Original Article

Effect of host risk factors in identifying mortality in COVID-19 pneumonia and a new COVID-19 mortality index: Co-AMSCA

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Abstract:

BACKGROUND AND AIM: The purpose of the study was to examine the host risk factors related to mortality in patients hospitalized with coronavirus disease 2019 (COVID-19) pneumonia and to find a COVID-19 mortality score based on these factors.

METHODS: Subjects hospitalized with COVID-19 pneumonia between March 11, 2020, and October 1, 2020, were retrospectively analyzed. The age, gender, smoking status, body mass index, blood group, severity of pneumonia, comorbidity, reverse transcriptase-polymerase chain reaction positivity, use of angiotensin-converting enzyme (ACE) inhibitors, radiological changes, and mortality rates of the patients who had proven COVID-19 pneumonia were recorded. Patients were divided into two groups according to mortality status, and the two groups were compared. The cutoff values, sensitivity and specificity values, and odds ratios were calculated to predict mortality of the new scoring system.

RESULTS: A total of 422 patients (51 mortal and 371 nonmortal) participated in the study. The univariate regression analysis showed that age, male gender, smoking, comorbidity, and using ACE inhibitors were prognostic host risk factors for COVID-19-related mortality. A new scoring model with the combination of risk factors named Co-AMSCA was created in the study. The cutoff value of the system was found to be 3.5 with 88.4% sensitivity and 65.5% specificity. The mortality risk in patients with a Co-AMSCA mortality score above 3.5 points was 7.8 times higher than that in patients whose score was lower than 3.5 points. In multivariate logistic regression analysis, older age and smoking were significant risk factors for mortality.

CONCLUSIONS: A mortality score was created based on host risk factors, which are easy to calculate and do not need laboratory tests and do not waste the time of the clinicians. This study showed that by using Co-AMSCA scoring model, it is possible to achieve a mortality prediction in COVID-19 patients who are hospitalized due to pneumonia.

Keywords:

COVID-19, host risk factors, mortality

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), still has a huge impact on health with increasing mortality. Total death numbers exceeded five million throughout the world in 20 months since the beginning of the pandemic.[1,2]

Early detection is essential because thousands of people die from COVID-19. Clinicians need to predict which cases possibly have poor progression because patients with a severe course may be mortal. For this reason, epidemiological, demographic, clinical, laboratory, and radiological characteristics were examined in some studies to determine the severity of COVID-19.[3–6]

Advanced age, presence of concomitant cardiovascular and cerebrovascular disease, lactate dehydrogenase (LDH) and d-dimer levels, and CD3+CD8+T-cell levels were examined in recent studies as predictors of mortality. Although many scoring studies have been conducted so far, a simple scoring system is still required to predict mortality. It was reported that the severity of COVID-19 is affected by age and comorbidities.[3–5] A simple scoring system will be useful to the clinicians at the time of patient admission to predict mortality in hospitalized patients infected with COVID-19 by evaluating personal risk factors (i.e., age, gender, smoking, body mass index (BMI), angiotensin-converting enzyme (ACE) inhibitor use, blood type, and comorbidity) rather than laboratory and radiological findings, which require additional time and laboratory analyses. For this reason, the aim of the study was to determine the personal risk factors associated with mortality in COVID-19 patients who are hospitalized for pneumonia and also to find a COVID-19 mortality score based on these.

Materials and Methods

Study population

The approval of the Scientific Committee and the Ministry of Health COVID-19 Scientific Research Evaluation Committee was obtained for the study (date/no.: May 4, 2020/3801) and carried out in accordance with the Declaration of Helsinki. Subjects hospitalized with the diagnosis of COVID-19 pneumonia between March 11, 2020, and October 1, 2020, were retrospectively analyzed for the study.

Clinical diagnosis for COVID-19 was made by either positive reverse transcriptase-polymerase chain reaction (RT-PCR) of oro-nasopharyngeal swabs, or compatible clinical, laboratory, and radiological findings with the positive antibody tests. The diagnostic criteria, method, and severity of the disease were defined according to the Scientific Committee Guidelines of the Ministry of Health.[7]

Mild-to-moderate pneumonia

Patients who had fever, muscle/joint pains, cough, and sore throat and who also had respiratory rate <30 min^{-1}, SpO_2 level > 90% in room air, and mild-to-moderate pneumonia findings on chest X-ray or tomography were considered in this category.[7]

Severe pneumonia

Patients who had symptoms such as fever, muscle/joint pains, cough and sore throat and tachypnea (≥30/minute), an SpO_2 level of ≤90% in room air, and bilateral diffuse pneumonia findings on chest X-ray or tomography were considered in this category.[7]

Data collection

The clinical features and laboratory parameters of the study population were obtained from the hospital records. The age, gender, smoking status, BMI, blood group, severity of pneumonia, comorbidity, RT-PCR test results for SARS-CoV-2, use of ACE inhibitors, radiological regression, and mortality were recorded. When necessary, patient phone contact numbers were used for missing data. Cases whose data could not be reached were excluded from the study. Due to the retrospective design of the study, written informed consent could not be obtained. Two groups were formed (mortal and nonmortal) and compared.

Statistical analysis

The SPSS software v. 25.5 (IBM, NY, USA) was used for the analyses. The Shapiro–Wilk test and the Kolmogorov-Smirnov normality test were used to find out whether the continuous data were distributed normally. The Mann-Whitney U test and Student's t-test were used to compare continuous variables, and the Chi-squared test and Fisher's exact test were used to compare the categorical data. The results were given as mean±SD, median (min-max), numbers, and percentages (%). A value of $p<0.05$ was considered significant. The predictive values of the parameters for mortality were calculated with univariate-multivariate logistic regression analyses. The optimal cutoff value, sensitivity-specificity, and probability ratios

that were used to predict mortality were calculated with ROC analysis using the area under the curve (AUC) and Youden's index. The results were given within 95% confidence interval.

Results

Demographic characteristics of patients

A total of 422 patients were included in the study. The demographic data and characteristics of the patients according to mortality are given in Table 1. The diagnosis was made with PCR positivity in 72.5% of the cases and with clinical, laboratory, and radiological findings in the positive antibody tests in 27.5%. When the distribution of age between the mortal and nonmortal groups was evaluated, it was found that there were older patients in the mortal group ($p<0.001$). Male gender, being smoker, presence of comorbidity, and history of using ACE inhibitor drugs were statistically higher in the mortal group ($p=0.046$, 0.001, 0.001, and 0.004, respectively). The blood groups and BMI values were not found to be significant between the mortal and nonmortal groups ($p=0.145$ and 0.383, respectively) (Table 1).

Predicting mortality and severity of pneumonia

When the univariate analysis was used to evaluate the predictive power of host risk factors for mortality, it was found that patients >65 years of age had a 21.1-fold higher mortality risk (OR=21.1; 95% CI=4.89–91.5; $p<0.001$). Similarly, the mortality risk of male patients was higher than female patients (Table 2). Smoker patients had a 4.07 times higher mortality than nonsmoker patients (OR=4.07; 95% CI=2.128–7.796; $p<0.001$), and the mortality risk of patients who had more than one comorbid disease was 4.9 times higher than those with no comorbid disease (OR=4.07; 95% CI=2.128–7.796; $p<0.001$) (Table 2).

A scoring model

To obtain a simple scoring for mortality in COVID-19 patients, a scoring model was created under the abbreviation "Co-AMSCA" (Age, Male, Smoking status, Comorbidity, ACE) with scores of 0–7 points (Table 3). The cutoff value of the system (including only host risk factors) determining mortality risk was 3.5 with 88.4% sensitivity and 65.5% specificity (AUC=0.761; 95% CI=0.697–0.826; $p<0.001$) [Fig. 1]. The mortality risk in patients with a Co-AMSCA mortality score >3.5 points was 7.8-fold higher (OR=7.8; $p<0.001$).

When the predictive power of each risk factor in Co-AMSCA model regarding mortality risk was assessed with multivariate logistic regression analysis, older age and smoking (ever smoker) were found to be significant risk factors for mortality (OR=12.09; 95% CI=2.564–57.054; $p=0.004$ and OR=3.1; 95% CI=1.381–7.295; $p=0.007$, respectively) (Table 4).

Discussion

Using a simple scoring system at admission during the COVID-19 outbreak can be life-saving in terms of predicting patients who will have a mortal progression. For this reason, with this study, using only the host risk factors without the radiology and laboratory findings of patients at the time of admission, we defined the risk factors consisting of age, male, smoking, comorbidity, using ACE inhibitor, and the risk score called Co-AMSCA to predict the risk of COVID-19 mortality. The mortality risk was predicted to be 7.8-fold higher in patients with a Co-AMSCA score above 3.5 points.

The demographic, radiological, laboratory data, and treatment modalities were investigated in many studies to determine the severity and mortality risk of COVID-19.[3–6,8,9] However, in the literature, a scoring system created with host risk factors was detected only in one study.[10] In that study, which was conducted by Shi et al.,[10] three risk factors and a risk score were defined to detect severe COVID-19 cases. These risk factors were determined as ≥50 years of age, male gender, and hypertension as an additional disease. Our study also showed that advanced age, which is the first risk factor we identified, increases mortality, which is similar to other studies.[11–13] The second and third host risk factors, which determined mortality in our study, were male gender and smoking history. In some previous studies, male gender and smoking were reported as poor prognostic factors according to sociodemographic data.[8,9] It was reported in other studies that having one or more comorbid diseases was a risk factor in estimating mortality, as in our study.[8–10,14] However, unlike our study, it was observed in these studies that a mortality risk score was created by adding laboratory parameters (lymphocyte, d-dimer, CRP, and LDH) to host risk factors.[13,14] Of course, one parameter will not be sufficient to predict severe patients and mortality. For this reason, there are novel scoring systems developed to predict COVID-19 severity (CALL) and also other scores

Table 1: Comparison of demographic findings of COVID-19 patients (mortal and nonmortal)

Characteristics	Total (n=422)		Mortal (n=51)		Nonmortal (n=371)		p
	n	%	n	%	n	%	
Age (median) (min-max)	55.5±15.4 (18.0–91.0)		65.5 (36.0–91.0)		54.0 (18.0–88.0)		**<0.001**
Age group							
<50 years	151	35.8	2	3.9	149	40.2	**<0.001**
50–64 years	151	35.8	23	45.1	128	34.5	
≥65 years	120	28.4	26	51.0	94	25.3	
Gender							
Male	252	59.7	37	72.5	215	58.0	**0.046**
Female	170	40.3	14	27.5	156	42.0	
BMI, median (min-max)	26.3±4.2 (16.8–46.9)		24.5 (18.9–39.2)		25.4 (16.8–46.9)		0.142
BMI group							
Thin	5	1.2	0	0.0	5	1.3	0.383
Normal	189	44.8	26	51.0	163	43.9	
Preobese	156	37.0	20	39.2	136	36.7	
Obese	72	17.1	5	9.8	67	18.1	
Obesity	72	17.0	5	9.8	67	18.1	0.142
Overweight	51	12.0	25	49.0	26	51.0	0.444
Cigarette							
Smoker	64	15.2	5	9.8	59	15.9	**<0.001**
Ex-smoker	119	28.2	32	62.7	87	23.5	
Nonsmoker	239	56.6	14	27.5	225	60.6	
Cigarette							
Ever smoker	183	43.3	37	72.5	146	39.4	**<0.001**
Nonsmoker	239	56.6	14	27.5	225	60.6	
Blood Group							
A	174	41.2	16	31.4	158	42.6	0.145
B	74	17.5	9	17.6	65	17.5	
AB	52	12.3	11	21.6	41	11.1	
0	122	28.9	15	29.4	107	28.8	
Pneumonia							
Mild	182	43.1	8	15.7	174	46.9	**<0.001**
Middle	153	36.3	2	3.9	151	40.7	
Severe	87	20.6	41	80.4	46	12.4	
PCR							
Positive	306	72.5	45	88.2	261	70.4	**0.007**
Negative	116	27.4	6	11.8	110	29.6	
Comorbidity							
Yes	234	55.5	42	82.4	192	51.8	**<0.001**
No	188	44.5	9	17.6	179	48.2	
Comorbidity							
No	188	44.5	9	17.6	179	48.2	**<0.001**
Single	118	28.0	19	37.3	99	26.7	
Multiple	116	27.5	23	45.1	93	25.1	
COPD	64	15.2	14	27.5	50	13.5	**0.009**
Cardiac diseases	70	16.6	14	27.5	56	15.1	**0.026**
Hypertension	109	25.8	19	37.3	90	24.3	**0.047**
Diabetes mellitus	64	15.2	11	21.6	53	14.3	0.174
Asthma	19	4.5	3	5.9	16	4.3	0.612
Cerebrovascular disease	18	4.3	4	7.8	14	3.8	0.178
Malignancy	53	12.6	19	37.3	34	9.2	**<0.001**
Using ACE inhibitor							
Present	105	24.9	21	41.2	84	22.6	**0.004**
Absent	317	75.1	30	58.8	287	77.4	
Radiological progression							
Present	68	16.1	35	68.6	33	9.0	**<0.001**
Absent	349	82.7	16	31.4	333	91.0	

The conformity of the data to the normal distribution was checked with the SPSS Shapiro-Wilk Test. SPSS Student's t-test was used to compare normally distributed data between the groups, and the results were presented as mean±SD. The Mann-Whitney U test was used to compare the data that did not fit the normal distribution, and the results were presented as the median (min-max). The Chi-squared test and Fisher's exact test were used to compare qualitative data, and the results were given as n, %. A value of $p<0.05$ was considered statistically significant. BMI: Body mass Index, PCR: Polymerase chain reaction, COPD: Chronic obstructive lung disease

Table 2: Univariate analysis of host risk factors for mortality in patients with COVID-19

Parameters	Univariate analysis			
	β	OR	95% CI	p
Age				
<50 vs 50–65 years	2.591	13.343	3.095–57.527	0.001
<50 vs >65 years	3.052	21.165	4.895–91.516	<0.001
Gender				
Female vs male	0.651	1.918	1.002–3.668	0.049
Cigarette				
Nonsmoker vs ever smoker	1.404	4.073	2.128–7.796	<0.001
Comorbidity				
Absent vs single	1.339	3.817	1.664–8.756	0.002
Absent vs multiple	1.593	4.919	2.187–11.060	<0.001
Using ACE inhibitor				
Absent vs present	0.872	2.392	1.302–4.394	0.005

OR: Odds ratio, CI: Confidence interval, ACE: Angiotensin-converting enzyme

adapted to COVID-19 (MuLBSTA, qSOFA, CURB-65, and NEWS2).[13–17] However, these are difficult to apply in clinical practice, and there are technical- and laboratory-requiring difficulties, and they are time consuming in terms of scoring. In our study, another host risk factor in determining mortality was the use of ACE inhibitors by the patient. ACE2 plays vital roles in RAS. Ang II enhances atherosclerosis in the cardiovascular system along with inflammation, oxidative stress, migration of endothelial cells, and vascular smooth muscle cells.[18] ACE2 owns protective effects on many diseases with decreased expression of ACE2, such as hypertension, diabetes, and cardiovascular diseases because it antagonizes the role of angiotensin II (Ang II).[19]

Some previous studies argued that COVID-19-related mortality is higher in males and elderly women, but ACE2 level was not.[20,21] Also, Zhang et al.[22] reported that ACEI/ARB was related to lower mortality rates in hypertensive COVID-19 patients.

Ji et al.[14] suggested a new scoring system to detect severe COVID-19 patients called CALL score. It was improved for progressive risk prediction with four parameters (i.e., comorbidity, age, lymphocyte number, and LDH). With a 6-point cutoff value, the positive–negative predictive values were found to be 50.7% (38.9%–62.4%) and 98.5% (94.7%–99.8%), respectively.[14] Zhang et al.[16] also suggested a scoring system to predict the severity of COVID-19 patients with age, WBC, neutrophil, GFR, and myoglobin. Myrstad et al.[17] reported that a NEWS2 score ≥6 at admission predicted severe disease

Table 3: Calculation of AMSCA score for mortality in COVID-19 patients

Parameter	Score (point)
Age group	
<50 years	0
50–65 years 1	
>65 years	2
Gender	
Female	0
Male	1
Cigarette	
Nonsmoker	0
Ever smoker	1
Comorbidity	
Absent	0
Single	1
Multiple	2
Using ACE inhibitor	
Absent	0
Present	1
Total score (maximum)	7 point

ACE: Angiotensin-converting enzyme, AMSCA: Age, Male, Smoking status, Comorbidity, ACE

with 80.0% sensitivity and 84.3% specificity (AUC=0.822; 95% CI=0.690–0.953) and argued that NEWS2 was better than qSOFA score ≥2 (AUC=0.624; 95% CI=0.446–0.810; p<0.05) and other clinical risk scores in this regard. The mortality score of the Co-AMSCA cutoff value was 3.5 and above in our study, and sensitivity, specificity, NPV, and PPV were 80.4%, 65.5%, 96.0%, and 24.3%, respectively. The reason why PPV was partially low was that laboratory and radiological findings were included in the scoring in other studies. Varol et al.[4] obtained the CoLACD mortality score by adding the age, lymphope-
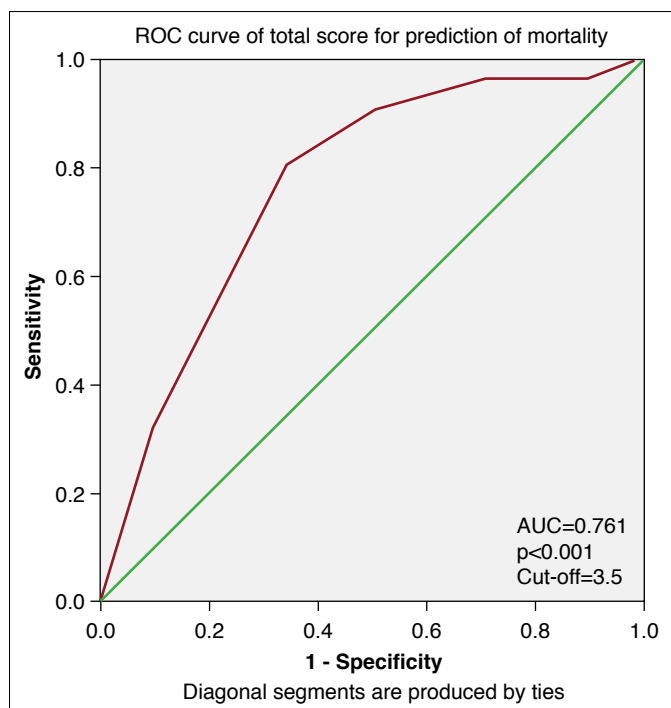
Figure 1: ROC curve of AMSCA

ROC: Receiver operating characteristic, AMSCA: Age, Male, Smoking status, Comorbidity, ACE,
AUC: Area under the curve

nia, and dyspnea parameters as well as the Charlson Comorbidity Score. They reported that the mortality risk was 11.8-fold more in patients who had a CoLACD mortality score higher than 2.5 compared with patients who had a score lower than 2.5.

Contrary to previous studies, no relations were detected in our study between BMI, which is one of the host risk factors, and mortality. Cai et al.[23] in their study observed

that the risk of developing severe pneumonia was 86% higher in overweight patients and 2.42 times higher in obese patients. In the study conducted by Wu et al.,[24] BMI values of patients with severe COVID-19 were statistically higher than those with mild disease. Kalligeros et al.[25] also reported that patients with BMI ≥35 kg/m² had 5.4 times higher risk of requiring ICU care. Unlike the results of our study, Mehra et al.[26] conducted a study and reported that those who developed mortality had higher mean BMI scores. In another study by Docherty et al.,[27] obesity was found to be associated with increased hospital mortality. Because of the retrospective design of our study, height and weight measurements were based on patient statements, and it was considered that this may be the reason for the inability to detect a relation between BMI and mortality.

No relations were detected between blood groups and mortality in our study. However, when the incidence of COVID-19 infection was evaluated in a meta-analysis, it was shown that blood group A is vulnerable to infections.[28] In a donor cohort study with the primary aim not to determine the relations between the ABO blood group and COVID-19 infection, the mortality risk in COVID-19 patients with blood group A was reported to be significantly higher than in those with blood group O.[29]

However, the study also had some limitations. First of all, it had a single-center, retrospective, and cohort design; however, all COVID-19 patients admitted to our hospital during the time from the onset of the pandemic were included in it. Therefore, the confidence interval

Table 4: Multivariate logistic regression analysis of mortality risk factors for patients with COVID-19

Parameters	Multivariate analysis			
	β	OR	95% CI	p
Age				
<50 vs 50–65 years	2.224	9.435	2.087–42.645	**0.004**
<50 vs >65 years	2.493	12.095	2.564–57.054	**0.002**
Gender				
Female vs male	0.008	1.009	0.434–2.342	0.984
Cigarette				
Nonsmoker vs ever smoker	1.155	3.174	1.381–7.295	**0.007**
Comorbidity				
Absent vs single	0.431	1.539	0.613–3.861	0.359
Absent vs multiple	0.431	1.549	0.594–3.990	0.375
Using ACE inhibitor				
Absent vs present	0.263	1.301	0.650–2.604	0.458

OR: Odds ratio, CI: Confidence interval, ACE: Angiotensin-converting enzyme

was wide in the univariate analysis, especially for age. The hospital where the study was conducted was a specific tertiary reference hospital for chest diseases in the Aegean Region. All of the components of the Co-AMSCA score were obtained from hospital data.

Conclusion

We created a simple mortality score, which is easily calculated and does not require laboratory tests and time consumption. This study also found that a new model that included five parameters, age, male gender, smoking, comorbidity, and using ACE inhibitor, achieved a prediction of mortality in COVID-19 patients hospitalized for pneumonia. If the Co-AMSCA score is validated with prospective studies, it can be used for decreasing mortality and effective utilization of medical resources in the COVID-19 pandemic. Also, we believe that the host risk score we found will be a useful tool for the prevention and treatment of this disease in its detection and more serious follow-up of individuals with high risks.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the Scientific Committee and the Ministry of Health COVID-19 Scientific Research Evaluation Committee (No: 3801, Date: 04/05/2020).

Peer-review
Externally peer-reviewed.

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