Thorac Res Pract. 2023; 24(2): 53-60 DOI: 10.5152/ThoracResPract.2023.22029

Original Article

Clinical and Laboratory Predictors of Mortality in Severe COVID-19 Pneumonia: A Retrospective Study from India

Swathi Karanth Marsur Prabhakar[1], Swapna Ramaswamy[1], Vanitha Basavarajachar[2], Anushree Chakraborty[1], Akshata Shivananjiah[1], Nagaraja Chikkavenkatappa[3]

[1]Department of Pulmonary Medicine, Shanthabai Devarao Shivaram Tuberculosis Research Center & Rajiv Gandhi Institute of Chest Diseases, Bangalore, Karnataka
[2]The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) Projects, Swami Vivekananda Youth Movement, Bangalore, Karnataka
[3]Shanthabai Devarao Shivaram Tuberculosis Research Center & Rajiv Gandhi Institute of Chest Diseases, Bangalore, Karnataka

Cite this article as: Karanth Marsur Prabhakar S, Ramaswamy S, Basavarajachar V, Chakraborty A, Shivananjiah A, Chikkavenkatappa N. Clinical and laboratory predictors of mortality in severe COVID-19 pneumonia: A retrospective study from India. *Thorac Res Pract.* 2023;24(2):53-60.

Abstract

OBJECTIVE: Wide arrays of laboratory parameters have been proposed by many studies for prognosis in COVID-19 patients. In this study, we wanted to determine if the International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium score in addition to certain clinical and laboratory parameters would help in predicting mortality. We wanted to determine if a greater severity score on chest x-ray at presentation translated to poor patient outcomes using the COVID-19 chest radiography score.

MATERIAL AND METHODS: This retrospective study was conducted at SDS TRC and Rajiv Gandhi Institute of chest diseases, Bangalore from March 2021 to June 2021. This study included 202 real-time-polymerase chain reaction-positive COVID-19 patients aged above 18 years admitted to the intensive care unit of our hospital. Demographic characteristics and baseline hematological and inflammatory markers (serum C-reactive protein, lactate dehydrogenase, troponin-I, ferritin, and D-dimer) were collected. Radiological severity on a chest x-ray was assessed using the validated COVID-19 chest radiography score. The International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium score was assigned to each patient within 24 hours of intensive care unit admission. Outcome studied was in-hospital mortality.

RESULTS: The overall mortality was 54.9% (111 cases). Age more than 50 years, >4 days of symptoms, peripheral oxygen saturation/fraction of inspired oxygen ratio less than 200, elevated serum lactate dehydrogenase >398.5 IU/L, and hypoalbuminemia (<2.95 g/dL) were detected as independent predictors of mortality. A significant correlation of risk stratification with mortality ($P = .057$) was seen with International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium score. There was no significant correlation between the COVID-19 chest radiography score and mortality.

CONCLUSION: Age >50 years, peripheral oxygen saturation/fraction of inspired oxygen ratio <200, mean symptom duration of >4 days, elevated serum lactate dehydrogenase, and hypoalbuminemia are independent predictors of mortality in severe COVID-19 pneumonia. International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium score was different in the survivors and deceased.

KEYWORDS: COVID-19 mortality, 4C score, CARE score, inflammatory markers, SPO2/FIO2 ratio
Received: *February 11, 2022* ***Accepted:*** *October 5, 2022* ***Publication Date:*** *March 28, 2023*

INTRODUCTION

COVID-19 (SARS-CoV2) disease has had a devastating impact on the world. The wide spectrum of SARS-CoV2 disease has been a great challenge to physicians in medical history in both the waves of this pandemic. Approximately, 15%-30% of patients develop respiratory failure and require intensive care management.[1,2] Managing this pandemic demanded rigorous re-organization and scaling up of the existing healthcare and if unprepared, caused unacceptably high mortality rates due to critical shortage of ventilators and intensive care unit (ICU) all over the world. Mortality due to COVID-19 varies from 61.5% to 94%.[3] India was under the complete grip of the second wave of COVID-19 with lakhs of patients succumbing to this disease, with a considerable younger population being lost. Double and triple variants of the virus have been identified making them more transmissible and pathogenic, thus indicating more waves that we have to be prepared for.[4] Hence, a well-planned and meticulous allotment of health resources is a subject of prime concern.

Scientifically backed triage of COVID-19 patients with careful stratification to handle the different severity of this disease in the right setup was the need of the hour. However, many risk stratification scores are proposed and adopted clinically along with an array of inflammatory markers to guide the management of severe COVID-19 patients in whom refractory hypoxemia remains a hallmark. Several characteristics have been associated with severe COVID-19 disease like advanced age, comorbidities, duration of symptoms, and high levels of inflammatory markers (C-reactive protein (CRP), serum ferritin,

Corresponding author: Swapna Ramaswamy, e-mail: swapnar1209@gmail.com

lactate dehydrogenase (LDH), and D-dimer) thereby directing several therapeutic strategies to counter the cytokine storm. Many guidelines recommend repeated and constant monitoring of these inflammatory markers which is financially very exhausting. In any country, adequate utilization of existing resources is the key to effective management of any emergency. Hence, we aimed to determine the prognostic implications of the inflammatory markers (CRP, LDH, troponin-I, ferritin, and D-dimer) and their utility as mortality predictors in severe COVID-19 patients admitted to the ICU. We also aimed at studying the application of infections Consortium-Coronavirus Clinical Characterization Consortium score (ISARIC 4C mortality score) and if greater COVID-19 chest radiography score (on applying CARE score) at presentation translated to poor patient outcomes in due course.

MATERIAL AND METHODS

Study Design and Study Participants

This retrospective study was conducted at SDSD TRC and Rajiv Gandhi Institute of Chest Diseases, Bangalore from March 2021 to June 2021 after ethical clearance (PDCEC/01/33/2021-22). All real-time-polymerase chain reaction (RT-PCR)-positive COVID-19 patients who were aged above 18 years and admitted to the ICU of our hospital were included in the study. Patients with COVID-like illness (RT-PCR-negative) though managed on similar lines were excluded from the study.

Data Collection

Data from 202 patients who were admitted to ICU during our study period were retrieved and thoroughly scrutinized. Demographic characteristics like age, sex, and clinical data including co-morbidities, symptoms, and duration of symptoms were collected and tabulated.

Baseline hematological investigations like a complete blood picture, renal and liver function tests, serum electrolytes, and arterial blood gas analysis were recorded. Neutrophil lymphocyte ratio and peripheral capillary oxygen saturation / fraction of inspired oxygen (SPO_2/FIO_2) ratio were computed.

MAIN POINTS

- Age more than 50 years, peripheral oxygen saturation/ fraction of inspired oxygen ratio of less than 200, mean symptom duration of >4 days, elevated serum lactate dehydrogenase (LDH) (>398.5 IU/L), and hypoalbuminemia (<2.95 g/dL) were found to be independent predictors of mortality in severe COVID-19 pneumonia.
- International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium score has good prognostic utility and can be used in all levels of healthcare.
- COVID-19 chest radiography score on a chest x-ray had no significant impact on mortality.
- The sensitivity and specificity of serum LDH at cut-off value of 398.5 IU/L in predicting mortality were 71% and 68%, respectively. At a cut-off of <2.95 g/dL, serum albumin has a sensitivity of 68.6% and specificity of 56.8%.

Baseline inflammatory markers panel included serum CRP, serum LDH, troponin-I, ferritin, and D-dimer. In addition, sputum bacterial culture reports were also recorded.

A chest x-ray (CXR) at baseline was assessed for severity using the validated CARE score. Two pulmonologists with 8 and 4 years of experience performed the chest x-ray scoring. The International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium (ISARIC-4C) score was assigned to each patient to clinically identify those at a higher risk of having poor outcomes. This risk stratification was done within 24 hours of ICU admission. The treatment protocol followed was strictly in adherence to the Karnataka state guidelines and the same was documented. All patients had received remdesevir, steroids, and anticoagulants along with other supportive measures for appropriate duration. The primary outcome studied was in-hospital mortality. The need for non-invasive ventilator (NIV), invasive mechanical ventilator (IMV), and length of stay in the hospital were other surrogate parameters that were looked for as secondary outcomes.

Operational Definitions

Severe COVID-19 pneumonia was defined as per National guidelines issued by the Ministry of health and family welfare, Government of India.[5] COVID-19 infection diagnosed on the basis of positive RT-PCR testalong with the presence of one of the below characteristics—SPO_2 <90% at room air, respiratory rate of more than 30, or presence of severe respiratory distress.

International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium was calculated using the following variables: age, gender, number of co-morbidities, respiratory rate, SPO_2 at room air, Glasgow coma scale score, blood urea, and serum creatinine. Scores were assigned for each variable at the time of admission and the total score was calculated. International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium ranges from 0 to 21with risk groups defined as low (0-3), intermediate (4-8), high (9-14), and very high (≥15).[6]

COVID-19 chest radiography score: To calculate CARE score, each lung was divided into 3 zones. Scores were given separately for the presence of ground-glass opacities (GGO) and consolidation depending on the proportion of the zones affected.[7]

Statistical Analysis

Data were entered in Microsoft excel and were analyzed using Statistical Package for Social Sciences (SPSS) version 24.0 (IBM Corp.; Armonk, NY, USA). Proportion, mean, and standard deviation (SD) were used wherever necessary to describe the population. The comparison of demographics and clinical data between survivors and non-survivors was calculated using chi-square test for categorical variables and *t*-test for continuous variables. Univariate analysis was done to get odds ratio. Those with $P < .2$ were included in the multivariate regression analysis to find adjusted odds ratio. $P < .05$ was considered significant.

RESULTS

Demographic Characteristics

Out of total of 820 COVID-19 cases admitted to our hospital during the specified study period, 202 patients had severe COVID-19 pneumonia mandating ICU management. The mean age was 52 years with a male predominance [129; 63.9%] (Table 1). Older age strongly correlated with mortality (P = .02), whereas gender did not (Table 1).

Clinical Characteristics

Fever was the most common presenting symptom (168; 83.16%) followed by dyspnea (165; 81.68%) and fatigue (145; 71.7%) (Table 1). Co-morbidities were present in 141 patients (73.76%) of which diabetes mellitus was the commonest (118; 58.41%) (Table 1). We observed no statistically significant effect of co-morbidity on mortality (Table 1). The mean duration of symptoms before hospitalization was 5.95 days (SD=3.69) (Table 1).

International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium Risk Stratification

As per ISARIC-4C score, 83 patients (41.08%) were categorized into intermediate risk group, 80 patients (39.60%) to high risk, 8 (3.96%) to very-high risk, and 2 to low-risk group (0.9%).There was a significant correlation between risk stratification with mortality (P = .057) (Table 2).

Radiological Characteristics

Chest radiograph of these patients revealed lower-zone predilection of either GGO or frank consolidation in all cases (202; 100%). Mid-zone involvement was present in 196 cases (97.02%) and 135 patients (66.83%) had upper-zone involvement as well. The mean CARE score of survivors and the deceased was 20.64 (7.85) and 21.21 (7.64), respectively. There was no statistically significant difference in the mean CARE score among survivors and non-survivors (Table 2).

Table 1. Baseline Demographic and Clinical Characteristics of Severe COVID-19 Patients Admitted to Intensive Care Unit

Variables	Total (n = 202)	Survived (n = 91)	Death (n = 111)	*P**
Age [years]; mean (SD)	52.0 (13.97)	49.65 (15.43)	54.36 (13.14)	**.02**
Male, n [%]	129 (63.9)	53 (58.2)	76 (68.5)	.132
Female	73 (36.1)	38 (41.8)	35 (31.5)	
Symptoms, n (%)				
Dyspnea	165 (81.68)	76 (83.5)	89 (80.2)	.542
Fever	168 (83.16)	75 (82.4)	93 (83.8)	.796
Fatigue	144 (71.3)	70 (76.9)	74 (66.7)	.109
Dry cough	94 (46.53)	38 (41.8)	56 (50.5)	.218
Productive cough	88 (43.56)	44 (48.4)	44 (39.6)	.214
Headache	14 (6.9)	6 (6.6)	8 (7.2)	.864
Loss of appetite	14 (6.9)	8 (8.8)	6 (5.4)	.126
Sore throat	9 (4.4)	4 (4.4)	5 (4.5)	.745
Chills	15 (7.4)	9 (9.9)	6 (5.4)	.226
Vomiting	6 (3.0)	3 (3.3)	3 (2.7)	.805
Diarrhea	6 (3.0)	2 (2.2)	4 (3.6)	.558
Chest pain	5 (2.4)	1 (1.1)	4 (3.6)	.121
Altered sensorium	4 (2.0)	0 (0)	4 (3.6)	.051
Hemoptysis	4 (2.0)	1 (1.1)	3 (2.7)	.416
Loss of taste	3 (1.4)	3 (3.3)	0 (0)	.054
Mean duration of symptoms before hospitalization [SD]	5.95 [3.69]	5.88 [3.144]	6.01[4.107]	.804
Comorbidities [n]	149 (73.76)	65 (71.4)	84(75.7)	.495
Diabetes	118 (58.4)	50 (54.9)	68 (61.3)	.365
Hypertension	61 (30.19)	28 (30.8)	32 (28.8)	.764
Chronic lung disease	27 (13.36)	14 (15.4)	13 (11.7)	.445
Heart disease	19 (9.4)	10 (11.0)	9 (8.1)	.485
Obesity	3 (1.4)	1 (1.1)	2 (1.8)	.210
Hypothyroidism	12 (5.9)	7 (7.7)	5 (4.5)	.340
Old cerebro vascular accident	6 (2.9)			

SD, standard deviation.
*P-value is statistically significant.

Table 2. Baseline Risk Stratification and Course in the Hospital of Severe COVID-19 Patients Admitted to Intensive Care Unit

Variables	Total (n = 202)	Survived (n = 91)	Death (n = 111)	*P**
Risk stratification applying ISARIC 4C score [n]				
Low risk	2 (1.2)	1 (1.1)	1 (1.3)	**.057**
Intermediate risk	83 (48)	47 (58.8)	36 (38.7)	
High risk	80 (46.2)	30 (37.5)	50 (53.8)	
Very-high risk	8 (4.6)	2 (2.5)	6 (6.5)	
CARE score, mean [SD]	20.96 (7.7)	20.65 (7.85)	21.22 (7.64)	.604
Complications [n]	**77 (38.11)**	19 (20.87)	58 (52.25)	**<.0001**
Mean duration of ICU stay [SD]	6.87 [5.88]	6.98 [5.829]	6.48 [5.995]	.55
Mean duration of hospital stay [SD]	19.18 [9.508]	24.2 [8.54]	15.07 [8.225]	**<.001**

ISARIC 4C, International Severe Acute Respiratory and emerging infections Consortium—Coronavirus Clinical Characterization Consortium score; SD, standard deviation. *P* Value in bold indicates its statistical significance.
**P*-value is statistically significant.

Clinical Course in Hospital

Although most of the patients in ICU required NIV support (122; 60.39%) and high-flow nasal cannula (70; 34.65%), only 36 of them (17.82%) eventually mandated IMV support, of whom none survived. The mean duration of ICU and hospital stay was 6.87 ± 5.88 and 19.18 ± 9.5, respectively. Complications were noted in 77 patients with secondary bacterial infection being the commonest (41; 20.29%). The frequently isolated microorganisms were Klebsiella species and coagulase-negative staphylococcus and streptococcus viridians. Other encountered complications were sepsis (20; 9.9%) acute kidney injury (14; 6.9%), diabetic ketoacidosis (7; 3.4%), hypokalemia (4; 1.9%), cerebrovascular accident (3; 1.4%), subacute emphysema with pneumo-mediastinum (2; 0.9%), pneumothorax (1; 0.4%), pulmonary thromboembolism (2; 0.9%), myocardial infarction (1; 0.4%), supraventricular tachycardia (1; 0.4%), and delirium (2; 0.9%). Complications were significantly more among the deceased than survivors (Table 2).

Outcome

The overall mortality was 54.9% (111 cases). Most deaths were observed within 7 days of hospitalization (64; 57.65%) and 29 patients (29.62%) succumbed between 7 and 14 days and 18 patients (16.21%) after 14 days of hospitalization. The mean duration of hospitalization among discharged was 24.2 ± 8.5 days and 28 patients (30.07%) were discharged with short-term oxygen therapy.

Mortality Predictors

On multivariate regression analysis, we found that age of more than 50 years, more than 4 days of symptoms, SPO_2/FIO_2 ratio less than 200, elevated serum LDH, and hypoalbuminemia are the independent predictors of mortality in severe COVID-19 pneumonia (Table 3). The cut-off value of 398.5 IU/L sensitivity and specificity of serum LDH in predicting mortality was 71% and 68%, respectively. For serum albumin as a mortality predictor, with a cut-off of <2.95, a sensitivity of 68.6% and a specificity of 56.8% were noted (Figure 1).

DISCUSSION

The severity of COVID-19 and mortality is influenced by multiple factors like genetics, individual immune response, co-morbidities, type of variant causing the disease, and demographic characteristics of the affected population. The management of COVID-19 has evolved since the beginning of the pandemic and has greatly influenced the mortality rate. Advanced age, smoking, male sex, lymphocytopenia, D-dimer, CRP, co-morbidities, SPO_2/FIO_2 ratio, and serum LDH are a few reported mortality predictors.[8-10] Wide heterogeneity in mortality predictors that are reported by several multivariate analyses from different countries can be observed. Of these diverse variables, advanced age is the single most variable that is consistently reported to have prognostic utility. Advanced age (>60 years) has been shown to behave as an independent mortality predictor in several studies.[9,10] Decreased immunity in elderly secondary to reduced T-cell subset and increased cytokine storm render them prone to severe disease. In our study, it was observed that age more than 50 years acted as an independent mortality predictor as enumerated in Table 3, a finding that resonates with the available evidence.[11,12]

Some studies have proposed male gender as a risk factor for higher mortality[13-15] On the contrary, we failed to notice any such association and our findings are consistent with few other studies.[9,16]

The presence of comorbidities is reported to increase the mortality by 2.85-fold.[9,17] Diabetes , hypertension, and cardiovascular conditions are the most commonly associated co-morbidities with increased mortality.[9,13] However, in our study, no such association was encountered.

A delay in access to healthcare facility especially in times of imposed lockdown was a major concern in COVID-19 management. The mean duration of symptoms of more than 4 days was significantly associated with mortality in our study as depicted in Table 3. Another Indian study has reported

Table 3. Multivariate Regression Analysis of Variables Associated with Mortality in Severe COVID-19 Pneumonia Patients

		Survived	Died	OR (95%CI)	aOR (95%CI)	*P*
Age	<50 years	46 (50.5)	41 (36.9)	-	-	.03
	>50 years	45 (49.5)	70 (63.1)	1.74 (0.9-3.1)	1.99 (1.1-3.6)	
Sex	Male	53 (58.2)	76 (68.5)	-	-	.27
	Female	38 (41.8)	35 (31.5)	0.64 (0.3-1.1)	0.6 (0.3-1.3)	
Comorbidities	No	26 (28.6)	27 (24.3)	-	-	-
	Yes	65 (71.4)	84 (75.7)	1.24 (0.6-2.3)	-	
Duration of symptoms	<4 days	36 (39.6)	52 (46.8)	-	-	.04*
	>4 days	55 (60.4)	59 (53.2)	0.74 (0.4-1.3)	0.5 (0.2-0.9)	
SPO_2/FIO_2	>2	48 (52.7)	32 (28.8)	-	-	.01*
	<2	43 (47.3)	79 (71.2)	2.75 (1.5-4.9)	2.28 (1.1-4.3)	
ISARIC 4C score	<3	1 (1.1)	1 (0.9)	-	-	-
	>3	90 (98.9)	110 (99.1)	1.2 (0.7-19.8)	-	
CARE score	<13	18 (19.8)	20 (18.0)	-	-	-
	>13	73 (80.2)	91 (82.0)	1.12 (0.5-2.2)	-	
N/L		8.53 (6.5)	10.5 (7.5)	1.04 (1.0-1.1)	1.02 (0.9-1.1)	.21
ESR		66.8 (44.5)	55.9 (48.3)	0.99 (0.9-1.1)	-	-
Serum albumin		3.17 (0.9)	2.78 (1.2)	0.72 (0.5-0.9)	0.64 (0.4-0.8)	.005*
Serum CRP		98.23 (83.1)	110.3 (88.2)	1.01 (0.9-1.1)	-	-
D-Dimer		810.7 (1224.7)	1307.4 (2335.2)	1.1 (1.0-1.2)	1.1 (0.9-1.2)	.6
Trop I		0.477 (0.199)	0.1157 (0.524)	1.79 (0.5-5.6)	-	-
Serum LDH		386.57 (251.1)	509.2 (306.6)	1.1 (1.0-1.2)	1.1 (0.9-1.2)	.04*
Serum ferritin		527.28 (546.5)	587.65 (563.3)	1.1 (1.0-1.2)	-	-
AST		48.02 (31.6)	48.3 (38.6)	0.99 (0.9-1.1)	-	-
ALT		38.9 (26.6)	35.7 (34.5)	0.98 (0.8-1.1)	-	-

aOR, adjusted odds ratio; ALT, alanine transaminase; AST, aspartate transaminase; CARE score, COVID-19 chest radiography score; CRP, C-reactive protein; ISARIC 4C, International Severe Acute Respiratory and emerging infections Consortium—Coronavirus Clinical Characterization Consortium score; LDH, lactate dehydrogenase; L/N, neutrophil/lymphocyte; SPO_2/FIO_2, peripheral oxygen saturation-fraction of inspired oxygen; Trop I, troponin I.
**P*-value is statistically significant.

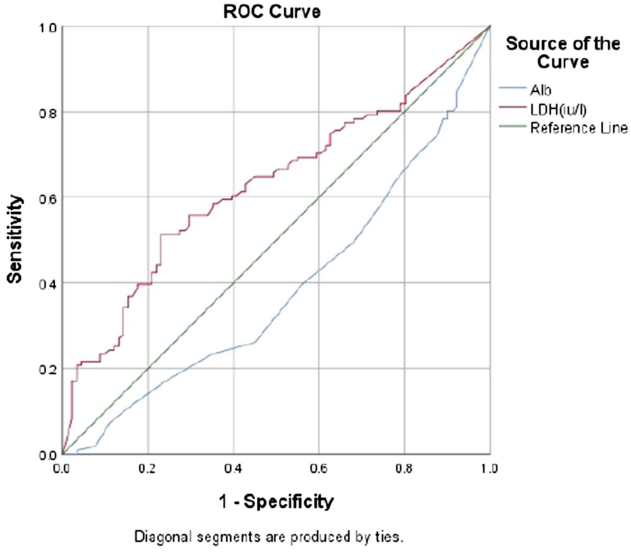

Figure 1. Receiver operating charactestic curve (ROC) of predictors of mortality.

higher mortality in those individuals who present to hospital after 4 days of symptom onset.[13]

Peripheral oxygen saturation/fraction of inspired oxygen ratio is a proxy indicator of oxygenation which can be used as a surrogate of PaO_2/FiO_2 (PaO_2-arterial oxygen pressure) ratio in resource-limited countries. Rice et al[18] observed significant correlation of SpO_2/FiO_2 ratio of 235 and 315 with PaO_2/FiO_2 ratio of 200 and 300, respectively. In our study, a SpO_2/FiO_2 ratio of <200 at admission was found to be an independent mortality predictor as shown in Table 3. Choi [19] reported increased mortality in those with a SpO_2/FiO_2 ratio of <315 at admission. Another study reported an S/F ratio of <400 as an independent predictor of mortality.[13] In resource-limited countries where management of moderate to severe COVID-19 patients is done at every level of health care, this simple non-invasive variable can replace PaO_2/FIO_2 as a mortality predictor.

International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization

Consortium score, a mortality predictor score developed and validated on the UK population, has been shown to have good applicability in other population as well.[20] This simple and easy to calculate score categorizes patients into 4 categories of severity by combining readily available variables upon admission. It reflects patient's demography, comorbidities, physiological characteristics, and lab investigations with the mortality increasing with each category. The mortality rate was 62% with a score of 15 and 1% with a score of 3 or less in the UK population.[6] After its initial development, several studies were conducted to assess its external validity and reported similar results as the original study.[21-23] International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium score of >9 had sensitivity and specificity of 70.5% and 73.97%, respectively, in predicting mortality as reported by Mumtaz et al.[20] We also observed a statistically significant increase in mortality with higher risk strata as enumerated in Table 2. To the best of our knowledge, this is the first time the ISARIC-4C score has been used to stratify the risk of mortality in COVID-19 patients in India.

Several pre-existing scores have been used and compared to determine the most reliable score to predict the mortality risk in COVID-19 patients. Fan et al[24] in 2019 retrospectively evaluated the role of existing scores in predicting mortality in COVID-19 patients and concluded that the A-DROP score [age, dehydration, respiratory failure, orientation disturbance, and systolic blood pressure] which is a modification of the CURB-65 [confusion, urea, respiratory rate, blood pressure, age] score performed better when compared to CURB-65, PSI [pneumonia severity index], SMART-COP [systolic blood pressure, multi-lobar CXR involvement, albumin, respiratory rate, tachycardia, confusion, oxygen saturation, pH], NEWS2 [National early warning score], CRB-65 [confusion, respiratory rate, blood pressure], and qSOFA [quick sequential Organ failure assessment] for in-hospital death. Age, dehydration, respiratory failure, orientation disturbance, systolic blood pressure presented the highest discrimination (area under curve [AUC] = 0.87) followed by CURB-65 (AUC = 0.85), PSI (AUC = 0.85), SMART-COP (AUC = 0.84), NEWS2 (AUC= 0.85), CRB-65 (AUC=0.80), and qSOFA (AUC =0.73) in predicting in-hospital death, though the difference between A-DROP and CURB-65 and PSI was not significant.[24]

In 2020, the prognostic utility of ISARIC-4C score in all cohorts (n = 606) of community-acquired pneumonia (CAP), invasive pneumococcal disease (IPD), COVID-19 infection, and other fatal common respiratory infections was looked at and its performance was compared to the already existing scores CURB65, CRB65, qSOFA, and NEWS and found that the ISARIC-4C score had the greatest AUC in COVID 19, CAP, and IPD patients (0.83, 0.78, and 0.74, respectively) and found that it was the only score that performed statistically significantly better than chance across all 4 cohorts. They concluded that the ISARIC-4C score performed well in predicting 30-day mortality in COVID-19 and other common respiratory infection populations in comparison to other scores.[25]

In another study on 481 patients by Doğanay and Ak[26] in 2021, CURB-65, ISARIC-4C, and COVID-GRAM scores were assessed and compared in terms of predicting in-hospital mortality and ICU requirement in patients hospitalized with COVID-19 disease. In terms of in-hospital mortality, the AUC of CURB-65, ISARIC-4C, and COVID-GRAM were 0.84, 0.78, and 0.70 respectively, whereas, for ICU requirement, it was 0.89, 0.79, and 0.68, respectively. Confusion, urea, respiratory rate, blood pressure, age-65 score was concluded to perform better in predicting in-hospital mortality and ICU requirement in COVID-19 patients, whereas the ISARIC-4C score was found to be successful in identifying low-risk patients.

In another large study by Artero et al[27] on 10 238 patients, 3 scores were tested for their prognostic accuracy. A new score (MuLBSTA based on 6 parameters—multilobar infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hypertension, and age) was tested against the other scores (PSI, CURB-65, qSOFA,), and the authors concluded that PSI and CURB-65 as specific severity scores for pneumonia were better than qSOFA andMuLBSTA at predicting mortality in patients with COVID-19 pneumonia.

On the same line, when APACHE II [acute physiology and chronic health evaluation], CURB-65, and MuLBSTA scores were evaluated on 53 COVID patients, it was found that APACHE II performed better than the other 2 scores in predicting the severity, whereas the MuLBSTA was recommended to be used to determine the death risk.[28]

In resonation with above findings, in another retrospective study on 249 patients, the ISARIC-4C score calculated upon admission to the hospital was compared to the simplified acute physiology score (SAPS), APACHE II, and sequential organ failure assessment (SOFA) calculated upon admission to the ICU. The accuracy of the mortality risk scores was calculated for ICU survivors and ICU non-survivors. The authors concluded that the APACHE II had the best discrimination of mortality in ICU patients and both APACHE II and ISARIC-4C score independently predicted mortality risk and could be used concomitantly.[29]

Though CXR is less sensitive than computed tomography thorax in detecting early changes of COVID-19 pneumonia, it has been proposed to be invaluable in predicting mortality. Few studies have suggested a significant correlation between increased lung involvement on CXR and mortality.[30,31] We attempted to study the same by using the validated CARE score. Each lung was divided into 3 zones (6 in total) and a separate score was assigned to GGO and consolidation. COVID-19 chest radiography score of 17.5 showed 75% sensitivity and 69.9% specificity in predicting mortality.[7] However, we did not notice any statistically significant difference in CARE score among survivors and non-survivors.

Lactate dehydrogenase, an intracellular enzyme, is present in almost all tissues. Multiorgan injury, hypoxia, tissue hypo perfusion, metabolic acidosis, and severe infections can cause elevation in serum LDH. As severe COVID-19 pneumonia is characterized by all of the above, an increase in serum LDH is an expected lab parameter. Elevation of serum LDH at the time of admission is known to have an association with severe COVID and more than 16-fold increase in odds of

mortality.[32] Poor prognosis in those with elevated LDH has been observed in several studies.[33-35] Lactate dehydrogenase has also been identified as a prognostic marker in COVID-19 with positive correlation of time to normalization of serum LDH with radiological resorbtion.[36] In our study, elevated LDH at the time of admission was an independent mortality predictor with value of >398.5 has sensitivity and specificity of 71% and 68%, respectively. Martha et al[37] reported sensitivity and specificity of LDH in predicting mortality as 74% and 69%, respectively. No other inflammatory markers showed any association with mortality in our study (Table 3). As the elevation of inflammatory markers is influenced by multiple factors like severity of disease, presence of comorbidities, different laboratory cut-off points, and variation in laboratory diagnostic methods, heterogeneity in findings can be expected.

Hypoalbuminemia has been observed in severe COVID-19 infection. Increased albumin clearance, consumption of amino acids by viral replication, reduced albumin transcription, and impaired liver protein synthesis are plausible mechanisms explaining hypoalbuminemia in severe COVID-19 infection.[38] We observed hypoalbuminemia as an independent mortality predictor. Huang et al[38] reported an albumin level of <35 g/L at admission as an independent predictor of mortality and also observed increased risk of death by 6-fold in those with hypoalbuminemia. Serial monitoring of serum albumin also has prognostic significance. Improvement in serum albumin has been noted with recovery.[39] However, therapeutic benefits of serum albumin transfusion in severe COVID-19 are still not established.[39]

Our study describes various clinical, demographic, and laboratory predictors of mortality in severe COVID-19 pneumonia. We hope that the findings from our study help in proper prognostication and guide healthcare services to properly utilize resources on salvageable patients. However, our study has some limitations. Data were collected only at the time of hospital admission based on the patient's medical records and some variables were not available. Since it was a retrospective single-center study, selection bias was a major concern.

CONCLUSION

Age of more than 50 years, SpO_2/FiO_2 ratio of less than 200, mean symptom duration of >4 days, elevated serum LDH, and hypoalbuminemia were all independent predictors of mortality in severe COVID-19 pneumonia. International Severe Acute Respiratory and Emerging Infections Consortium—Coronavirus Clinical Characterization Consortium score was different in the survivors and deceased. Given its easy application, optimal usage at all levels of healthcare facility at the time of admission can be done. However, the CARE score failed to demonstrate its prognostic performance.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Pranav Diagnostic Center Ethics Committe (ECR/1217/Inst/KA/2019) (Approval No: PDCEC/01/M33/2021-22).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.K.M.P., S.R., A.C., A.J.S.; Design – S.K.M.P., S.R., A.C., N.C.; Supervision – A.J.S., V.B., N.C.; Materials – S.K.M.P., S.R., A.C., A.J.S., N.C.; Data Collection and/or Processing – S.K.M.P., S.R., A.C.; Analysis and/or Interpretation – V.B., A.J.S., N.C., S.K.M.P.; Literature Review – S.K.M.P., S.R., A.J.S., A.C.; Writing – S.K.M.P., S.R., A.J.S.; Critical Review – N.C., V.B., A.J.S., S.R.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323(20):2052-2059. [CrossRef]; published correction appears in *JAMA*. 2020;323(20):2098. (https://doi.org/10.1001/jama.2020.7681)
2. Docherty AB, Harrison EM, Green CA, et al. Features of 20133 UK patients in hospital with Covid-19 using the ISARIC WHO Clinical Characterization Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985. [CrossRef]
3. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943. [CrossRef]; published correction appears in *JAMA Intern Med*. 2020;180(7):1031.
4. Asrani P, Eapen MS, Hassan MI, Sohal SS. Implications of the second wave of COVID-19 in India. *Lancet Respir Med*. 2021;9(9):e93-e94. [CrossRef]
5. *Revised Covid-19 Treatment for COVID-19 in India. Google Search*. Available at: https:\\covid19.karnataka.gov.in. Accessed November 19, 2020.
6. Knight SR, Ho A, Pius R, et al. Risk stratification of patients admitted to hospital with Covid-19 using the ISARIC WHO Clinical Characterization Protocol: development and validation of the 4C Mortality Score. *BMJ*. 2020;370:m3339. [CrossRef]; published correction appears in *BMJ*. 2020;371:m4334.
7. Giraudo C, Cavaliere A, Fichera G, et al. Validation of a composed COVID-19 chest radiography score: the CARE project. *ERJ Open Res*. 2020;6(4). [CrossRef]
8. Albalawi O, Alharbi Y, Bakouri M, et al. Clinical characteristics and predictors of mortality among COVID-19 patients in Saudi Arabia. *J Infect Public Health*. 2021;14(8):994-1000. [CrossRef]
9. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020:55(5). [CrossRef]; published correction appears in *Eurrespir J*. 2020;56(3).
10. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of Covid-19: systematic review and critical appraisal. *BMJ*. 2020;369:m1328. [CrossRef]; published correction appears in *BMJ*. 2020;369:m2204.
11. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol*. 2020;92(7):797-806. [CrossRef]
12. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. 2020;133(9):1025-1031. [CrossRef]
13. Mahendra M, Nuchin A, Kumar R, Shreedhar S, Mahesh PA. Predictors of mortality in patients with severe COVID-19 pneumonia - a retrospective study. *Adv Respir Med*. 2021;89(2):135-144. [CrossRef]

14. Jain AC, Kansal S, Sardana R, Bali RK, Kar S, Chawla R. A retrospective observational study to determine the early predictors of in-hospital mortality at admission with COVID-19. *Indian J Crit Care Med*. 2020;24(12):1174-1179. [CrossRef]
15. Kokturk N, Babayigit C, Kul S, et al. The predictors of COVID-19 mortality in a nationwide cohort of Turkish patients.*Respir Med*. 2021;183:106433. [CrossRef]
16. Pandita A, Gillani FS, Shi Y, et al. Predictors of severity and mortality among patients hospitalized with COVID-19 in Rhode Island. *PLoS One*. 2021;16(6):e0252411. [CrossRef]
17. Shi C, Wang L, Ye J, et al. Predictors of mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. *BMC Infect Dis*. 2021;21(1):663. [CrossRef]
18. Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO_2/FIO_2 ratio and the PaO_2/FIO_2 ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132(2):410-417. [CrossRef]
19. Choi KJ, Hong HL, Kim EJ. The association between mortality and the oxygen saturation and fraction of inhaled oxygen in patients requiring oxygen therapy due to COVID-19-associated pneumonia.*Tuberc Respir Dis (Seoul)*. 2021;84(2):125-133. [CrossRef]
20. Mumtaz SA, Shahzad SA, Ahmed I, et al. External validation of 4C ISARIC mortality score in the setting of a Saudi Arabian ICU. Retrospective study. *SSRN Journal*. 2021. [CrossRef]
21. Van Dam PMEL, Zelis N, van Kuijk SMJ, et al. Performance of prediction models for short-term outcome in COVID-19 patients in the emergency department: a retrospective study. *Ann Med*. 2021;53(1):402-409. [CrossRef]
22. Covino M, De Matteis G, Burzo ML, et al. Predicting in-hospital mortality in COVID-19 older patients with specifically developed scores. *J Am Geriatr Soc*. 2021;69(1):37-43. [CrossRef]
23. Verma AA, Hora T, Jung HY, et al. Characteristics and outcomes of hospital admissions for COVID-19 and influenza in the Toronto area. *CMAJ*. 2021;193(12):E410-E418. [CrossRef]
24. Fan G, Tu C, Zhou F, et al. Comparison of severity scores for COVID-19 patients with pneumonia: a retrospective study. *Eur Respir J*. 2020;56(3). [CrossRef]
25. Wellbelove Z , Walsh C, Perinpanathan T, Lillie P. Letters to the editor. *J Infect*. 2021;82:414-451.
26. Doğanay F, Ak R. Performance of the CURB-65, ISARIC-4C and COVID-GRAM scores in terms of severity for COVID-19 patients. *Int J Clin Pract*. 2021;75(10):e14759. [CrossRef]
27. Artero A, Madrazo M, Fernández-Garcés M, et al. Severity scores in COVID-19 pneumonia: a multicenter, retrospective, cohort study .*J Gen Intern Med*. 2021;36(5):1338-1345. [CrossRef]
28. Cheng P, Wu H ,Yang J, et al. Pneumonia scoring systems for severe COVID19: which one is better . *Virol J*. 2021;18(1):33. [CrossRef]
29. Vicka V , Januskeviciute E , Miskinyte S, et al. Comparison of mortality risk evaluation tools efficacy in critically ill COVID-19 patients. *BMC Infect Dis*. 2021;21(1):1173. [CrossRef]
30. Mushtaq J, Pennella R, Lavalle S, et al. Initial chest radiographs and artificial intelligence (AI) predict clinical outcomes in COVID-19 patients: analysis of 697 Italian patients. *Eur Radiol*. 2021;31(3):1770-1779. [CrossRef]
31. Al-Smadi AS, Bhatnagar A, Ali R, Lewis N, Johnson S. Correlation of chest radiography findings with the severity and progression of COVID-19 pneumonia. *Clin Imaging*. 2021;71:17-23. [CrossRef]
32. Henry BM, Aggarwal G, Wong J, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. *Am J Emerg Med*. 2020;38(9):1722-1726. [CrossRef]
33. Huang Y, Lyu X, Li D, et al. A cohort study of 676 patients indicates D-dimer is a critical risk factor for the mortality of COVID-19. *PLOS ONE*. 2020;15(11):e0242045. [CrossRef]
34. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol*. 2020;146(1):110-118. [CrossRef]
35. Ramos-Rincon JM, Buonaiuto V, Ricci M, et al. Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. *J Gerontol A Biol Sci Med Sci*. 2021;76(3):e28-e37. [CrossRef]
36. Wu MY, Yao L, Wang Y, et al. Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-19) pneumonia. *Respir Res*. 2020;21(1):171. [CrossRef]
37. Martha JW, Wibowo A, Pranata R. Prognostic value of elevated lactate dehydrogenase in patients with COVID-19: a systematic review and meta-analysis. *Postgrad Med J*. 2022;98(1160):422-427. [CrossRef]
38. Huang J, Cheng A, Kumar R, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *J Med Virol*. 2020;92(10):2152-2158. [CrossRef]
39. Xu Y, Yang H, Wang J, et al. Serum albumin levels are a predictor of COVID-19 patient prognosis: evidence from a single cohort in Chongqing, China. *Int J Gen Med*. 2021;14:2785-2797. [CrossRef]