Original Article

Risk Factors and a Novel Score (CARI-65) Predicting Mortality in COVID-19 Patients

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Abstract

Purpose: The rapid spread of severe acute respiratory syndrome coronavirus-2 infection resulted in an exponential increase in hospitalizations and mortality. We aimed to explore the determinants of mortality and formulate a score that can predict mortality in patients hospitalized due to coronavirus disease 2019 (COVID-19). **Materials and Methods:** In this retrospective study, 1024 COVID-19 patients hospitalized between March 2020 and October 2020 were included. Patient demographics, underlying comorbid illnesses, clinical features, vital signs at admission, disease severity, and laboratory parameters, were collected from hospital medical records and analyzed to derive risk factors for in-hospital mortality and formulate a mortality prediction score. **Results:** The median age of the study population was 56 years (interquartile range [IQR], 45–65) and was significantly higher in nonsurvivors than in survivors (62 [IQR 55–70] vs. 52 [IQR 40–65]; $P = 0.001$). Hypertension and diabetes were the most common associated comorbid illnesses seen in 50.5% ($n = 518$) and 29.1% ($n = 299$) of patients, respectively. The presence of altered level of consciousness (C), azotemia with serum creatinine >1.5 mg/dl (A), respiratory rate >25/min (R), interleukin-6 >25 pg/ml (I), and age ≥65 years were independent predictors of mortality. A six-point COVID-19 mortality prediction score, "CARI-65," was developed using variables predicting mortality in multivariate regression analysis. The CARI-65 score ≥3 had a sensitivity and specificity of 87.1% and 57.3%, respectively, and positive and negative predictive values of 42.52% and 92.45%, respectively, in predicting mortality. **Conclusion:** This study demonstrated various demographic, clinical, and laboratory parameters that predict mortality in hospitalized COVID-19 patients. We also proposed a simple risk stratification score to predict mortality in hospitalized COVID-19 patients, so that effective triaging of patients can be done to utilize health-care resources efficiently.

Keywords: Mortality in coronavirus disease 2019, mortality score in coronavirus disease 2019, predictors of mortality

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified as a novel coronavirus toward the end of the year 2019. After its recognition as an etiology for a cluster of pneumonia patients in China, this unknown disease named coronavirus disease 2019 (COVID-19) spread expeditiously across the globe, hence being declared a pandemic by the WHO on March 11, 2019.[1] As of December 24, 2021, there are nearly 276,436,619 confirmed COVID-19 cases worldwide with 5,374,744 deaths, of which 34,765,976 cases and 478,759 deaths have been reported from India.[2] With almost 2 years into the pandemic and evolving literature about COVID-19, the heterogeneity of its clinical presentation is known to range from asymptomatic or mild illness to critical disease. Mortality due to COVID-19 varies in different parts of the world.[3] In India, the highest cases and deaths are reported from Maharashtra, while in the Union territory of Jammu and Kashmir, there have been 3,40,293 cases and 4518 (1.3%) deaths till December 24, 2021.[4]

Various clinical, laboratory, and patient-related factors are associated with an increased risk of death in COVID-19. However, limited data, mainly from India, specifically evaluated factors associated with increased mortality risk in

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hospitalized COVID-19 patients.[5-7] Considering the growing disease burden and exhausted health-care infrastructure, especially in developing countries, it has become imperative to prognosticate patients. This would help patients to be triaged to different levels of health care. In this context, we planned a retrospective analysis of data from hospitalized COVID-19 patients to explore the determinants of mortality and formulate a predictive mortality score.

Materials and Methods

This observational study was conducted at the Sher I Kashmir Institute of Medical Sciences, a tertiary care center in the union territory of Jammu and Kashmir. Except for the initial few months of the COVID-19 pandemic, our hospital served as a referral center for the management of moderate-to-critically ill COVID-19 patients. The institutional ethical committee approved the study.

Study population

Patients with moderate-to-severe COVID-19 (based on positive reverse transcriptase-polymerase chain reaction from a nasopharyngeal swab) aged more than 18 years were included in the study. Those with grossly incomplete medical records, patients who died within 24 h of presentation, and pregnant/lactating women were excluded from the analysis.

For the initial few months of the pandemic, all patients with proven COVID-19 illness were admitted. Later on, due to a change in hospital policy, only patients with moderate to critical illness requiring oxygen supplementation, high flow nasal oxygen (HFNO), noninvasive (NIV) ventilation, or invasive mechanical ventilation (IMV) were hospitalized. Patients were classified into various grades of disease severity based on the criteria provided by the World Health Organization (WHO).[8] COVID-19 patients were managed in areas of the hospital dedicated exclusively to COVID-19 care. Severe or critically ill patients were managed in high dependency units and dedicated COVID-19 intensive care units (ICUs). Referrals to our center, the only tertiary center designated for COVID-19, were strictly coordinated by the administration based on the availability of beds and ventilators. Management of patients was based on the hospital protocol that was updated from time to time by the institutional COVID-19 team in accordance with national and international guidelines for the management of COVID-19 patients. Patient case files were retrieved from the medical record section of the hospital and were screened for inclusion in the study. Data regarding patient demographics, underlying comorbidities, clinical presentation, vital signs at admission, disease severity, and laboratory parameters (blood counts, kidney and liver functions, lactate dehydrogenase, serum ferritin, d-dimer, and interleukin [IL]-6 levels) were noted on a specific case record form and then entered and maintained on an excel spreadsheet.

Statistical analysis

Categorical variables were expressed as the number of cases and percentage. Continuous data were either expressed as mean with standard deviation in case of normally distributed data or median with interquartile range if data were skewed. The Chi-square test or Fisher's exact test (whichever applicable) was used to determine the difference between categorical variables. Student's *t*-test and Mann–Whitney *U*-test were used to analyze the difference between continuous variables. Some of the continuous variables were dichotomized into the normal limit and above or below normal limits as per the standard reference range as follows: low leukocyte count <4.5, low platelet count <100 × 10^3/µl, high serum creatinine >1.5 mg/dl, high LDH >250 U/L, high serum ferritin >500 ng/ml, and high D-dimer >500 ng/ml. The optimal cutoff of neutrophil–lymphocyte ratio (NLR) and IL-6 in predicting mortality was calculated by applying the Receiver operating curve (ROC). Univariate logistic regression analysis evaluated the association between demographic, clinical, or laboratory parameters and mortality risk. Factors significantly associated with risk of mortality on univariate analysis were evaluated in multivariate logistic regression to know the independent predictors of mortality. $P < 0.05$ was considered to indicate statistical significance. The statistical analysis was conducted using the Statistical Package for the Social Sciences Ver. 20.0 (SPSS, Chicago, IL, USA).

Results

A total of 1024 diagnosed cases of COVID-19 patients were included in the study, of which 78.5% (n = 803) had moderate-to-severe illness. Out of 1024 patients, 30.3% (n = 311) died while 69.6% (n = 713) were discharged. The median age of the study participants was 56 (IQR: 45–65) years, with the majority of them being males (64.3%). The median age of patients who died was significantly higher than those who were discharged (62 [IQR: 55–70] vs. 52 [IQR: 40–65]; $P < 0.001$). Patients who belonged to the age group of ≥65 years had significantly higher mortality compared to those aged <65 years (35% vs. 19.6%, relative risk [RR]: 1.68, 95% confidence interval [CI]: [1.39–2.01]). Hypertension (50.5%) and diabetes mellitus (29.1%) were our study's most commonly associated comorbid illnesses [Table 1]. The presence of comorbid illnesses including hypertension, chronic kidney disease, chronic liver disease, and chronic lung diseases significantly increased the risk of mortality, whereas the absence of any underlying comorbid illness was associated with a higher likelihood of survival (odds ratio [OR], 2.23, 95% CI (1.62–3.05), $P \leq 0.001$).

Fever was the most common presenting symptom reported in 67.1% of patients, followed by dyspnea (58.8%) and cough (55.8%). A relatively lesser percentage of patients reported rhinitis, anosmia, loss of taste, nausea/vomiting, and diarrhea. Reduced level of consciousness was observed in 5.27% (n = 54) of patients and was associated with higher mortality (12.9% vs. 2%, $P \leq 0.001$). Respiratory support (oxygen supplementation and mechanical ventilation) was required by 803 (78.5%) patients. Oxygen supplementation

via nonrebreather mask was provided to 214 (26.6%) patients and high flow nasal cannula in 41 (5.1%). NIV ventilation was provided to 65 (8.09%) and IMV to 45 (5.6%) patients. Various demographic, clinical, and laboratory parameters of the study population and their comparison between survivors and nonsurvivors are given in Tables 1 and 2.

On univariant analysis, various factors associated with increased risk of mortality are given in Table 3.

The optimal cutoff value using receiver operating curve (ROC) for NLR and IL-6 at presentation was 8.79 (area under the curve [AUC] 0.72, sensitivity 61% and specificity 72.7%) and 21.7 pg/ml (AUC 0.68, sensitivity 87% and specificity 46.3%), respectively, in predicting mortality [Figure 1a and b and Table 4].

On multivariate regression analysis, age ≥65 years, respiratory rate >25/min, presence of altered sensorium, serum

Table 1: Clinical parameters of survivors and nonsurvivors

Patient characteristics	Total (*n*=1024)	Survivors (*n*=713)	Nonsurvivors (*n*=311)	*P*
Age (years), median (IQR)	56 (45-65)	52 (40-65)	62 (55-70)	<0.001
Age group (years)				
<65	775 (75.6)	573 (80.4)	202 (65)	<0.001
≥65	249 (23.4)	140 (19.6)	109 (35)	
Gender, *n* (%)				
Males	659 (64.3)	454 (63.7)	205 (65.9)	0.491
Females	365 (35.6)	259 (36.3)	106 (34.1)	
No underlying comorbidities	325 (31.7)	261 (36.6)	64 (20.58)	<0.001
Comorbidities, *n* (%)				
Hypertension	518 (50.5)	330 (46.5)	188 (60.5)	<0.001
Diabetes mellitus	299 (29.1)	198 (27.8)	101 (32.5)	0.128
Hypothyroidism	126 (12.3)	93 (13)	33 (10.6)	0.276
Chronic kidney disease	86 (8.3)	38 (5.3)	48 (15.4)	<0.001
Malignancy	85 (8.3)	54 (7.6)	31 (10)	0.202
Chronic lung disease	53 (5.17)	29 (4.1)	24 (7.7)	0.015
Chronic liver disease	25 (2.4)	10 (1.4)	15 (4.8)	<0.001
Cardiovascular disease	23 (2.24)	14 (2)	9 (2.9)	0.356
Cerebrovascular disease	21 (2.05)	14 (2)	7 (2.3)	0.765
Postorgan transplant	10 (0.97)	7 (1)	3 (1)	0.98
Symptoms, *n* (%)				
Fever	688 (67.1)	483 (67.7)	205 (65.9)	0.567
Dyspnea	603 (58.8)	379 (53.2)	224 (72)	<0.001
Cough	572 (55.8)	382 (53.6)	190 (61.1)	0.025
Myalgias	143 (13.9)	120 (16.8)	23 (7.4)	<0.001
Fatigue	116 (11.3)	83 (11.6)	33 (10.6)	0.032
Sore throat	60 (5.8)	55 (7.7)	5 (1.6)	<0.001
Altered mental status	54 (5.27)	14 (2)	40 (12.9)	<0.001
Nausea/vomiting	49 (4.7)	25 (3.5)	24 (7.7)	0.004
Headache	20 (1.95)	19 (2.7)	1 (0.3)	0.012
Hemoptysis	15 (1.46)	12 (1.7)	3 (1)	0.374
Diarrhea	15 (1.46)	9 (1.3)	6 (1.9)	0.186
Rhinitis	14 (1.36)	11 (1.5)	3 (1)	0.464
Anosmia	9 (0.87)	8 (1.1)	1 (0.3)	0.207
Loss of taste	7 (0.68)	7 (1)	0 (0)	0.079
Skin Rash	2 (0.19)	1 (0.1)	1 (0.3)	0.548
Vital signs, *n* (%)				
Heart rate (beats/min)	92 (81-106)	90 (80-104)	100 (85-112)	<0.001
<100	668	499 (70.7)	169 (54.9)	>0.001
≥100	346	207 (29.3)	139 (45.1)	
Systolic blood pressure (mmHg)	120 (110-130)	120 (110-130)	120 (106-132)	0.712
Mean blood pressure (mmHg)	83 (75-93)	89 (83-97)	70 (60-80)	<0.001
Respiratory rate	20 (18-26)	20 (18-24)	24 (20-30)	<0.001
Severity of illness, *n* (%)				
Mild to moderate	355 (34.7)	318 (44.6)	37 (11.9)	<0.001
Severe to critical	669 (65.3)	395 (55.4)	274 (88.1)	

IQR: Interquartile range

Table 2: Laboratory parameters of survivors and nonsurvivors

Laboratory parameters (n=1024)	Total	Survivors	Nonsurvivors	*P*
Hemoglobin (g/dl), mean±SD	11.89 (2.54)	12.1 (2.4)	11.1 (2.6)	<0.001
Total leukocyte count (10^3/µl)	8.40 (4.52)	7.7 (3.7)	10.1 (5.7)	<0.001
NLR	6.3 (2.2-12.5)	4.86 (2.32-9.33)	11.19 (6.15-21.25)	<0.001
Platelet count (10^3/µl)	153.09 (86.82)	158 (86.6)	140 (86)	0.004
Serum creatinine (mg/dl)	1.03 (0.8-1.51)	0.95 (0.77-1.27)	1.48 (0.96-2.53)	<0.001
Serum bilirubin (mg/dl)	0.63 (0.5-0.89)	0.60 (0.49-0.80)	0.73 (0.53-1.03)	<0.001
Alanine transaminase (U/L)	36 (23-60.5)	37 (23-61)	34 (22-60)	0.371
Aspartate transaminase (U/L)	38.5 (23-51.75)	35 (23-48)	43 (37-60)	0.05
Alkaline phosphatase (U/L)	94 (74-124)	92 (73-118)	103 (78-142)	0.002
Serum albumin (g/dl)	3.32 (0.67)	3.45 (0.63)	2.9 (0.61)	<0.001
Lactate dehydrogenase (U/L)	535 (262.24)	401 (254)	548 (259)	<0.001
Creatinine phosphokinase (U/L)	95 (44-212)	89 (39-184)	151 (66-299)	0.002
Serum ferritin (ng/ml)*	480 (286.7-933)	440 (253-873)	711 (396-1031)	0.003
Interleukin-6 levels (pg/ml)**	33.77 (12.6-80.2)	26 (9-70)	61 (29-136)	<0.001
INR	1.15 (1.05-1.30)	1.13 (1.04-1.28)	1.19 (1.09-1.34)	0.002
APTT	32.7 (30.4-36.8)	32.8 (30.5-36.9)	32.45 (30.2-36.5)	0.455
D-dimer (ng/ml)***	638 (244.5-1873.25)	584 (215-1454)	1080 (528-2519)	0.006
Prothrombin time (s)	15.7 (4.17)	15.45 (3.68)	16.61 (5.31)	0.013

*n=252,**n=274and***n=314(n=numberofpatients).NLR:Neutrophil–lymphocyteratio,SD:Standarddeviation,APTT:Activatedpartialthromboplastintime

Table 3: Risk factors predicting mortality in coronavirus disease-2019 patients on univariant and multivariant analysis

Risk factors	Univariant analysis		Multivariant analysis	
	OR (95%CI)	*P*	OR (95% CI)	*P*
Age (years) ≥65	2.20 (1.63-2.97)	<0.001	3.13 (1.50-6.53)	0.002
Hypertension	1.49 (1.23-2.81)	<0.001	1.14 (0.63-2.06)	0.354
Chronic kidney disease	1.98 (1.58-2.42)	<0.001	1.89 (0.16-3.9)	0.91
Chronic lung disease	1.53 (1.09-2.02)	0.015	1.53 (0.54-4.31)	0.41
Chronic liver disease	2.02 (1.36-2.64)	<0.001	1.76 (0.428-3.16)	0.187
Altered sensorium	7.36 (3.91-13.34)	<0.001	6.46 (1.06-39.06)	0.042
Heart rate/min >100	1.98 (1.5-2.62)	<0.001	1.23 (0.71-2.12)	0.462
Systolic blood pressure (mmHg) <90	3.07 (1.7-5.82)	<0.001	3.32 (0.86-8.84)	0.08
Mean blood pressure (mmHg) <65	3.65 (3.17-4.17)	0.001	1.33 (1.05-2.19)	0.30
Respiratory rate/min >25	2.5 (2.06-3.001)	<0.001	2.25 (1.04-4.85)	0.038
NLR >10	4.75 (3.09 to 7.25)	<0.001	1.32 (0.65-2.64)	0.435
Platelet count (×10^3/µl) <100	1.99 (1.47-2.69)	0.001	1.67 (0.94-2.96)	0.078
Serum creatinine (mg/dl) >1.5	4.59 (3.36-6.33)	<0.001	3.51 (1.64-7.53)	0.001
LDH >250	2.30 (1.25-4.28)	0.007	1.76 (1.12-4.60)	0.764
Serum ferritin (ng/ml) >500	2.18 (1.15-4.18)	0.017	1.79 (0.86-3.73)	0.525
Interleukin-6 (pg/ml) >25	3.8 (1.44-10.33)	<0.001	3.74 (1.96-7.14)	0.003
D-dimer (ng/ml) >500	1.99 (1.15-3.47)	0.012	1.79 (0.46-6.97)	0.399

NLR: Neutrophil–lymphocyte ratio, LDH: Lactate dehydrogenase, OR: Odds ratio, CI: Confidence interval

creatinine >1.5 mg/dl, and IL-6 >25 pg/ml at presentation were independently associated with an increased risk of death in hospitalized COVID-19 patients [Table 3].

The odds ratio of individual risk factors for mortality determined by multivariate analysis was used to create a predictive "COVID-19 mortality score." Based on this, the presence of altered level of consciousness at admission (C), azotemia, i.e., serum creatinine >1.5 mg/dl (A), respiratory rate >25/min (R), and age ≥65 (A) received a score of 1-point each, while IL-6 >25 ng/ml (I) was given a score of 2-points to give a total score of 6 points (CARI-65; minimum score 0; maximum score 6). Among nonsurvivors, the CARI-65 score was significantly higher compared to survivors (median 2 [IQR: 2–3] in survivors vs. median 3 [IQR: 3–4) in nonsurvivors, $P < 0.001$) [Figure 2]. Based on ROC, the CARI-65 score ≥3 had a sensitivity of 87.1%, specificity of 57.6%, positive predictive (PPV) of 42.86%, and negative predictive value (NPV) of 94.25% in predicting hospital mortality among COVID-19 patients [Table 4 and Figure 1c]. Sensitivity, specificity, and positive and NPVs (PPV and NPV) of various CARI-65 scores are given in Table 5.

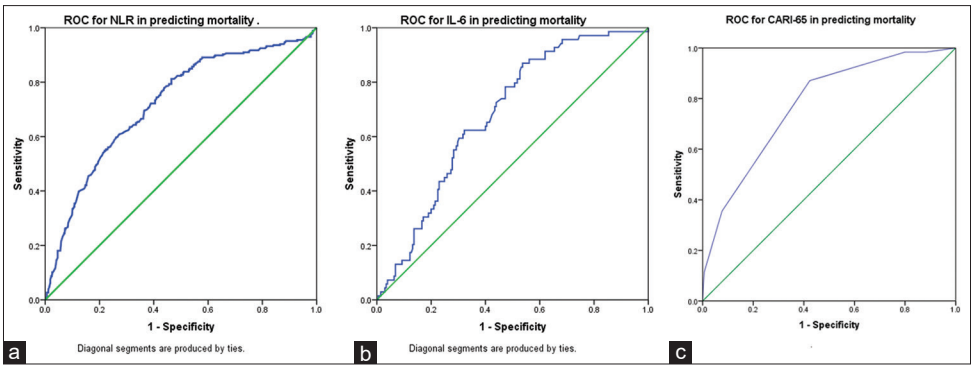

Figure 1: (a) ROC for neutrophil–lymphocyte ratio in predicting mortality. (b) ROC for interleukin-6 in predicting mortality. (c) ROC for Optimal cutoff for CARI-65 in predicting mortality

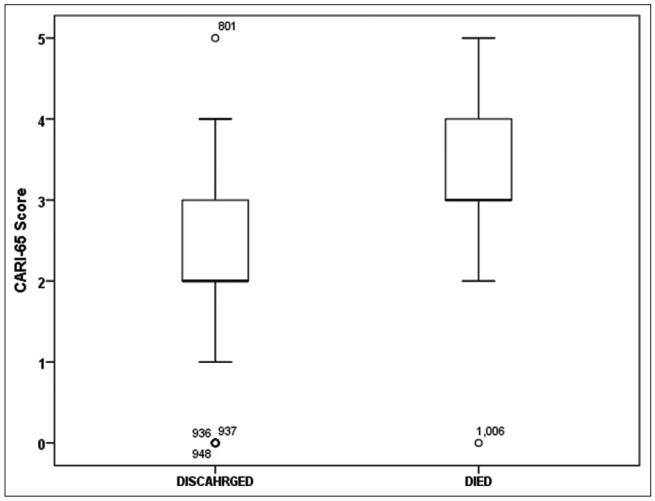

Figure 2: Box and Whisker plot comparing median values of CARI-65 score among survivors and nonsurvivors

Table 4: Optimum cutoff values for neutrophil–lymphocyte ratio, interleukin-6, and CARI-65 score in predicting mortality

Variable	Cutoff value	AUC	Sensitivity (%)	Specificity (%)
NLR	8.79	0.72	61	72.7
IL-6	21.7	0.68	87	46.3
CARI-65	≥3	0.775	87.1	57.6

NLR: Neutrophil–lymphocyte ratio, IL-6: Interleukin-6, AUC: Area under the curve

Discussion

This retrospective review determined various parameters that predicted mortality in hospitalized COVID-19 patients. We observed that advanced age, altered sensorium, respiratory distress, azotemia, and raised serum IL-6 levels were associated with an increased risk of death.

Our study's overall mortality in hospitalized patients with COVID-19 was approximately 30%. It is important to stress that the majority (88%) of the nonsurvivors had severe to critical illness at hospitalization. Previous studies report an 8%–21% mortality in patients hospitalized for COVID-19, with higher mortality (16%–78%) in patients requiring ICU care.[9-12] A prospective study from Mexico, including 800 patients with severe COVID-19, reported hospital mortality of 30.1%.[13] Similarly, Wang *et al*. reported mortality of 36.8% in severe to critical COVID-19 patients.[14] In another study by Mahendra *et al*., higher mortality (54.64%) was observed in severe COVID-19.[7]

Patients with severe illness were managed with oxygen supplementation (Non rebreather mask, high flow nasal oxygenation), non invasive ventilation (NIV) or invasive mechanical ventilation (IMV) in dedicated COVID-19 ICU's. Mortality among COVID-19 patients requiring IMV is reported to be higher even in well-resourced health-care systems. We observed that a total of 36 (80%, $n = 45$) patients who received IMV and 51 (78.4%, $n = 65$) who received NIV died. In a study from the United States, 164 ($n = 1023$) patients with COVID-19 required IMV. Of these, 70 (42.7%) died and 94 (57.3%) were alive at the time of data collection.[15] In a recent review of 23 studies ($n = 4776$), higher mortality was reported in patients who required NIV to manage COVID-19-related respiratory failure. NIV support was used in 46% of patients, with a failure rate of 47.7%. For those who failed NIV, 40.9% died, and 26.5% were managed with IMV.[16]

Advanced age has been associated with higher mortality in COVID-19. In the present study, patients who died were older than those discharged. Furthermore, age ≥65 years was an independent risk factor predicting mortality. Several studies from around the world found that patients with COVID-19 who were older had a higher mortality rate.[7,17-24] In a study by Du *et al*., age >65 years was associated with higher mortality (odds ratio [OR], 3.76; 95% CI, 1.14–17.39; $P = 0.023$).[25] The production of excess Type-2 cytokines due to age-related defects in B and T-cell function results in sustained proinflammatory responses and a deficiency in control of viral replication, thus leading to a poor outcome.[26]

Numerous studies, including a recent systematic review and meta-analysis, have shown the presence of comorbid illnesses (particularly cardiovascular and diabetes) to be associated with increased mortality in COVID-19.[27,28]

Table 5: Sensitivity, specificity, positive predictive value, and negative predictive value of CARI-65 scores for mortality in coronavirus disease-2019

CARI-65 score	Died (%)	Sensitivity (%s)	Specificity (%)	PPV (%)	NPV (%)	Relative risk
0	4.7	1.6	88	4.7	71.09	0.164
1	0	0	91.76	0	71.56	0
2	9.8	11.29	62.35	9.8	65.84	0.28
3	35.16	51.61	65.29	35.16	78.72	1.6
4	55.56	24.19	92.94	55.56	77.07	2.42
5	87.5	11.29	99.41	87.50	75.45	3.56

PPV: Positive predictive value, NPV: Negative predictive value

In our study, the presence of certain comorbid illnesses, including hypertension, chronic lung disease, chronic renal failure, and chronic liver disease, was more frequently observed in nonsurvivors than in survivors. However, none could independently predict mortality. In a study including COVID-19 patients requiring ICU admission, the presence of comorbid illnesses was not associated with increased mortality on multivariate regression analysis.[29] We also observed that the likely hood of survival was significantly higher in patients with the absence of any comorbid illness. A similar observation was made in a study including COVID-19 patients of varying severity, where the absence of comorbid illness was associated with lower mortality and a reduced need for mechanical ventilation.[5]

The correlation between the presence of neurological symptoms and severity of COVID-19 was first reported by Mao L *et al*. They observed impaired consciousness in 7.5 % of COVID-19 patients which was significantly higher in patients with severe disease compared to non-severe illness (14.8% vs. 2.4 %).[30] We observed presence of reduced level of consciousness at the time of hospitalization to be associated with increased risk of mortality. In a study by Kenerly MJ *et al*, an increase in risk of mortality in COVI-19 patients was reported in patients who had presented with altered mental status (30.1% vs. 14.8%; OR 2.13).[23]

Chachkiani *et al,* reported that development of altered mental status during hospitalization in COVID-19 patients did not predicted mortality however was associated with increased hospital stay.[31]

Respiratory rate is a marker of severity in patients with respiratory failure. It is an integral part of prognostic scoring systems used in community-acquired pneumonia like CURB-65 and pneumonia severity index.[32,33] In our study, nonsurvivors had a significantly higher respiratory rate at presentation compared to survivors. The presence of tachypnea with a respiratory rate of ≥25/min was an independent predictor of mortality. Chatterjee *et al*. reported 1.9–3.2-fold higher mortality among COVID-19 patients with a respiratory rate of >22/min at admission.[34] Similarly, various studies have reported a higher respiratory rate among nonsurvivors of COVID-19 than survivors.[7,22,35,36]

In this study, nonsurvivors had significantly higher serum creatinine than survivors at presentation. Moreover, serum creatinine >1.5 mg/dl at presentation could independently predict in-hospital mortality. In a study including COVID-19 patients, serum creatinine was higher among nonsurvivors than survivors (110 μmol/L ± 97 vs. 169.5 ± 192; $P = 0.0056$) and could predict mortality.[22] Similarly, other studies have observed comparatively higher serum creatinine in nonsurvivors among hospitalized COVID-19 patients.[17,21,36,37]

Mortality in COVID-19 is largely due to cytokine storm characterized by hyperinflammation and uncontrolled immune response.[38] Among various inflammatory markers studied, IL-6 appears superior in predicting respiratory failure in COVID-19.[39,40] Predominant role of IL-6 in COVID-19 is supported by the evidence of clinical benefit observed with the use of IL-6 inhibition in these patients.[41,42] We observed that IL-6 levels >10 pg/ml on presentation could independently predict mortality in hospitalized COVID-19 patients. The optimal cutoff level of IL-6 at presentation predicting mortality was 21.7 pg/ml with a sensitivity and specificity of 87% and 46.3%, respectively [Figure 1]. Sabaka *et al*. reported that IL-6 levels >24 pg/ml at presentation could predict the development of hypoxemia in COVID-19 with a sensitivity and specificity of 100% and 88.9%, respectively.[43] The correlation of elevated levels of IL-6 with disease severity and mortality has also been documented in other studies.[39,44-50]

Our study's optimal cutoff of NLR predicting mortality was 8.79 with a sensitivity and specificity of 61% and 72.7%, respectively. Various studies have reported NLR values ranging from 3.3 to 11.75 to predict higher mortality. A recent meta-analysis including 25 studies reported higher NLR associated with increased mortality in COVID-19 patients.[51]

Although systolic and mean blood pressure was significantly lower among nonsurvivors at presentation, it did not predict mortality on multivariate analysis. Aksel *et al*. reported no significant difference in blood pressure among survivor and nonsurvivor groups of COVID-19.[35] Similarly, blood pressure did not predict mortality among hospitalized COVID-19 patients in various other studies.[21,22,36] This observation of relative preservation of hemodynamics in hospitalized COVID-19 patients needs further research.

We attempted to derive a score that could predict mortality in COVID-19. Based on factors associated with increased in-hospital mortality identified on multivariant regression analysis, we proposed a 6-point score "CARI-65." It consists

of clinical and laboratory parameters, including altered consciousness (C), azotemia (A), respiratory rate (R), serum IL-6 (I), and age (A). CARI-65 ≥3 had a sensitivity of 87.1% and specificity of 57.6%, with an NPV of 94.25%. A high NPV of 94.25% indicates that patients with CARI-65 score of 0–2 have 94.25% chances of being discharged alive.

Chen *et al*. proposed a 5-point "CAPRL" score for predicting mortality in COVID-19. The score incorporated high-sensitivity C-reactive protein (C; >50 = 1), age (A; >50 = 1), platelet count (P; <100 × 10^3/μL = 1), respiratory rate (R; >30 = 1), and serum LDH (L; >400 = 1). The CAPRL score of 0, 1, 2, 3, and ≥4 had 30-day mortality of 0%, 1.8%, 12.9%, 43%, and 76.7%, respectively.[52] In a scoring system proposed by Gue *et al*. incorporating age, sex, platelet count, international normalized ratio, Glasgow Coma Scale, respiratory rate, and blood pressure, a score of ≥4 had sensitivity and specificity of 67.59% and 78.36%, respectively, in predicting 30-day mortality.[53] Similarly, Altschul *et al*. put forth a score consisting of age, oxygen saturation, mean arterial blood pressure, blood urea nitrogen, C-reactive protein, and international normalized ratio. The score ranges between 0 and 10 with mortality of 11.8%, 39%, and 78% for a patient with low (0–3), moderate (4–6), and high (7–10) COVID-19 severity score, respectively.[54] Our proposed scoring system has better sensitivity (87.1%) than other scoring systems and a higher NPV (92%). Although this score requires external validation, it can be useful to prognosticate hospitalized COVID-19 patients.

This study has a few limitations. First, we have included various clinical and laboratory parameters at admission without following their trend during the hospital stay. Furthermore, the severity of hypoxemia at presentation was not included for analysis due to a lack of information about required FiO2to maintain target saturation. In addition, this study did not include the severity of lung involvement based on radiology which might have been another parameter determining patient outcome. Finally, being a single-center retrospective study, our results may not be generalized to other populations.

Conclusion

This study provides an insight into the risk factors one should look at in patients of COVID-19 to triage them to different levels of health-care effectively. Patients with age ≥65 who present with altered level of consciousness, tachypnea (RR >25/min), azotemia (serum creatinine >1.5), and raised IL-6 (>10 pg/ml) represent a subgroup of COVID-19 patients who are at high risk of mortality and therefore should be managed in high dependency areas. Furthermore, the proposed CARI-65 score could help identify patients at high risk of mortality and guide their management and site of care.

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Conflicts of interest

There are no conflicts of interest.

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