS includes many factors associated with in-hospital mortality and poor outcomes. Previous studies showed that advanced age and male gender were associated with poor outcomes in hospitalized COVID-19 patients[19,20]. In the present study, median age was higher in the M-HASBLED RS ≥3 group and also both age and male gender were found as independent factors related to in-hospital mortality. Tope et al.

reported that COVID-19 had a poor outcome in patients with hepatic and renal dysfunction[21]. They explained the situation as being caused by immune system dysfunction and inflammation[22]. Renal and hepatic dysfunction are components of the M-HASBLED RS, and creatinine and ALT were higher in the M-HASBLED RS≥3 group.

Çetindal et al. found that the M-CHA2DS2-VASc RS accurately predicted poor outcomes in hospitalized COVID-19 patients[11]. The male gender was used instead of the female gender. The M-CHA2DS2VASc RS includes comorbid diseases such as HT, DM, CAD, and CVD. In previous studies, HT, DM, CAD, and CVD were evaluated separately and associated with the severity of disease and in-hospital mortality in COVID-19 patients[23-25]. In our study, M-CHA2DS2VASc RS was higher in the M-HASBLED RS ≥3 group compared to the other group. HT, DM, CAD, and CVD were observed at a higher rate in the M-HASBLED RS ≥3 group. This finding can also be interpreted as M-HASBLED RS may indirectly indicate comorbid diseases. As a result, vulnerable patients and the presence of comorbid diseases during hospitalization can be identified using a single risk score.

PNI is a biomarker associated with inflammation, nutritional status, and immune system functions, including lymphocyte count and albumin. Albumin is a parameter that shows the nutritional status and is affected by many factors[26]. The plasma level decreases in cases of malnutrition and intense inflammation. Low albumin and lymphocytopenia have been found to be related to the severity of disease and poor outcomes in COVID-19 patients[27-29]. Therefore, we included albumin in the M-HASBLED RS, as it may reflect the nutritional status and inflammation. In our study, PNI was lower in the M-HASBLED RS ≥3 group compared to the other group, and albumin level and lymphocyte count were also lower in this group. In previous studies, NLR has been identified as a blood parameter associated with the severity of disease and mortality in COVID-19 patients[8,30]. It is an indicator of systemic inflammation, and neutrophil count increases in response to inflammation and lymphocyte count decreases due to apoptosis. In our study, NLR was higher in the M-HASBLED RS ≥3 group compared to the other group. In addition, CRP, ferritin, and pro-calcitonin levels, which indicate systemic inflammation and the severity of disease, were higher in the M-HASBLED RS ≥3 group. As a result of these findings, it was observed that M-HASBLED RS is compatible with other biomarkers that are indicators of nutritional status and inflammation.

A relationship between anemia and nutritional status has been shown in previous studies. The incidence of malnutrition in patients with anemia is around 30%[28]. Poor nutritional status can cause immune system failure and inflammation by increasing cytokine release[31]. Anemia has been found to be related to the severity of disease in COVID-19 patients[32]. Low hemoglobin concentration reduces oxygen transport to tissues[33]. As a result, low hemoglobin exacerbates hypoxia and contributes to respiratory failure caused by COVID-19 pneumonia. Anemia is a parameter of the M-HASBLED risk score. In our study, hemoglobin was significantly lower in the M-HASBLED RS ≥3 group compared to the other group.

Studies with PNI, NLR, and CHA2DS2-VASc RS are intended to determine high-risk patients for COVID-19 complications. These studies showed that low PNI, high NLR, and high CHA2DS2-VASc RS are associated with in-hospital mortality and disease severity in COVID-19 patients. Our study showed that mortality, intubation, NIMV, hospitalization, and intensive care need rates were higher in the M-HASBLED RS ≥3 group, and the M-HASBLED score was independently related to in-hospital mortality. In the ROC

analysis, the highest area under the curve was observed in the M-HASBLED score compared to other biomarkers and scores. As a result, M-HASBLED RS is a simple risk score that can show patients' nutritional status, inflammation, comorbid diseases, and vulnerability and may show poor outcomes better than the other parameters.

Study limitations

This is an observational study and, like all similar studies, there may be some limitations. The single-center nature of our study may reduce the effect of different patient populations on outcomes. Due to the retrospective nature of our study, some parameters might not be fully recorded in all patients. Therefore, randomized, controlled studies are needed to validate the relationship between HASBLED score and in-hospital mortality in COVID-19 patients.

CONCLUSIONS

We found that a high M-HASBLED score is successful in demonstrating poor in-hospital outcomes and is an independent factor associated with in-hospital mortality. Using M-HASBLED RS on admission might be useful to identify high-risk patients and so provide effective treatment and follow-up.

Ethics Committee Approval: The study was approved by the Gazi Yaşargil Education and Research Hospital's Clinical Research Ethics Committee of Clinical Studies on 11.06.2021 and 781 decision number.

Conflict of Interest: No conflict of interest was declared by the authors.

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