original article

Accuracy of conventional disease severity scores in predicting COVID-19 ICU mortality: retrospective single-center study in Turkey

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BACKGROUND: Disease severity scores are important tools for predicting mortality in intensive care units (ICUs), but conventional disease severity scores may not be suitable for predicting mortality in coronavirus disease-19 (COVID-19) patients.

OBJECTIVE: Compare conventional disease severity scores for discriminative power in ICU mortality.

DESIGN: Retrospective cohort

SETTING: Intensive care unit in tertiary teaching and research hospital.

PATIENTS AND METHODS: COVID-19 patients who were admitted to our ICU between 11 March 2020 and 31 December 2021 were included in the study. Patients who died within the first 24 hours were not included. SAPS II, APACHE II and APACHE 4 scores were calculated within the first 24 hours of ICU admission. A receiver operating characteristics (ROC) analysis was performed for discriminative power of disease severity scores.

MAIN OUTCOME MEASURE: ICU mortality

SAMPLE SIZE AND CHARACTERISTICS: 510 subjects with median (interquartile percentiles) age of 65 (56-74) years.

RESULTS: About half (n=250, 51%) died during ICU stay. Three disease severity scores had similar discriminative power, the area under the curve (AUC), SAPS II (AUC 0.79), APACHE II (AUC 0.76), APACHE 4 (AUC 0.78) (*P*<.001). Observed mortality was higher than predicted mortality according to conventional disease severity scores.

CONCLUSION: Conventional disease severity scores are good indicators of COVID-19 severity. However, they may underestimate mortality in COVID-19. New scoring systems should be developed for mortality prediction in COVID-19.

LIMITATION: A single-center study

CONFLICT OF INTEREST: None.

original article

From the beginning of the coronavirus disease-19 (COVID-19) outbreak over 360 million cases have been confirmed and more than 5 million people died as of 29 January 2022.[1] Case fatality rates have varied from 0.2% to 6.6% in different countries.[2] The mortality rate varies from 12% to 23% in hospitalized patients and the mortality of intensive care unit (ICU) patients was reported from 25% to 85% in the early period of the outbreak.[3-6] Determination of disease severity is important for the prediction of patient outcome. Disease severity scores are important tools in the ICU for predicting mortality, comparison of study groups in clinical research, and assessment of the quality of care in the ICU.[7] Various disease severity scores such as Acute Physiology And Chronic Health Evaluation I) (APACHE II) and the updated version APACHE IV and the Simplified Acute Physiology Score II (SAPS II) have been used to predict mortality in the ICU.[7,8]

The predicted and observed outcomes should match in a good disease severity score. SAPS II and APACHE II have been used for many years in ICUs.[9,10] It is unclear how these two scoring systems perform in ICU patients with COVID-19. Zou et al reported that APACHE II had better discriminative ability when comparing confusion, urea, respiratory rate, blood pressure age 65 (CURB-65) and sequential organ failure assessment (SOFA) scores for predicting hospital mortality in COVID-19 patients.[11] In this paper, Zou et al reported that, APACHE II had good discriminitive power (AUC 0.966), but the average APACE II score was 15 and predicted mortality was lower than observed mortality (33.7%).Stephens et al reported that their patients had low median of severity illness score and relatively higher mortality rate.[12] Disease severity scores appear to underestimate mortality in ICU patients with COVID-19. We designed a retrospective study to compare disease severity scores (SAPS II, APACHE II, and IV) for the discriminative power of ICU mortality.

PATIENTS AND METHODS

This retrospective study was performed in Dr. Suat Seren Chest Disease and Thoracic Surgery Teaching and Research Hospital, İzmir, Turkey, between 15 March 2020 and 31 December 2021. The hospital has 23 ICU beds and patients with COVID-19 have been followed up since the beginning of the COVID-19 outbreak. Criteria for ICU admission were tachypnea (respiratory rate >35 breath/min), refractory hypoxemia, requirement of mechanical ventilation support (invasive or non-invasive), unstable hemodynamic condition, impaired consciousness, and cardiopulmonary arrest.

All patients included in the study were laboratory confirmed COVID-19 patients. Patients who died within the first 24 hours were excluded from study. All patients were treated according to the COVID-19 Guidelines published by the Turkish Ministry of Health.[13] Favipiravir was the main drug for antiviral treatment during the study period. Additional treatment such as tocilizumab or corticosteroids were decided on a patient basis. Lung-protective ventilation was applied to all mechanically ventilated patients. If a patient had $PaO_2/FiO_2<150$, the prone position was applied for at least 16 hours a day.[14] When any complications such as sepsis or acute kidney injury occurred, treatment followed current guidelines. The study was conducted after the local ethics committee approval (ethical approval number: 2022/1-21). The study was conducted according to the Helsinki Declaration (2013) and adhered to Good Clinical Practice guidelines. Patient demographic features, vital signs (pulse, arterial blood pressure, respiratory rate, and others.) laboratory findings at the first 24 hours of ICU were obtained from hospital medical records. SAPS II, APACHE II and APACHE IV scores were determined 24 hours after admission to the ICU.

We expressed continuous data as median (interquartile range) and categorical data as numbers (%). The Mann Whitney U test was used for comparison of continuous variables and the chi-square test was used for comparison of categorical variables. A receiver operating characteristics (ROC) analysis was performed for the discriminative power of the disease severity scores. We conducted a multivariable logistic regression analysis to explore factors that might be independently associated with mortality. The variables associated with blood culture positivity in univariate analyses (P<.05) and other clinically relevant variables were included in logistic regression analysis. The cut of value of each disease severity score was determined by the maximum Youden Index. A *P* value of <.05 was accepted as statistically significant. IBM SPSS version 26 (IBM SPSS, Inc., Armonk, NY, USA) was used for statistical analysis.

RESULTS

From 15 March 2020 to 31 December 2021, 531 COVID-19 patients were followed-up in the ICU. Twenty-one were not included in the final analysis, because they died within the first 24 hours of the ICU stay. Of the remaining, 510 patients were included for the final analysis. Two hundred and sixty patients (51%) died during ICU stay (**Table 1**). Survivors were younger, had fewer comorbidities and had better laboratory

Table 1. Baseline characteristics and laboratory findings of the patients.

	All patients (n=510)	Survivors (n=250)	Non-survivors (n=260)	*P* value
Age	65.0 (56-74)	61.0 (50-69)	70 (63-78)	**<.001**
Male	339 (66.4)	162 (64.8)	177 (68.1)	.431
Body mass index	26.1 (24-29.1)	27.1 (24.2-30.1)	25.7 (23.4-27.1)	**.<001**
Charlson comorbidity index	3 (2-4)	2 (1-4)	4 (3-5)	**<.001**
Acute Physiology and Chronic Health Evaluation II scores	14 (10-21)	11 (8-15)	18 (13-28)	**<.001**
Simplified Acute Physiology II scores	38 (28-59)	30 (22-39)	51 (35-70)	**<.001**
Acute Physiology and Chronic Health Evaluation IV scores	72 (61-108)	63 (56-74)	92 (70-126)	**<.001**
Laboratory findings				
White blood cells, ×10^9/L	11.0 (8.0-14.9)	9.7 (7.8-13.4)	12.1 (8.2-16.5)	**<.001**
Lymphocyte, ×10^9/L	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.5 (0.3-0.8)	**.002**
Hematocrit, %	36 (32-39)	36 (33-40)	35 (30-39)	**.017**
Platelet, ×10^9/L	282 (212-364)	293 (230-378)	266 (198-343)	**.002**
D-Dimer, ng/mL	1525 (922-3512)	1347 (789-2221)	1970 (1069-5733)	**<.001**
Ferritin, ng/mL	727 (336-1388)	646 (332-1257)	779 (338-1573)	.080
C-reactive protein, mg/L	111 (60-185)	102 (56-168)	116 (69-191)	**.010**
Procalcitonin, ng/mL	0.23 (0.1-0.73)	0.15 (0.09-0.35)	0.36 (0.13-1.35)	**.001**
Creatinine, mg/dL	0.89 (0.72-1.35)	0.83 (0.66-1.04)	1.0 (0.78-1.54)	**<.001**
Pro B-type natriuretic peptide	806 (272-2891)	471 (170-1480)	1415 (468-5733)	**<.001**
pH	7.43 (7.33-7.47)	7.45 (7.39-7.49)	7.40 (7.26-7.46)	**<.001**
PaO$_2$	64 (58-76)	63 (58-71)	66 (59-82)	**.002**
PaCO$_2$	36 (32-45)	36 (31-43)	37 (32-51)	**.040**
SaO$_2$	92 (90-95)	93 (90-94)	92 (89-95)	.802
FiO$_2$	50 (40-50)	40 (40-50)	50 (50-60)	**<.001**
PaO$_2$/FiO$_2$	139 (116-164)	146 (120-168)	130 (110-160)	**<.001**
Fever (°C)	36.5 (36.4-36.7)	36.5 (36.4-36.7)	36.5 (36.4-36.7)	.900
Respiratory rate (breaths per min)	27 (24-31)	27 (24-32)	27 (24-30)	.351
Pulse (beats per min)	81 (65-107)	80 (65-102)	90 (66-114)	**.002**
Mean arterial pressure (mmHg)	76 (68-89)	78 (72-93)	72 (66-84)	**<.001**
Respiratory support in first 24 hours				
Only O$_2$ support	176 (34.5)	125 (50)	51 (19.6)	**<.001**
Non-invasive mechanical ventilation	183 (35.9)	97 (38.8)	86 (33.1)	
Invasive mechanical ventilation	151 (29.6)	28 (11.2)	123 (47.3)	
Length of stay (days)	10 (6-19)	8 (4-14)	13 (7-23)	**<.001**

Data are shown as n (%) or median (25th–75th percentiles).

findings in the first 24 hours of ICU. SAPS II score (51 vs 30, *P*<.001), APACHE II score (18 vs 11, *P*<.001), APACHE 4 score (92 vs 63, *P*<.001) were higher in non-survivors than survivors (**Table 1**). A ROC analysis was used to determine the discriminative power of disease severity scores for ICU mortality. The three scores had similar discriminative power, area under the curve (AUC), SAPS II (AUC 0.79), APACHE II (AUC 0.76), APACHE IV (AUC 0.78) (*P*<.001) (**Figure 1**) with the cut-off points 35, 12, and 66, respectively. When the expected and observed mortality rates were compared according to APACHE-2, APACHE-4 and SAPS II scores, the observed mortality was higher than the expected in APACHE II and SAPS II, especially in lower scores (**Table 2**). Observed mortality was consistent with expected mortality by APACHE IV. Body mass index body, Charlson comorbidity index, count of white blood cells, PaO_2, PaO_2/FiO_2, and need for IMV in the first 24 hours were associated with ICU mortality in univariate regression analysis. In the multiple logistic regression analysis, the need for invasive mechanical ventilation and Charlson comorbidity index were the strongest risk factors for increased mortality risk (OR=3.6, 95% CI, 1.6-8.1, *P*=.002) and (OR=1.6, 95% CI, 1.4-1.8, *P*≤.001) respectively (**Table 3**).

DISCUSSION

This study was conducted retrospectively to evaluate mortality prediction of disease severity scores in COVID-19 patients followed in the intensive care unit. Three disease severity scores had good discriminative power in terms of mortality. The discriminative power of SAPS II, APACHE II, and APACHE 4 was comparable. However, observed mortality was higher when compared to predicted mortality according to disease severity scores.

SAPS II, APACHE II, and APACHE 4 are validated disease severity scores and have been used globally for a long time. Disease severity scores are important tools for ICU to predict mortality and monitor the quality of care in the ICU. Several studies have shown that conventional disease severity scores provide valuable information about COVID-19 severity. Zou et al reported that the higher APACHE II score was independently associated with hospital mortality in COVID-19 and APACHE II had the better discriminative ability when compared with SOFA and CURB65.[11] Vandenbrande et al demonstrated that APACHE 4 had better discriminative power when compared to APACHE II and SOFA.[15] Vicka et al reported that both APACHE II and

SAPS II had good discriminative power for mortality (AUC; 0.77 and 0.75 respectively), but mortality risk for SAPS II (10%) and mortality risk for APACHE II (15%) were lower than observed mortality (41%).[16] There are inconsistencies between the predicted mortality and observed mortality according to disease severity scores in the literature. The median APACHE II score was 15 and observed mortality was 37% in Scotland, the median APACHE II score was 20, the median SAPS II score was 51, and observed mortality 67% in Poland , while the median APACHE II score was 15 and observed mortality was 37% in UK.[17-19] In contrast, observed mortality was lower than predicted mortality in Australia-New Zealand and Switzerland the median APACHE II score were 17 and 22 while observed mortality was 8.3% and 19%, respectively.[20,21] In our study predicted mortality rates were 18% and 35% according to APACHE II and SAPS II, respectively; however, observed mortality was 51%. Our mortality rate was slightly higher than in Europe (33.4%) and North America (40%), but lower than in the Middle East (61.9%).[22]

Although there is a significant relationship between conventional disease severity scores and the severity of COVID-19, conventional disease severity scores may underestimate mortality in COVID-19. This may
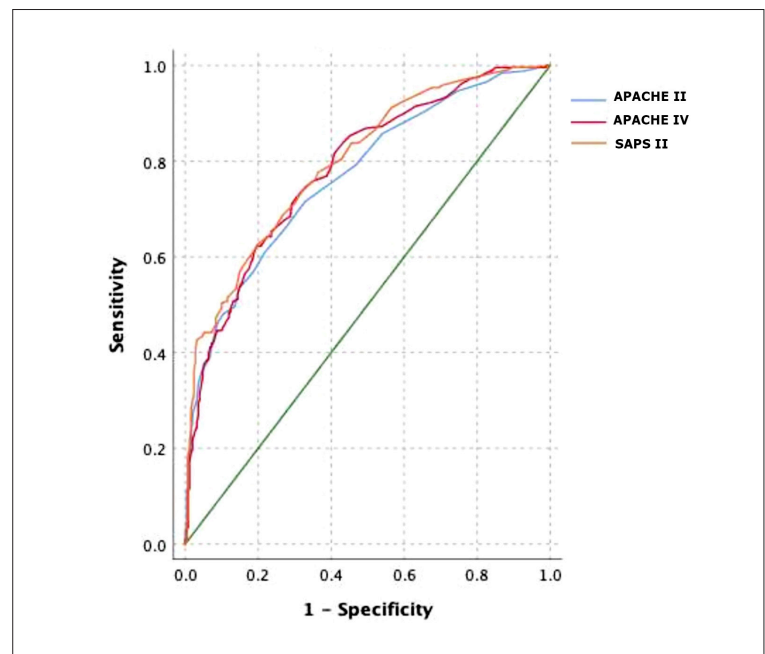
Figure 1. The Receiver Operating Characteristics-Area Under the Curve for mortality scores in ICU (APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score).

Table 2. Predicted and observed mortality according to APACHE 2, SAPS 2, and APACHE 4.

	Patients	Non-Survivors	Predicted mortality	Observed mortality	P value
Acute Physiology and Chronic Health Evaluation II scores					
0-5	21	3	4%	14%	.293
6-10	131	34	8%	26%	<.001
11-15	144	64	15%	44%	<.001
16-20	72	39	25%	54%	<.001
21-25	56	42	40%	75%	<.001
26-30	38	32	55%	84%	.006
31-35	27	26	75%	96%	.021
36-40	13	12	>85%	92%	.539
41-45	6	6	>85%	100%	.900
46-50	2	2	>85%	100%	.900
Simplified Acute Physiology II scores					
10-20	24	1	15%	4%	.296
21-30	131	34	25%	26%	.775
31-40	123	54	32%	44%	.048
41-50	71	39	45%	55%	.240
51-60	36	19	54%	53%	.921
61-70	52	44	64%	85%	.013
71-80	41	38	75%	95%	.034
81-90	23	22	85%	95%	.295
91-100	7	7	95%	100%	.900
101-110	2	2	95%	100%	.934
Acute Physiology and Chronic Health Evaluation IV scores					
<40	13	1	8.3%	7.7%	.923
40-49	28	1	12.3%	3.6%	.159
50-59	73	20	22.8%	27.4%	.442
60-69	112	41	23.9%	36.6%	.028
70-79	79	39	33.7%	49.4%	.023
80-89	36	25	47.3%	69.4%	.032
90-99	23	14	58.7%	60.6%	.764
100-109	21	12	66.7%	57.1%	.525
110-119	37	29	75.7%	78.4%	.782
120-129	26	21	84.7%	80.8%	.713
130-139	29	27	90.2%	93.1%	.639
>139	33	30	>95%	90.9%	.302

Table 3. Multiple logistic regression analysis of baseline characteristics for mortality.

	Estimate	Standard error	Z	Odds ratio (95% CI)	P value
Intercept	-0.2603	0.80664	-0.323	0.771 (0.159-3.746)	.747
Body mass index	-0.0644	0.02161	-2.980	0.938 (0.899-0.978)	**.003**
Charlson comorbidity index, median	0.4563	0.06540	6.977	1.578 (1.388-1.794)	**<.001**
White blood cell count	0.0321	0.01917	1.672	1.033 (0.944-1.072)	**.095**
PaO_2	0.0402	0.01324	3.039	1.041 (1.014-1.068)	**.002**
PaO_2/FiO_2	-0.0207	0.00571	-3.628	0.979 (0.969-0.991)	**<.001**
Invasive mechanical ventilation	1.2796	0.41589	3.077	3.595 (1.591-8.123)	**.002**

Model fit measures: deviance: 525, Nagelkerke R square: 0.400, Overall test: *P*<.001

be due to several reasons. First, the respiratory system is primarily affected in COVID-19 while the laboratory findings are relatively at normal ranges in the first 24 hours of ICU care. Other organ system impairments often occur after the first 24 hours. We found that the need for IMV in the first 24 hours was the most important risk factor for mortality. Respiratory support is one of the most important determinants of COVID-19 mortality, but the impact of respiratory support may not be high enough in traditional disease severity scores. Second, having pre-existing comorbidities may increase mortality in COVID-19. As the number of comorbid diseases increases, the mortality risk can increase up to 4.8 times.[23] APACHE-2 scoring includes chronic health measures, and SAPS scoring includes hematological malignancies and solid organ malignancies, but certain diseases other than malignancy, such as coronary artery disease, dementia, diabetes mellitus, hypertension, and COPD, were associated with increased mortality in COVID-19.[23] Inadequate coverage of comorbid diseases in the conventional scoring may have led to an underestimated mortality. Third, the increase in ICU patient load may have decreased the quality of patient care and caused the mortality to be higher than predicted. Bravata et al reported that patients who were treated in an ICU with a higher COVID-19 load had a 2-fold increased risk of mortality when compared with patients who were treated in an ICU with a lower

COVID-19 patient load. In this study, the median APACHE II score was 13 points in high COVID-19 ICU demand periods and 10 points in low COVID-19 ICU demand periods.[24] Fourth, laboratory parameters such as D-Dimer, ferritin, and procalcitonin were associated with mortality in COVID-19 patients.[25-27] The conventional disease severity scores do not cover these laboratory parameters so this may have led to underestimate mortality in patients with COVID-19.

Our study had several limitations. First the results of our study cannot be generalized, since it is a retrospective single-center study with a relatively small number of patients. Second, the effects of treatment approaches such as antiviral drugs, steroid use, and anti-cytokine therapy on mortality were not evaluated in this study. Last but not least, complications such as septic shock and acute kidney injury were not included in the analysis. Complications during the follow-up of the patients in the ICU will increase mortality, but in this study, we aimed to examine the effects of demographic characteristics and first-day characteristics of patients on mortality. There seems to be a strong association between conventional disease severity scores and ICU mortality for COVID-19, which is especially prominent for APACHE IV. However, conventional disease severity scores may underestimate mortality in COVID-19. This condition should be taken into account in predicting mortality of COVID-19 patients in the ICU.

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