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Prediction of mortality and the development of critical illness in the course of COVID-19 with tertiary hospital data: vaccines? Critical illness scores? Mortality scores?

E. GUZEL[1], K. AYDIN[2], O. BAYDAR TOPRAK[1]

[1]Department of Chest Diseases, Faculty of Medicine, Cukurova University, Adana, Turkey
[2]Department of Internal Medicine, Division of Intensive Care Unit, Faculty of Medicine, Cukurova University, Adana, Turkey

Abstract. – OBJECTIVE: Even though COVID-19 affects some risk groups more severely than others, there are still unknowns concerning the intensive care procedure and death in non-risk categories, making it vital to identify critical sickness and fatality risk factors at this time. The purpose of this study was to look into the efficacy of critical illness and mortality scores, as well as other risk factors in COVID-19.

PATIENTS AND METHODS: Two hundred twenty-eight inpatients diagnosed with COVID-19 were included in the study. Sociodemographic, clinical, and laboratory data were recorded and risk calculations were made with the help of web-based patient data-based calculation programs called COVID-GRAM Critical Illness and 4C-Mortality score.

RESULTS: The median age of 228 patients included in the study was 56.5 years, 51.3% of them were males, and ninety-six (42.1%) were unvaccinated. According to the multivariate analysis, the factors affecting the development of critical illness were cough [odds ratio=0.303, 95% CI (0.123,0.749), *p*=0.010], creatinine [odds ratio=1.542, 95% CI (1.100, 2.161), *p*=0.012], respiratory rate [odds ratio=1.484, 95% CI (1.302, 1.692), *p*=0.000], COVID-GRAM Critical Illness Score [odds ratio=3.005, 95% CI (1.288, 7.011), *p*=0.011]. Factors affecting survival were vaccine status [odds ratio=0.320, 95% CI (0.127,0.802), *p*=0.015], blood urea nitrogen (BUN) [odds ratio=1.032, 95% CI (1.012, 1.053), *p*=0.002], respiratory rate [odds ratio=1.173, 95% CI (1.070, 1.285), *p*=0.001], COVID-GRAM-critical-illness score [odds ratio=2.714, 95% CI (1.123, 6.556), *p*=0.027].

CONCLUSIONS: The findings suggested that risk assessment might employ risk scoring, such as COVID-GRAM Critical Illness, and that immunization against COVID-19 will reduce the occurrence of mortality.

Key Words:
COVID-19, COVID-GRAM-critical-illness risk scoring, 4C Mortality scoring, ICU, Mortality, Vaccination.

Introduction

Although the effects of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) epidemic have decreased somewhat recently, this and similar respiratory diseases will continue to pose serious threats to people and all health systems for longer periods of time. In general, the disease is more severe and devastating in certain risk groups, while some uncertainties regarding the intensive care process and mortality in non-risk groups remain up-to-date. Reports[1-5] in the early stages of COVID-19 pandemic indicate that up to 20% of those who contract the disease develop serious illness requiring hospitalization, while among those who are hospitalized, up to a quarter require admission to intensive care unit (ICU) which is approximately 5 to 8% of the infected population[2-7].

ICU admission rates in COVID-19 might vary, according to various research[3,5]. For instance, admission rates for hospitalized patients to the critical care unit ranged from 7% to 26% across cohorts from China[2,3,8-10]. Similarly, in Italy, between 5-12% of hospitalized patients were admitted to ICU[7,8]. Rates of admission to critical care units in the USA and Canada varied from 5-81%[5,9-11]. The admission rates to ICU were reported to be 24.1% and 31%, respectively, in two separate studies done in Turkey[12,13]. The application and admission criteria used by the ICU,

Corresponding Author: Efraim Guzel, MD; e-mail: efraimguzel@gmail.com

as well as the demographic characteristics of the region the ICU serves, may differ locally, culturally, and geographically, which may also have an impact on patient admission rates.

Many studies[3,7,9] on ICU admission and mortality risk in COVID-19 patients have addressed different risk factors. In a meta-analysis[14] evaluating many studies on the intensive care process of COVID-19 disease, the most important risk factors for ICU were advanced age (>60 years), male gender, the emergence of comorbidities [as a chronic obstructive pulmonary disease (COPD), cardiovascular diseases, diabetes mellitus (DM), obesity], high or increased white blood cells (WBC) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, total bilirubin, D-dimer, prothrombin time (PT), C-reactive protein (CRP), creatine kinase, lactate dehydrogenase (LDH) and diminished PaO_2/FiO_2 ratio, albumin, platelet, and lymphocyte counts. Although these risk indicators are included in a number of scoring systems, there is no universal agreement on this matter.

The COVID-GRAM Critical Illness Risk Score and the 4-C Mortality Score are two independent scoring systems that have been used in a few studies in the literature[15,16]. The purpose of this study was to describe the clinical importance and utility of COVID-GRAM and 4-C Mortality Score, as well as risk variables for the development of critical illness and fatality in hospitalized COVID-19 patients.

Patients and Methods

Study Design

This single-center, retrospective, descriptive study was conducted with patients diagnosed with COVID-19 in the inpatient and ICU at Cukurova University Faculty of Medicine Balcali Hospital, Adana, Turkey. Following the 1964 Helsinki Declaration and its latest amendmentds, informed consent was requested from the participants. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Cukurova University Faculty of Medicine on March 4, 2022 (48/120).

Setting

After the approval of the Ethics Committee on 04.03.2022, 228 patients who were hospitalized in the hospital's COVID-19 inpatient service and ICU between 01.08.2021 and 01.02.2022 that met the inclusion criteria were included in the study. Between the relevant dates, the clinical, and radiological data of these patients in the hospital database and the follow-up results of these patients were recorded.

Participants

A total of 228 patients among 276 screened patients, over 18 years of age, with clinical-radiologic and laboratory findings compatible with COVID-19, positive reverse transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal swab and followed up in the inpatient ward or ICU of the hospital, met the inclusion criteria. Patients who refused to participate in the study by themselves or through a relative were excluded. In addition, patients with suspected COVID-19 who were RT-PCR negative and COVID-19 patients under the age of 18 were also excluded. Thus, a total of 48 patients were excluded from the study.

The study population was divided into 2 groups: critically ill and non-critically ill. The critical illness group included COVID-19 patients who were hospitalized with severe conditions or who were predicted to have a progressive course based on their clinical, laboratory, and radiological data. The study model, including the selection of participants, and the effects of risk scoring and vaccination status on critical illness and disease outcome, is detailed in Figure 1.

Variables

A standard study form recorded patients' age, gender, height, body weight, body mass index, comorbidities, smoking history, Glasgow Coma Scale (GCS) score, Charlson Comorbidity Index (CCI), COVID-19 4C Mortality Score, COVID-GRAM Critical Illness Risk Score, patient's symptoms, oxygen treatments applied to patients (nasal oxygen, diffuser mask, mask with reservoir, high flow nasal cannula), chest X-ray and Computed Tomography (CT) findings (if any), vital signs (fever, heart rate, respiratory rate, systolic/diastolic blood pressure), oxygen saturation (SaO_2), treatments given to patients (antiviral, corticosteroid, anti-cytokine therapy, anticoagulant), 28-day mortality, type of discharge, length of hospital stay, Acute Physiological and Chronic Health Assessment (APACHE) II score (if admitted to ICU), laboratory parameters routinely checked in patients hospitalized with COVID-19.

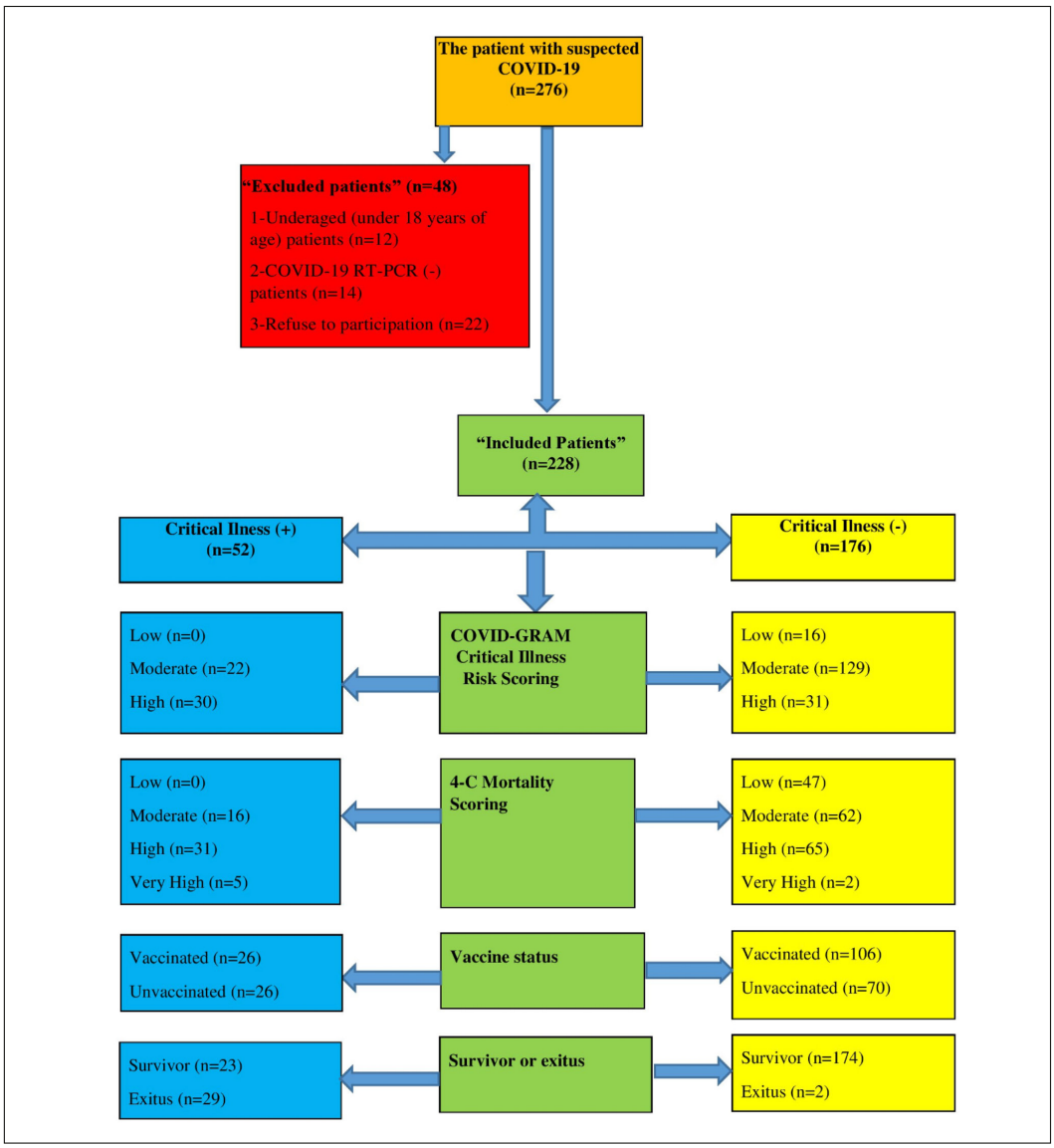

Figure 1. Flowchart of critical illness and mortality prediction in COVID-19.

Data Source/Measurement

Charlson Comorbidity Index (CCI)

According to CCI, patients' comorbidities were classified as "0 points low, 1-2 points moderate, 3-4 points high, and 5 points and above very high risk".

COVID-GRAM Critical Illness Risk Score

The COVID-GRAM Critical Illness Risk Score developed by Liang et al[15], used to evaluate the risk of developing critical illness in patients with COVID-19 disease, was calculated using a web-based calculator. Ten variables, including X-ray abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, LDH level, neutrophil-lymphocyte ratio (NLR), direct bilirubin level were used to calculate COVID-GRAM Critical Illness Risk Score. In terms of the risk of developing critical illness, patients were divided into three groups as low (<1.7%), moderate (1.7% to < 40.4%), and high (≥40.4) risk[15].

4C Mortality Score

4C Mortality is a score to estimate in-hospital mortality in COVID-19 patients. In the calculation of 4C Mortality Score, a web-based calcu-

lator with eight variables, including age, gender, number of comorbidities, respiratory rate, SaO_2, GCS score, blood urea nitrogen (BUN) level, and CRP was used. According to scoring results, patients were divided into four groups as low (0-3 points), moderate (4-8 points), high (9-14 points), and very high (15-21 points) risk. In-hospital mortality estimation was accepted as 1.2-1.7%, 9.1-9.9%, 31.4%-34.9%, and 61.5%-66.2%, respectively, from low risk to very high risk[16].

Vaccines

The fourth dose of the COVID-19 vaccine was available in Turkey when all of our patients had already been included in the study, with the first dose of the vaccine being provided on January 13, 2021, and the subsequent doses of the vaccine being administered during the course of the following time. By querying the hospital information management system, vaccination status for COVID-19 (whether there is a COVID-19 vaccine, type, and dose of vaccine) was recorded.

Bias

All consecutive hospitalized patients who met the inclusion criteria were included in the study in order to avoid any kind of selection bias.

Study Size

The results from the literature[5-11,15,16] suggest that patients hospitalized for COVID-19 may experience critical illness at varying rates. According to the results of our power analysis, which we did with 95% accuracy and 5% margin of error, we needed at least 163 patients to carry out our study if the average incidence of severe illness development was calculated as 12% based on previous studies[15-17]. The study included 228 patients who met the eligibility criteria.

Quantitative Variables

In the study, risk factors were determined due to simple statistical and univariate analyses of quantitative variables, and multivariate analyses were performed for these variables.

Statistical Analysis

The IBM SPSS Statistics Version 20.0 package program (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Visual (histograms and probability graphs) and analytical (Kolmogorov-Smirnov tests) methods were used to determine whether variable distributions were normal. Continuous measurements were summarized as median (Q1-Q3) and, categorical variables as numbers and percentages. To compare categorical variables, the Chi-square or Fisher's exact test (when Chi-square test assumptions did not hold due to low expected cell counts) was used. The patients were divided into two groups based on disease process: those who were discharged with recovery and those who were admitted to ICU. According to 28-day mortality, patients were divided into two groups (survivor and exitus). To compare continuous measurements between groups, Mann-Whitney U test was used. In univariate analysis, logistic regression analysis was used to examine factors influencing the development of critical illness and survival. The model included parameters that were significant in univariate analysis. In a multivariate analysis, logistic regression analysis was used to examine independent predictors of critical illness development and survival using potential factors identified in previous analyses. The diagnostic decision-making features of the COVID-GRAM Critical Illness Risk Score in predicting the risk of developing critical illness and the 4C Mortality Score in predicting in-hospital mortality were examined using ROC curve analysis. The Youden index was used to determine the best cut-off value. In the presence of significant cut-off, sensitivity, specificity, and positive and negative predictive values of these limits were calculated. The statistical significance level was chosen as "0.05" and below for the *p*-value.

Results

The primary outcome of the study is to determine the diagnostic accuracy of the COVID-GRAM Critical Illness Risk Score in the risk of developing critical illness and the 4C Mortality Score in-hospital mortality. Secondary outcomes highlight risk factors for critical illness and mortality in hospitalized COVID-19 patients.

The median age of 228 patients included in the study was 56.5 (41-68.75) years, 51.3% of them were males, and ninety-six (42.1%) were unvaccinated. Critical illness developed in 26 unvaccinated patients, and 18 of these patients died. In the vaccinated group, 2 doses of CoronaVac (17.1%), then 2 doses of BNT162b2 (11%) and 3 doses of CoronaVac (10.1%) vaccines were administered. While 12.3% of our patients

had no radiological evidence of lung involvement at presentation, the most common radiologic finding was subpleural diffusely localized ground-glass-shaped typical COVID-19 findings (78.9%). No statistical significance was found between radiologic findings and the occurrence of critical illness or mortality (p=0.267; p=0.467, respectively).

Older age, poorer GCS score, higher heart and respiratory rate, decreased peripheral oxygen saturation, and elevated CRP-procalcitonin-D-dimer-BUN-Creatinin-LDH levels were associated with the critically-ill patient group (22.8%) (p=0.003; p<0.001; p=0.011; p<0.001; p<0.001; p=0.001; p<0.001; p=0.001; p=0.001; p=0.001; p=0.006 respectively). Older age, non-vaccination, a lower GCS score, increased respiratory rate, a lower peripheral oxygen saturation, and higher CRP-procalcitonin-D-Dimer-BUN-Creatinin levels were found to be significant in the group whose disease caused mortality (13.6%) (p=0.005, p=0.053, p=0.047, p<0.001, p<0.001, p=0.040, p<0.001, p=0.001, p=0.001, p=0.001 respectively). Table I and Table II present comprehensive sociodemographic, laboratory, and radiological data of the study population.

The most common respiratory symptoms were dyspnea (63.6%) and cough (49.6%), and systemic symptoms were weakness-fatigue (42.5%) and fever (41.7%). The most common comorbidities were hypertension (HT) (81%) and DM (78%). The presented study figures out that the critically-ill patient group was more likely to experience symptoms such as dyspnea (p=0.003), cough (p=0.014), arthralgia-myalgia (p=0.040), and unconsciousness (p=0.012), notably hypertension (p=0.013), coronary artery disease and heart failure (CAD and HF) (p=0.001), and high Charlson Comorbidity Index (CCI) (p=0.001). In the group that experienced death, dyspnea (p=0.012), a high number of comorbidities (p=0.033), a high CCI (p=0.001), HT (p=0.044), DM (p=0.028), CAD and HF (p=0.003), and chronic renal disease (CRD) (p=0.022) were more commonly seen. Table III provides detailed data on the patients' symptoms and comorbidities.

While 39.5% of our patients did not need any oxygen support, 7.9% were provided with oxygen support at a high flow rate. Methylprednisolone was the steroid that 65.4% of our patients used most frequently. Need for oxygen support, steroid use (especially dose-independent use of Methylprednisolone), and anti-cytokine therapy were important in the development of critical illness and had a statistical significance. Furthermore, 4C Mortality Score, COVID-GRAM Critical İllness Score, and 28-day mortality were statistically significantly higher in those with a critical illness. COVID-GRAM Critical Illness Score and 4C Mortality Score were statistically significantly higher in non-survivors. Table IV includes comprehensive analytical findings.

By using logistic regression analysis, the following variables were assessed with regard to critical illness: advanced age, HT, CAD and HF, CCI, dyspnea, cough, muscle-joint pain, altered consciousness, CRP, procalcitonin, BUN, creatinine, LDH, respiratory rate, heart rate, SaO_2 (%), GCS, steroid use, anti-cytokine therapy, COVID-GRAM Critical Illness Risk Score, and 4C Mortality Score. According to multivariate analysis, factors affecting the development of critical illness were cough [odds ratio=0.303, 95% CI (0.123, 0.749), p=0.010], creatinine [odds ratio=1.542, 95% CI (1.100, 2.161), p=0.012], respiratory rate [odds ratio=1.484, 95% CI (1.302, 1.692), p=0.000], COVID-GRAM Critical Illness Score [odds ratio=3.005, 95% CI (1.288, 7.011), p=0.011].

In terms of mortality, in univariate analysis, parameters affecting survival were evaluated with logistic regression analysis. Advanced age, HT, DM, CAD and HF, CRD, CCI, hemoptysis, vaccination status, BUN, creatinine, respiratory rate, SaO_2 (%), GCS, steroid use, anti-cytokine therapy, COVID-GRAM Critical Illness Risk Score, 4C Mortality Score variables were included. Factors affecting survival according to multivariate analysis were vaccine status [odds ratio=0.320, 95% CI (0.127, 0.802), p=0.015], BUN [odds ratio=1.032, 95% CI (1.012, 1.053), p=0.002], respiratory rate [odds ratio=1.173, 95% CI (1.070, 1.285), p=0.001], COVID-GRAM Critical Illness Score [odds ratio=2.714, 95% CI (1.123, 6.556), p=0.027] (Table V).

A ROC analysis was performed to determine the diagnostic accuracy of COVID-GRAM Critical Illness Risk Score and 4C Mortality Score (Figure 2, Table VI). The best cut-off of COVID-GRAM Critical Illness Score to predict critical illness was ≥102.5 with 0.801 AUC; application of this threshold resulted in 92.3% sensitivity and 52.3% specificity (p=0.001). The best cut-off value for 4C Mortality Score to predict in-hospital mortality was ≥7.5 with 0.756 AUC; application of this threshold resulted in 80.6% sensitivity and 54.3% specificity (p=0.001).

Table I. Demographic characteristics, vaccination status and clinical findings of patients according to critical illness status and 28-day mortality.

Characteristics	All patients (n = 228)	Critical illness		p	Outcome		p
		No (n = 176)	Yes (n = 52)		Survivor (n = 197)	Exitus (n = 31)	
	n (%) or Median (Q1-Q3)						
Age (years)	56.5 (41-68.75)	52.5 (39-67)	63 (49.25-76.75)	**0.003**	54 (40-67)	63 (52-73)	**0.005**
Gender				0.595			0.972
Female	111 (48.7)	84 (47.7)	27 (51.9)		96 (48.7)	15 (48.4)	
Male	117 (51.3)	92 (52.3)	25 (48.1)		101 (51.3)	16 (51.6)	
Smokers	70 (30.7)	55 (31.3)	15 (28.8)	0.741	63 (32)	7 (22.6)	0.292
Smokers, pack/years	20 (15-30)	1 (1-1)	1 (1-1)	0.621	20 (15-30)	20 (5-30)	0.713
Vaccine Status				0.189			**0.053**
Unvaccinated	96 (42.1)	70 (39.8)	26 (50)		78 (39.6)	18 (58.1)	
Vaccinated	132 (57.9)	106 (60.2)	26 (50)		119 (60.4)	13 (41.9)	
Vaccine Status				0.836			0.204
Unvaccinated	96 (42.1)	70 (39.8)	26 (50)		78 (39.6)	18 (58.1)	
1 dose CoronaVac	12 (5.3)	10 (5.7)	2 (3.8)		11 (5.6)	1 (3.2)	
2 doses CoronaVac	39 (17.1)	29 (16.5)	10 (19.2)		31 (15.7)	8 (25.8)	
1 doses BNT162b2	18 (7.9)	15 (8.5)	3 (5.8)		17 (8.6)	1 (3.2)	
2 doses BNT162b2	25 (11)	21 (11.9)	4 (7.7)		23 (11.7)	2 (6.5)	
3 doses CoronaVac	23 (10.1)	18 (10.2)	5 (9.6)		22 (11.2)	1 (3.2)	
2 doses CoronaVac &1 doses BNT162b2	13 (5.7)	11 (6.3)	2 (3.8)		13 (6.6)	0	
2 doses CoronaVac & 2 doses BNT162b2	2 (0.9)	2 (1.1)	0		2 (1)	0	
Glasgow Coma Scale							
< 15	21 (9.2)	8 (4.5)	13 (25)	**0.001**	15 (7.6)	6 (19.4)	**0.047**
15	207 (90.8)	168 (95.5)	39 (75)		182 (92.4)	25 (80.6)	
Respiratory rate, breaths/min	22 (18-24)	22 (18-24)	26 (24-32)	**< 0.001**	22 (18-24)	26 (24-30)	**< 0.001**
Heart rate, beats/min	89 (80-102)	88 (79.3-98)	92.5 (85-114.8)	**0.011**	89 (80.5-100)	90 (80-108)	0.362
Peripheral oxygen saturation on room air (%)	91 (85-95)	94 (88-96)	84.5 (80-89.5)	**0.001**	92 (87-96)	85 (80-92)	**< 0.001**

Table II. Demographic characteristics, vaccination status and clinical findings of patients according to critical illness status and 28-day mortality.

Characteristics	All patients (n = 228)	Critical illness		p	Outcome		p
		No (n = 176)	Yes (n = 52)		Survivor (n = 197)	Exitus (n = 31)	
	N (%) or Median (Q1-Q3)						
Radiological findings				0.267			0.467
Negative	28 (12.3)	26 (14.8)	2 (3.8)		27 (13.1)	1 (3.2)	
Typical	180 (78.9)	135 (76.7)	45 (86.5)		152 (77.2)	28 (90.3)	
Lobar consolidation	11 (4.8)	7 (4)	4 (7.7)		9 (4.6)	2 (6.5)	
Pleural effusion	7 (3.1)	6 (3.4)	1 (1.9)		7 (3.6)		
Organizing pneumonia	1 (0.4)	1 (0.6)	0		1 (0.5)		
Other findings	1 (0.4)	1 (0.6)	0		1 (0.5)		
Absolute lymphocyte count ($\times 10^9$/L)	0.8 (0.6-1.3)	0.9 (0.6-1.4)	0.8 (0.8-1.2)	0.086	0.8 (0.6-1.3)	0.8 (0.5-1.3)	0.587
Absolute neutrophil count ($\times 10^9$/L)	5.2 (3.2-7.6)	4.9 (3.2-7.3)	5.9 (3.2-9.7)	0.236	5.3 (3.2-7.6)	4.4 (2.2-7.6)	0.348
C-reactive protein (mg/L)	73.35 (30.45-117)	65.8 (27.1-109)	106 (60.5-160.3)	**0.001**	69.4 (27.9-113)	93.2 (49.4-155)	**0.040**
Procalcitonin (ng/ml)	0.12 (0.06-0.43)	0.11 (0.05-0.25)	0.40 (0.12-1.30)	**< 0.001**	0.11 (0.05-0.31)	0.45 (0.19-1.34)	**< 0.001**
Ferritin (mg/dl)	259.6 (93-493.3)	255.1 (90.5-492.5)	297.1 (116.3-563)	0.454	256.1 (91-496.2)	330.7 (111.7-483.4)	0.561
D-dimer (mg/L)	0.97 (0.56-1.98)	0.90 (0.48-1.34)	1.58 (0.85-3.98)	**0.001**	0.92 (0.51-1.58)	1.75 (0.79-3.89)	**0.020**
Blood urea nitrogen (mg/dl)	16.8 (11.9-30)	15.4 (10.7-27.4)	21.7 (15.5-36.9)	**0.001**	16.2 (11.5-27.3)	30 (16.8-51)	**0.001**
Creatinine (mg/dl)	0.79 (0.6-1.13)	0.75 (0.56-1.08)	0.94 (0.74-2.23)	**0.001**	0.75 (0.57-1.06)	1.13 (0.86-2.47)	**0.001**
Lactate dehydrogenase (U/L)	316 (232.3-461.8)	307.5 (223.3-429.5)	387 (279.5-576.3)	**0.006**	313 (227.5-455.5)	387 (281-525)	0.059
Direct bilirubin (mg/dl)	0.44 (0.29-0.66)	0.45 (0.29-0.69)	0.42 (0.29-0.61)	0.435	0.44 (0.29-0.68)	0.42 (0.30-0.59)	0.850

mg: milligrams, L: liter, ng: nanograms, dl: deciliter, U: unit.

Table III. Symptoms and comorbidity of patients according to critical illness status and 28-day mortality.

Characteristics	All patients (n=228)	Critical illness		p	Outcome		p
		No (n=176)	Yes (n = 52)		Survivor (n = 197)	Exitus (n = 31)	
	n (%) or Median (Q1-Q3)						
Respiratory symptoms							
Dyspnea	145 (63.6)	103 (58.5)	42 (80.8)	**0.003**	119 (60.4)	26 (83.9)	**0.012**
Cough	113 (49.6)	35 (19.9)	4 (7.7)	**0.014**	99 (50.3)	14 (45.2)	0.598
Sputum	14 (6.1)	12 (6.8)	2 (3.8)	0.742	12 (6.1)	2 (6.5)	1.000
Chest pain	6 (2.6)	6 (3.4)	0 (0)		6 (3)	0 (0)	1.000
Hemoptysis	1 (0.4)	0 (0)	1 (1.9)	0.228	0 (0)	1 (3.2)	0.136
Systemic symptoms							
Fever	95 (41.7)	75 (42.6)	20 (38.5)	0.594	83 (42.1)	12 (38.7)	0.719
Gastrointestinal symptoms	34 (14.9)	27 (15.3)	7 (13.5)	0.738	28 (14.2)	6 (19.4)	0.425
Palpitation	2 (0.9)	0 (0)	2 (3.8)		0 (0)	2 (6.5)	
Weakness-fatigue	97 (42.5)	80 (45.5)	17 (32.7)	0.102	88 (44.7)	9 (29)	0.102
Arthrlagia-myalgia	39 (17.1)	35 (19.9)	4 (7.7)	**0.040**	36 (18.3)	3 (9.7)	0.237
Unconsciousness	13 (5.7)	6 (3.4)	7 (13.5)	**0.012**	10 (5.1)	3 (9.7)	0.394
No smell/taste	61 (26.8)	51 (29)	10 (19.2)	0.163	53 (26.9)	8 (25.8)	0.898
Number of comorbidities				0.055			**0.033**
0	60 (26.3)	48 (27.3)	12 (23.1)		53 (26.9)	7 (22.6)	
1	59 (25.9)	51 (29)	8 (15.4)		56 (28.4)	3 (9.7)	
≥ 2	109 (47.8)	77 (43.8)	32 (61.5)		88 (44.7)	21 (67.7)	
Comorbidities							
Hypertension	81 (35.5)	55 (31.3)	26 (50)	**0.013**	65 (33)	16 (51.6)	**0.044**
DM	78 (34.2)	56 (31.8)	22 (42.3)	0.161	62 (31.5)	16 (51.6)	**0.028**
CAD and HF	49 (21.5)	29 (16.5)	20 (38.5)	**0.001**	36 (18.3)	13 (41.9)	**0.003**
COPD	24 (10.5)	17 (9.7)	7 (13.5)	0.432	22 (11.2)	2 (6.5)	0.545
Malignancy	20 (8.8)	16 (9.1)	4 (7.7)	1.000	17 (8.6)	3 (9.7)	0.741
Hematological	15 (6.6)	11 (6.3)	4 (7.7)	0.751	11 (5.6)	4 (12.9)	0.129
Rheumatological	15 (6.6)	12 (6.8)	3 (5.8)	1.000	12 (6.1)	3 (9.7)	0.437
Neuropsychiatric	26 (11.4)	21 (11.9)	5 (9.6)	0.644	25 (12.7)	1 (3.2)	0.219
Chronic Renal Disease	23 (10.1)	15 (8.5)	8 (15.4)	0.149	16 (8.1)	7 (22.6)	**0.022**
Organ Transplant	9 (3.9)	7 (4)	2 (3.8)	1.000	8 (4.1)	1 (3.2)	1.000
Pregnancy	8 (3.5)	6 (2)	2 (3.8)	1.000	8 (4.1)	0	
Others	23 (10.1)	16 (9.1)	7 (13.5)	0.358	17 (8.6)	6 (19.4)	0.100
CCI	1 (0-3)	1 (0-2)	3 (1-3)	**0.001**	1 (0-3)	3 (2-3)	**0.001**

DM: Diabetes Mellitus, CAD&HF: Coronary artery disease &heart failure, COPD: Chronic obstructive pulmonary disease, CCI: Charlson Comorbidity Index.

Table IV. Demographic characteristics, vaccination status and clinical findings of patients according to critical illness status and 28-day mortality.

Characteristics	All patients (n=228)	Critical illness		p	Outcome		p
		No (n = 176)	Yes (n = 52)		Survivor (n = 197)	Exitus (n = 31)	
	n (%) or Median (Q1-Q3)						
Oxygen support				**0.001**			**0.001**
Negative	90 (39.5)	86 (48.9)	4 (7.7)		88 (44.7)	2 (6.5)	
Nasal cannula	84 (36.8)	64 (36.4)	20 (38.5)		72 (36.5)	12 (38.7)	
Non-rebreather mask	36 (15.8)	20 (11.4)	16 (30.8)		25 (12.7)	11 (35.5)	
High flow nasal cannula	18 (7.9)	6 (3.4)	12 (23.1)		12 (6.1)	6 (19.4)	
Steroid use	149 (65.4)	105 (59.7)	44 (84.6)	**0.001**	122 (61.9)	27 (87.1)	**0.006**
Methylprednisolone	147 (98.7)	104 (99)	43 (97.7)		120 (98.4)	27 (100)	
Dexamethasone	2 (1.3)	1(1)	1 (2.3)		2 (1.6)	0	
Methylprednisolone				**0.030**			0.188
1 mg/kg	140 (94)	100 (96.2)	38 (88.4)		114 (95)	24 (88.9)	
2 mg/kg	2 (1.3)	2 (1.9)	0		2 (1.7)	0	
Pulse steroid (250 mg)	7 (4.7)	2 (1.9)	5 (11.6)		4 (3.3)	3 (11.1)	
Anti-cytokine therapy	27 (11.8)	13 (7.4)	14 (26.9)	**0.001**	19 (9.6)	8 (25.8)	**0.016**
4C Mortality Score				**0.001**			**0.004**
Low	47 (20.6)	47 (26.7)	0		47 (23.9)	0	
Moderate	78 (34.2)	62 (35.2)	16 (30.8)		69 (35)	9 (29)	
High	96 (42.1)	65 (36.9)	31 (59.6)		76 (38.6)	20 (64.5)	
Very high	7 (3.1)	2 (1.1)	5 (9.6)		5 (2.5)	2 (6.5)	
4C Mortality Score	8 (4-11)	7 (3-10)	11.5 (7.3-14)	**0.001**	7 (4-11)	11 (8-16)	**0.001**
COVID-GRAM Critical Illness Score				**0.001**			**0.001**
Low	16 (7)	16 (9.1)	0		16 (8.1)	0	
Moderate	151 (66.2)	129 (73.3)	22 (42.3)		138 (70.1)	13 (41.9)	
High	61 (26.8)	31 (17.6)	30 (57.7)		43 (21.8)	18 (58.1)	
COVID-GRAM Critical Illness Score	112 (87-139.75)	101 (80.3-129.8)	144 (118.3-169)	**0.001**	105 (84-132.5)	141 (120-169)	**0.001**
28-day mortality	31 (13.6)	2 (1.1)	29 (55.8)	**0.001**			

mg: milligrams, kg: kilograms. Values are presented as median (Q1-Q3) or number (%).

Table V. Multivariable analyses of baseline predictors critical illness and 28-day mortality.

	B	S.E.	Wald	OR	95% CI	*p*-value
Critical illness*						
Cough	1.193	0.461	6.698	0.303	[0.123, 0.749]	0.010
Creatinine	0.433	0.172	6.324	1.542	[1.100, 2.161]	0.012
Respiratory rate	0.395	0.067	34.901	1.484	[1.302, 1.692]	0.000
COVID-GRAM Critical Illness Score	1.100	0.432	6.478	3.005	[1.288, 7.011]	0.011
28-day mortality**						
Vaccine Status	-1.141	0.470	5.899	0.320	[0.127, 0.802]	0.015
Blood urea nitrogen	0.032	0.010	9.467	1.032	[1.012, 1.053]	0.002
Respiratory rate	0.159	0.047	11.595	1.173	[1.070, 1.285]	0.001
COVID-GRAM Critical Illness Score	0.998	0.450	4.920	2.714	[1.123, 6.556]	0.027

*Nagelkerke R2 56.3%, Hosmer Lemeshow test $p = 0.323$, **Nagelkerke R2 31.8%, Hosmer Lemeshow test $p = 0.80$.

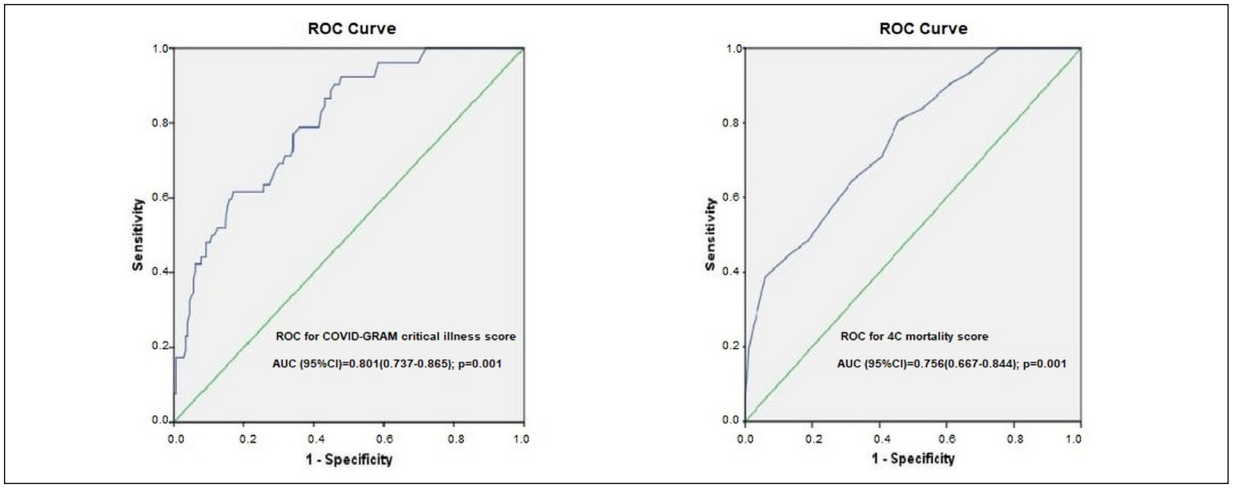

Figure 2. ROC analyses of COVID-GRAM critical illness score in order to predict critical illness and of 4-C mortality score in order to predict in-hospital mortality. AUC; Area under curve.

Discussion

In the presented study, critical illness developed in nearly a quarter of patients hospitalized for COVID-19, and the mortality rate was 13.6%. The risk factors for critical illness were the presence of cough, high creatinine levels, and increased respiratory rate, whereas vaccination, high BUN levels, and increased respiratory rate were important for survival. These results were consistent with the literature. In addition, our study found that the COVID-GRAM Critical Illness Risk Score can be used as a predictive risk scoring for both critical illness and mortality.

Table VI. ROC analyses results for COVID-GRAM critical illness score in order to predict critical illness and for 4C mortality score in order to predict in-hospital mortality.

Characteristics	AUC	*p*	95% CI	Sensitivity	Specificity	PPV	NPV	Youden index
COVID-GRAM Critical Illness Score	0.801	0.001	0.737-0.865	92.3	52.3	36.4	95.8	0.446
4C Mortality Score	0.756	0.001	0.667-0.844	80.6	54.3	21.7	94.7	0.349

AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value.

In a Chinese study[15] that included 1,590 patients from 575 hospitals, rates of critical disease development and mortality were 8.2% and 3.2%, respectively. In a Spanish retrospective observational study[17] with 523 participants, it was shown that 21% of patients experienced a severe illness, 10.3% of patients were admitted to ICU, and 13.8% of patients died within 30 days. It was discovered that the mortality rate varied between 12% and 78% in numerous studies[1-5,18] performed on hospitalized COVID-19 patients (average 25 to 50%). The presented study results were consistent with the literature about critical illness and mortality in COVID-19.

The first reports of SARS-CoV-2 virus particles being discovered in vital organs other than the lung, like the heart and kidney, were published in a study[19] where postmortem tissue samples from 2 victims were analyzed by electron microscopy. Numerous studies[3,4,20] examining risk factors for critical illness and ICU admission in COVID-19 identified some risk factors as indicators of admission, including advanced age, the emergence of comorbidities, particularly HT, DM, cardiovascular disease, or COPD, high levels of CRP, ferritin, procalcitonin, and proinflammatory markers like interleukin (IL)-1 and IL-6, progressive decrease in lymphocyte count, elevated respiratory and heart rate, and critically diminished SaO_2 (%). Wu et al[21] discovered that in COVID-19 patients, advanced age and the appearance of several comorbidities were linked to a greater risk of death and development of acute respiratory distress syndrome (ARDS). Another study[22] with 481 participants found that factors that increased the risk of ICU admission and mortality included advanced age, an increase in pulse and respiratory rate, low SaO_2 (%), low GCS, high levels of WBC, CRP, BUN, LDH, NLR, and scores on the confusion, urea, respiratory rate, blood pressure, and age ≥65 years (CURB-65), the international severe acute respiratory and emerging infections consortium-4C (ISARIC-4C), and COVID-GRAM. In the presented study, factors that may affect the development of critical illness were found to be advanced age, HT, CAD and HF, CCI, dyspnea, cough, muscle-joint pain, altered consciousness, CRP, procalcitonin, BUN, creatinine, LDH, respiratory rate, heart rate, SaO_2, GCS, steroid use, administration of anti-cytokine therapy. Additionally, the web-based risk calculation methods COVID-GRAM Critical Illness Risk Score and 4C Mortality Score were discovered to be higher in critically-ill patients. However, as a result of multivariate analysis with these parameters, we determined that the presence of cough, high creatinine levels, and increased respiratory rate may be risk factors for the development of critical illness. The high respiratory rate of tachypnea is one of the first indicators of clinical deterioration in patients with progressive disease and ICU requirements and has almost always been a predictor for severe disease.

Advanced age (>64 years), development of severe ARDS, and the need for mechanical ventilation are the most consistent and universal major risk factors for death in critically ill COVID-19 patients. Comorbidities (such as obesity, chronic heart and lung diseases, HT, DM, CRD, renal replacement therapy, cancer), markers of inflammation or coagulation (such as fever, D-dimer level >1 mcg/mL, elevated fibrin degradation products, elevated activated partial thromboplastin and prothrombin times), and laboratory findings (such as worsening lymphopenia, neutrophilia, elevated troponin) are additional risk factors for death in these patients[23-26]. Early in the pandemic, a study[24] carried out in Italy discovered that older men with comorbidities who required invasive mechanical ventilation (IMV) had a particularly low survival rate with severe COVID-19 disease. In particular, those with a history of DM, hypercholesterolemia, or COPD were independently related to death. Zhou et al[27] found that patients who died from COVID-19 had lower lymphocyte count, higher LDH, and more imaging abnormalities. According to this study's findings, which are consistent with the literature, mortality was found to be higher in patients with advanced age, DM, CAD and HF, CRD, a high CCI, high CRP and D-dimer levels, low SaO_2 (%), higher 4C-Mortality Score, and COVID-GRAM Critical Illness Scores. Various factors have been focused on survival in COVID-19. Corticosteroids, which are frequently used to treat hypoxemic patients, particularly in the inflammatory phase, have been proven[28-30] to have a good impact on survival because of their anti-inflammatory properties. There is a lot of data in the literature on the efficacy and safety of vaccines used in COVID-19, and it is mentioned[31] that vaccines are effective in reducing both symptoms related to COVID-19 and hospital admissions. In a South African study[32], two doses of Janssen Ad26.COV2.S vaccine and two doses of Pfizer BNT162b2 vaccine were shown to protect against the onset of severe disease, providing 72% and 70% protection

against hospitalization and 82% and 70% protection against ICU admission, respectively, during omicron ascending spread. A Chilean study[33] reported 87.5% protection against hospitalizations and 86.3% protection against death after full immunization with CoronaVac. In the vaccine efficacy study[34] conducted in England with 156,930 participants who were vaccinated with at least a single dose of BNT162b2 or ChAdOx1-S, fewer COVID-19-related hospitalizations and mortality rates were detected in the vaccinated group, and they stated that current vaccines are protective even with a single dose. According to research[35] done on 1,222 teenagers in the USA, youngsters who received the COVID-19 vaccine had nearly 94% lower risk of hospitalization and nearly 100% lower risk of mortality from disease. In a review[36] examining the characteristics and efficacy of vaccine variants and protocols administered in different countries, COVID-19 vaccines have been shown to provide more than 80% protection against all COVID variants, including Delta, especially on hospitalizations and death. In our study, we found that a high respiratory rate was the most important factor for critical illness and ICU admission. We found that vaccination decreased the development of critical illness and ICU admission, and increased survival. Our study cannot make a clear comment on recurrent COVID-19 cases and variants due to some sociological, political and administrative problems in our country. However, it provides valuable data as there is limited literature data showing the direct relationship between vaccination and intensive care unit hospitalization and mortality.

In research[22] using the critical illness and mortality risk scores CURB-65, ISARIC-4C, and COVID-GRAM, the AUC values were 0.898, 0.797, and 0.684 respectively; the positive predictive value (PPV) was 40.3, 22.5, and 17.8; and the negative predictive value (NPV) was found to be 97.9, 100, and 100. Additionally, ISARIC-4C had a sensitivity of 100% for ICU admission and 98.3% for death, whereas COVID-GRAM had a sensitivity of 100% for both ICU admission and mortality. A high COVID-GRAM score upon hospital admission was discovered to be an independent predictor of critical illness in different Spanish investigations[17], demonstrating strong sensitivity, specificity, and negative predictivity. In a study[37] that compared pneumonia risk scores, the sensitivity for pneumonia severity index (PSI), CURB-65, multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hypertension and age (MuLB-STA), and COVID-GRAM, which are prognostic scales for intubation in SARS-CoV 2, was 45.45, 63.63, 54.54, and 39.39, the specificity was 85.27, 65.89, 83.72, and 84.49, the PPV was 44.12, 32.30, 46.15, and 39.39, the NPV was 85.27, 87.63, 87.80, and 84.49, and the AUC values were 0.728 (0.64-0.82), 0.660 (0.55-0.77), 0.780 (0.69-0.86), and 0.76 (0.67-0.85), respectively. These findings showed that the most reliable test for identifying those with the highest mortality rate from COVID-19 patients is COVID-GRAM. The COVID-GRAM Critical Illness Score had the best cut-off value of 102.5; 4C Mortality Score had the best cut-off value of 7.5. In our investigation, COVID-GRAM and 4-C Mortality Scores had AUC values of 0.801 (0.737-0.865) and 0.756 (0.667-0.844), respectively, with sensitivity and specificity of 92.3% and 80.6%, 52.3% and 54.3%, PPV and NPV of 36.4% and 21.7%, and 95.8% and 94.7%, respectively. Our findings determined that the COVID-GRAM Critical Illness Risk Score can be used and is useful for early prediction of both critical illness and mortality risk.

Our study has both strengths and limitations. The results of this comprehensive single-center and cross-sectional study, in which there was no active surveillance and outpatients were excluded, are not representative of the entire population. We cannot comment on SARS-CoV-2 mutations and variants as mutations could not be examined from all participants in our study based on national policies and centralized findings. In this context, multicentre, large-scale, randomized controlled trials, including COVID-19 variants, are needed.

Conclusions

In outbreaks caused by respiratory viral diseases such as COVID-19, it is vital to identify risk factors for critical illness and mortality as soon as possible. As discussed above, risk scoring such as COVID-GRAM Critical Illness and 4-C Mortality can be used to predict critical illness and death. In addition, it is vital to ensure effective immunity through vaccination, especially for patients at risk, to prevent the development of severe disease and mortality. In conclusion, the use of similar risk scoring will help clinicians in early predicting the progressive course and mortality of COVID-19 in patients. In this respect, there is a need for new, multicenter, long-term cohort

studies with additional factors as well as an expansion of the use of current scoring systems in clinical practice.

The most frightening scenario for SARS-CoV-2, like all other respiratory infections that cause a pandemic, is the critical illness process, ARDS, and mortality.

The presented study contributes to the literature by specifying the risk-scoring method, which can indicate critical illness and mortality, and identifying vaccination, high BUN, and increased respiratory rate as the most important factors affecting survival. A good clinical-laboratory follow-up in respiratory system viral infections, and vaccination at the right time is of great importance.

Conflict of Interest

The authors declare that they have no potential conflict of interest, including any financial, personal or other relationships with other people or organizations that could inappropriately influence or be perceived to influence the presented work. The authors have no relevant financial or non-financial interests to disclose.

Authors' Contribution

EG, KA, OBT have made significant contributions to the working concept and design. EG, KA, OBT contributed to the data's collection, analysis, and interpretation. EG, KA, OBT have written the manuscript or significantly edited it, accepted the submitted version, and agreed to be held personally liable for their contributions. They have also promised to ensure that any concerns regarding the truthfulness or integrity of any portion of the work are resolved. All authors read and approved the final version of the manuscript.

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Ethics Approval

The study was conducted in accordance with the 1964 Declaration of Helsinki and ethical approval was obtained from the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee on March 4, 2022 (48/120).

Informed Consent

Informed consent was obtained from the participants or their first-degree relatives for the study.

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

ORCID ID

Efraim Guzel: 0000-0001-6677-9254
Kaniye Aydin: 0000-0001-5538-3692
Oya Baydar Toprak: 0000-0001-7320-976X.

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