ORIGINAL ARTICLE

Analysis of Predictors and Outcomes of COVID-19 Patients Requiring ICU Admission from COVID-19 Registry, India

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Abstract

Background: Patients admitted to intensive care units (ICUs) with severe coronavirus disease (COVID-19) are associated with high mortality. The present retrospective, multicenter study describes the predictors and outcomes of COVID-19 patients requiring ICU admission from COVID-19 Registry of Indian Council of Medical Research (ICMR), India.

Materials and methods: Prospectively collected data from participating institutions were entered into the electronic National Clinical Registry of COVID-19. We enrolled patients aged >18 years with COVID-19 pneumonia requiring ICU admission between March 2020 and August 2021. Exclusion criteria were negative in RT-PCR report, death within 24 hours of ICU admission, or incomplete data. Their demographic and laboratory variables, ICU severity indices, treatment strategies, and outcomes were analyzed.

Results: A total of 5,865 patients were enrolled. Overall mortality was 43.2%. Non-survivors were older (58.2 ± 15.4 vs 53.6 ± 14.7 years; $p = 0.001$), had multiple comorbidities (33.2% vs 29.5%, $p = 0.001$), had higher median D-dimer (1.56 vs 1.37, $p = 0.015$), higher CT severity index (16.8 ± 5.2 vs 13.5 ± 5.47, $p = 0.001$) and longer median hospital stay (10 vs 8 days, $p = 0.001$) and ICU stay (5 vs 4 days, $p = 0.001$), compared with survivors.

On multivariate analysis, high CRP (HR 1.008, 95% CI: 1.006–1.010, $p = 0.001$) and high D-dimer (HR 1.089, 95% CI: 1.065–1.113, $p < 0.001$) were associated with invasive mechanical ventilation while older age (HR 1.19, CI: 1.001–1.038, $p = 0.039$) and high D-dimer (HR-1.121, CI: 1.072–1.172, $p = 0.001$) were independently associated with mortality and while the use of prophylactic low molecular weight heparin (LMWH) (HR 0.647, CI: 0.527–0.794, $p = 0.001$) lowered mortality.

Conclusion: Among 5,865 COVID-19 patients admitted to ICU, mortality was 43.5%. High CRP and D-dimers were independently associated with the need for invasive mechanical ventilation while older age and high D-dimer were associated with higher mortality. The use of prophylactic LMWH independently reduced mortality.

Keywords: COVID-19, COVID-19 registry, ICU patients, Outcome.

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Highlights

- This study aims to describe the predictors and outcomes of COVID-19 patients requiring ICU admission in a large cohort of patients from multiple centers across India.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected approximately 225,024,781 persons, and claimed 4,636,153 lives till January 31, 2022.[1] The overall mortality in intensive care units (ICUs) reported worldwide is approximately 40–50%.[2] The first case of COVID-19 was reported on January 27, 2020 in India.[3] The Indian Council of Medical Research (ICMR) initiated a National Clinical Registry of COVID-19 to prospectively collect demographic, clinical, biochemical, radiological, therapeutic, and outcome data of patients admitted to hospitals across India. As of February 2022, 4.5 crore patients have been tested positive for COVID-19 and around 500,000 deaths have been reported.[4] To date, the United States has reported the maximum number of cases and deaths followed by Brazil and India.

The mortality rate among hospitalized patients with COVID-19 has been estimated to be around 17% in a large meta-analysis of 42

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studies.[5] However, outcomes in critically ill patients remain poorly reported. Single-center studies from China and USA reported 53.8% and 39% mortality, respectively, among critically ill patients.[6–8] In the COVID-ICU study from Europe, the investigators found an overall mortality of 31% among 4,315 ICU patients and a mortality of 37% in patients on mechanical ventilation.[2] There was a wide variation in the mortality rates reported from India. Non-survivors accounted for 53% of the ICU admission in the study by Kerai et al.[9] and 26.1% by Zirpe et al.[10] Various studies across the world have reported both early and late predictors of mortality. The common predictors included higher age, BMI, SOFA scores, D-dimer, and lower PaO_2 to FiO_2 ratio.[2,11,12] Few Indian studies have also analyzed predictors of mortality of which male gender, increasing CT score, and need for mechanical ventilation were the prominent ones.[10]

Most data from India are single-center retrospective analyses with a limited collection of therapeutic strategies and critical analyses of survival.[10] The primary aim of this study was to analyze the characteristics and outcomes of patients admitted to various ICUs across India. We also investigated predictors of poor outcomes, the utility of therapeutic strategies, and factors predisposing to invasive mechanical ventilation in patients with COVID-19.

Materials and Methods

Study Population and Settings

We analyzed the data of critically ill patients with COVID-19 admitted to 53 ICUs across India between March 2020 to August 2021, as recorded in the National Clinical Registry of COVID-19 (NCRC). SARS-CoV-2 infection was confirmed by Real-Time Polymerase Chain Reaction (RT-PCR) assays performed on nasopharyngeal swabs. Inclusion criteria were adults aged >18 years admitted to ICU with confirmed infection based on RT-PCR testing. Exclusion criteria were negative RT-PCR results for COVID-19, patients dying within 24 hours of ICU admission, or patients with incomplete data in the registry.

Outcomes

The primary outcome was to analyze the demographic, clinical, biochemical, imaging, and severity characteristics of patients with severe COVID-19 pneumonia and compare among survivors and non-survivors. Outcome measures, such as predictors of invasive ventilation and mortality along with ICU and hospital length of stay were incorporated in the analysis. The study was conducted according to the Declaration of Helsinki and ICMR-National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017.

Data Collection

Demographic details, medical history, laboratory results, radiological findings, vital parameters, treatment therapies (antivirals, steroids, immunomodulators, and organ support devices) in-hospital complications, and clinical outcomes of all patients admitted to ICU were entered in the ICMR COVID-19 Registry portal available on http://icmrcovidregistry.nic.in and maintained by ICMR-National Institute of Medical Statistics. All data were prospectively stored in electronic format and retrospectively analyzed.

Case Definition

Severe COVID-19 pneumonia was defined in patients presenting with fever, plus one of the following: respiratory rate >30 breaths/min, breathlessness, and oxygen saturation by pulse oximetry (SpO_2) < 90% on room air.[13] Critically ill patients included those who had severe pneumonia, shock, and organ dysfunction syndrome at admission or during the hospital stay.

Treatment Protocols

The Government of India (GOI)/ICMR guidelines were followed for treating patients admitted to ICU.[13] According to ICMR guidelines, oxygen therapy was titrated to target SpO_2 >92% with the use of oxygen delivery devices ranging from low-flow devices [nasal prongs, simple face mask), high-flow devices (venturi mask, high-flow nasal cannula (HFNC), noninvasive ventilation (NIV)] and invasive mechanical ventilation. Standard medical care including steroids, Remdesivir, and anticoagulation were administered as per the ICMR protocol. Supportive care for critically ill patients in the form of advanced hemodynamic monitoring, hemodynamic support, enteral nutrition, glycemic control, and stress ulcer prophylaxis was used in all eligible patients. Antibiotic and antifungal therapy were guided by cultures and sepsis markers. Renal replacement therapy and other supportive therapies/interventions were performed as per the clinical condition of the patients.

Statistical Methods

Descriptive statistics are expressed as mean with standard deviation (SD) for parametric data and median with interquartile range (IQR) for nonparametric continuous data. Categorical data are expressed as numbers (*n*, %). We used Student's *t*-test to compare the continuous data between the two groups. Furthermore, we used Pearson's Chi-square test or Fisher's exact test (as appropriate) to compare categorical data among the two groups. The main outcomes are reported as estimated effect sizes along with precision [95% confidence intervals (CIs)]. Binary logistic regression analysis was performed for the predictors of invasive mechanical ventilation and mortality. Kaplan–Meier overall survival curves until day 60 were computed and were compared using log-rank tests. Statistical significance was set at $p < 0.05$. All statistical tests were performed using SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA).

Results

A study flowchart is illustrated in Figure 1. Out of 29,509 patients entered in the National Clinical Registry of COVID-19 till August 2021, 5,978 patients were assessed for eligibility, and 113 patients were excluded due to insufficient data. Finally, 5,865 patients were included in the analysis, of whom 3,330 survived (58.8%) (Figure 1). The baseline demographic, clinical, laboratory, and radiological characteristics in the two groups are given in Table 1.

Comparison of Clinical and Laboratory Parameters of Survivor and Non-survivors

Non-survivors were significantly older in age as compared with survivors (58.2 ± 15.4 vs 53.6 ± 14.7 years, $p = 0.001$). Comorbidities,

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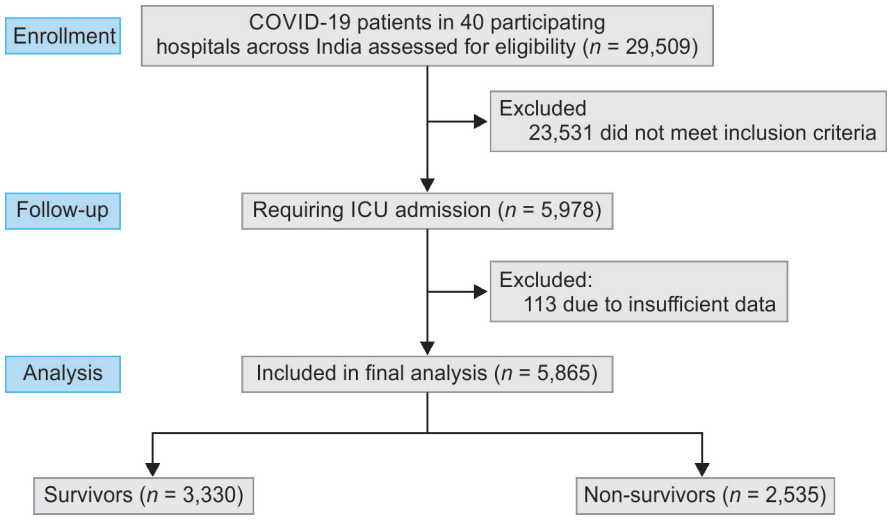


Fig. 1: Study flowchart

Table 1: Demographic, clinical, laboratory, and radiographic findings on admission of critically ill COVID-19 patients treated in ICU

Demographic and clinical characteristics	*All patients*	*Non-survivors*	*Survivors*	*p-value*
Outcomes	5,865	2,535 (43.2%)	3,330 (56.7%)	
Age,* (years)	55 ± 15.18	58.2 ± 15.4	53.61 ± 14.7	0.001
12–44 years	1,371 (23.3)	494 (19.5)	877 (26.3)	0.001
45–59 years	1,927 (32.8)	748 (29.5)	1,179 (35.4)	
>60 years	2,513 (42.8)	1,293 (51)	1,274 (38.2)	
Gender				
Males	3,840 (65.5)	1,670 (65.8)	2,170 (65)	0.404
Females	2,023 (34.4)	865 (34)	1,158 (34.7)	
Transgender	2 (0.1)	0	2	
BMI (kg/m^2) >25 (*n* %)	983 (16.8)	418 (16.4)	559 (17)	0.770
Comorbidity	3,687 (62.8)	1,951 (76.9)	1,736 (52.1)	0.001
Hypertension	2,303 (39.2)	1,087 (43)	1,216 (37)	0.818
Diabetes	1,967 (33.5)	896 (35)	1,071 (32)	0.434
Coronary artery disease	447 (7.6)	244 (10)	203 (6)	0.040
COPD	122 (2.0)	52 (2)	70 (2)	0.120
Chronic liver disease	63 (1.0)	42 (1.6)	21 (0.01)	0.02
Malignancy	55 (0.9)	28 (1)	27 (0.01)	0.571
Chronic kidney disease	312 (5.3)	171 (7)	141 (4)	0.394
Respiratory rate* (breaths/min)	23 ± 6.38	24.1 ± 6.2 (23.86–24.4)	23.7 ± 6.5 (23.52–24.06)	0.070
Heart rate* (*N* = 5,234)	94.8 ± 17.36	95.2 ± 17.1	94.56 ± 17.5	0.804
Blood pressure SBP*, mm Hg (*n* = 5,140)	127 ± 19	126.99 ± 18.5	127.54 ± 19.8	0.315
DBP*, mm Hg (*n* = 5,111)	79 ± 11.46	79.4 ± 11.2 (78.9–79.8)	79.4 ± 11.6 (79.0–79.9)	0.804
Symptoms				
Cough with sputum	900	546 (22)	354 (11)	0.001
Shortness of breath	3,985 (67.9)	2,132 (84)	1,853 (56)	0.023
Fever (Temp. ≥37.3°C)	3,719 (63.4)	2,166 (85)	1,553 (47)	0.413
Altered sensorium	145 (2.4)	96 (4)	49 (1)	0.001

Hemoglobin, gm/dL*(*N* = 3,812)	12.07 ± 2.03	12.1 ± 2.29	11.9 ± 2.32	0.010
Total leucocyte count, × 109 /L* (*N* = 3,773)	7.5 (6.6–14.3)	10.5 (6.9–14.4)	9.1 (6–14)	0.482
White blood cell count, × 109 /L (*N* = 3,840)				
< 4	253 (6.5)	92 (36.4%)	161 (63.3%)	0.061
4–10	1,622 (42.2)	718 (44.3%)	904 (55.7%)	
>10	1,898 (49.4)	823 (43.4%)	1,075 (56.6%)	
Neutrophil to lymphocyte ratio (*N* = 3,317)	7.5 (4.2–13)	7.5 (4.8–17.3)	7.5 (3.9–15)	0.942
Platelet count, × 109 per L (*N* = 3,745)	208 (154–277)	200 (141–265)	219 (150–280)	0.753
Bilirubin, mg/dL (*N* = 3,117)	0.6 (0.4–0.8)	0.68 (0.40–0.94)	0.70 (0.45–0.92)	0.711
Direct bilirubin	0.26 (0.19–0.46)	0.24 (0.16–0.40)	0.31 (0.20–0.41)	0.905
Albumin, g/dL (*N* = 2,520)	3.4 (3.0–3.7)	3.5 (3.1–3.9)	3.5 (3.2–3.9)	0.016
Creatinine, mg/dL (*N* = 3,330)	1 (0.9–1)	1.1 (0.8–1.62)	1.0 (0.8–1.6)	0.001
Lactate dehydrogenase, U/L (*N* = 1,989)	596 (408–843)	589 (377– 754)	519 (398–777)	0.515
D-dimer, µg/mL (*N* = 1,620)	1.26 (0.5–6.2)	1.56 (0.62–1.56)	1.37 (0.5–4.4)	0.015
Procalcitonin, (ng/mL) (*N* = 682)	0.32 (0.15–0.99)	0.23 (0.13–1.35)	0.33 (0.16–0.81)	0.437
<0.1	71 (10.4)	35 (5.1)	36 (5.2)	
≥0.1 to <0.25	200 (29.3)	101(14.8)	99 (14.5)	
≥0.25 to <0.5	144 (21.1)	63 (9.2)	71 (10.4)	
≥ 0–5	261 (38.2)	124 (18.18)	137 (20.1)	
Serum ferritin, ng/mL (*N* = 1,857)	641 (298–1062)	682 (399–1436)	609 (236–1289)	0.225
CRP, mg/L (*N* = 2,264)	77 (24–77)	69.05 (21.05–117.8)	36.7 (7.49–141.9)	0.248
<25	553 (24.4)	243 (10.7)	310 (13.6)	0.661
25–75	517 (22.8)	241 (10.6)	276 (12.1)	
>75	1,139 (50.3)	521 (23.1)	618 (27.2)	
PT, sec* (*N* = 1,518)	14.8 ± 4.79	14.86 ± 5.23 (14.47–15.24)	14.83 ± 4.45 (14.5–15.1)	0.929
INR (*N* = 1,556)	1.1 (1.02–1.27)	1.13 (1.00–1.25)	1.02 (1.00–1.27)	0.430
APTT , sec (*N* = 1,239)	29 (25–39)	26.8 (24.2–30)	30.8 (26.3–40.2)	0.597
CT severity score* (*N* = 604)	14.6 ± 5.5	16.8 ± 5.2	13.5 ± 5.47	0.001
<8	75 (12.4)	13 (2.1)	62 (10.2)	
8–15	244 (40.3)	52 (8.6)	192 (31.7)	
>15	285 (47.1)	139 (23.1)	146 (24.1)	

Data expressed as median (IQR), *n* (%). *data expressed as mean ± SD. *p*-values were calculated by Mann–Whitney *U* test, χ^2-test, or Fisher's exact test, as appropriate. APTT, activated partial thromboplastin time; BMI, body mass index; CRP,C-reactive protein; CT, computed tomography; DBP, diastolic blood pressure; HDU, high dependency unit; ICU, intensive care unit; INR, international normalized ratio; PT, prothrombin time; SBP, systolic blood pressure

such as hypertension, diabetes, coronary artery disease, and pulmonary disease were comparable in the two groups. Chronic liver disease was associated with a higher risk of mortality (66.7% vs 33.3%, $p = 0.020$, Table 1). Vital parameters, such as heart rate, respiratory rate, and blood pressure at admission were comparable. Non-survivors had significantly higher D-dimer (1.56 vs 1.36 µg/mL), higher CT severity score (16.8 ± 5.2 vs 13.5 ± 5.47, $p = 0.001$) at admission (Table 1).

Treatments and Outcomes

Survivors had shorter median hospital stays compared with non-survivors [8 (5–12) days vs 10 (6–15) days, $p = 0.001$]. Similarly, median ICU stay among survivors was significantly shorter in comparison to non-survivors [4(2–7) vs 5(3–10) days, $p = 0.001$]. Higher percentage of patients receiving dexamethasone (57% vs 51%, $p = 0.001$), remdesivir (58% vs 51%, $p = 0.008$), and low molecular weight heparin (LMWH) (44% vs 36%, $p = 0.001$) in the survivor

Table 2: Treatments and outcomes of critically ill COVID-19 patients treated in ICU

Outcomes	*All patients*	*Non-survivors (n = 2,535)*	*Survivors (n = 3,330)*	*p-value*
Duration of symptoms (in days)	5 (3–8)	5 (3–8)	5 (3–8)	0.120
Duration of hospital stay (in days) *n* = 5,865	9 (5–13)	10 (6–15)	8 (5–12)	0.001
Duration of ICU stay (in days)	7 (4–10)	5 (3–10)	4 (2–7)	0.001
Duration of HDU stay (in days)	1 (1–4)	3 (1–7.75)	1 (1–4)	0.001
Duration of ward stay (in days)	3 (1–6)	3 (2–6.5)	2 (1–3)	0.001
Time taken to resolution of major symptoms (in days)	7 (4–10)	8 (5–12)	7 (4–9)	0.001
Empiric antibiotics*	1,624 (73)	620 (24.5)	1,004 (30)	0.790
Remdesivir*	3,190 (89)	1,275 (50)	1,915 (58)	0.008
Dexamethasone*	3,152 (85)	1,445 (57)	1,707 (51)	0.001
Tocilizumab*	228 (9.5)	90 (3.5)	138 (4)	0.500
Prophylactic LMWH*	2,394 (41)	915 (36)	1,479 (44)	0.001
Therapeutic LMWH*	2,108 (36)	978 (39)	1,130 (34)	0.001
High-flow nasal cannula*	1,118 (64)	491 (19.3)	627 (19)	0.028
Noninvasive mechanical ventilation*	1,203 (20.5)	499 (20)	704 (21)	0.322
Invasive mechanical ventilation*	1,738 (29.6)	693 (11.8)	1,045 (31)	0.710
ECMO*	2 (0.03)	2	0	
Septic shock*	633 (10.7)	333 (13)	300 (9)	0.985
HAP*	389 (6.6)	170 (6.7)	219 (7)	0.165

Data expressed as median (IQR). *Data expressed as *n* (%). *p*-values were calculated by Mann-Whitney *U* test, χ^2-test or Fisher's exact test, as appropriate. COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HAP, hospital-acquired infection; HDU, high dependency unit; ICU, intensive care unit; LMWH, low molecular weight heparin

Table 3: Predictors of invasive ventilation and mortality using ROC analysis

Variable cut-off	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*p-value*
Predictor of invasive ventilation *(N* = 1,738*)*				
CRP (>75 mg/L)	0.73 (0.70–0.77)	77.3	65.9	<0.001
D-dimer (>1.5 ng/L)	0.75 (0.72–0.78)	74.0	63.0	<0.001
Ferritin (>500 ng/mL)	0.69 (0.65–0.72)	83.9	52.7	<0.001
Predictors of mortality (*N* = 2,535)				
Age (>55 years)	0.589 (0.574–0.604)	60.6	54	0.001
Hb (<11.7 mg/L)	0.527 (0.509–0.546)	62.2	42	0.004
RR (>22 breaths/min)	0.527 (0.509–0.546)	61.3	41	0.003
CTSI (>13.5)	0.681 (0.636–0.727)	77	49	0.001

AUC, area under the curve; CRP, C-reactive protein; CTSI, CT severity index; RR, respiratory rate

cohort. Two patients received ECMO, but none could survive. In hospital complications including septic shock, and hospital-acquired pneumonia were comparable (Table 2).

Predictors of Invasive Ventilation

On receiver operator characteristics (ROC) curves analysis (Table 3), the predictors of invasive mechanical ventilation were CRP >75 mg/dL (AUROC 0.73, sensitivity 77%, specificity 65.9%, $p < 0.001$), D-dimer >1.5 ng/L AUROC 0.75, sensitivity 77%, specificity 74%, $p < 0.001$), ferritin >500 ng/mL (AUROC 0.69, sensitivity 83.9%, specificity 52.7%, $p < 0.001$) (Table 3, Fig. 2).

On univariate analysis demonstrated, hemoglobin, NLR ratio, ESR, CRP, aPTT, creatinine, and ferritin were associated with invasive mechanical ventilation. On binary logistic regression analysis, higher CRP (HR 1.008, 95% CI: 1.006–1.010, $p < 0.001$) and D-dimer (HR 1.089, 95% CI: 1.065–1.113, $p < 0.001$) were associated with mechanical ventilation (Table 4).

Predictors of Mortality

On receiver operator characteristics curves analysis, the predictor of mortality was CTSI (CT severity index) >13.5 (AUROC 0.681, sensitivity 77%, specificity 49%, $p = 0.001$) and age >55 years (AUROC 0.589, sensitivity 60.6% specificity 54%, $p = 0.001$) (Table 3).

On univariate analysis depicted, age, use of dexamethasone, remdesivir, LMWH, creatinine, D-dimer, use of high-flow nasal cannula, and continuous positive airway pressure (CPAP) were associated with mortality. On binary logistic regression analysis, older age (HR 1.019, CI: 1.001–1.038, $p = 0.039$), high D-dimer (HR-1.121, CI: 1.072–1.172, $p < 0.001$) and use of prophylactic LMWH (HR 0.647, CI: 0.527–0.794, $p < 0.001$) were independently associated with mortality (Table 4).

Survival Analysis

Overall survival at day 60 was 58.8%. Patients with age >60 years (Fig. 3) and CT severity index >15 had lower survival at day 90 on Kaplan–Meier survival analysis (Fig. 4).

Discussion

This is one of the most extensive retrospective multicenter studies from India among COVID-19 patients who require ICU admission. The comprehensive information on their baseline characteristics and short-term mortality was analyzed from data obtained from the National Clinical Registry of COVID-19.

Overall mortality in our cohort was 43.2%, which is higher than the mortality rates reported from across the world. In the study by COVID-19 ICU group from Europe across 138 hospitals enrolling more than 4,000 critically ill patients,[2] the 90-day mortality reported was 31%. In contrast, the 60-day mortality was 61.5% in a multicentric study from China.[14] Gupta et al.[15] reported a mortality of 35.4% at 28 days among critically ill patients from the United States of America. The wide variations among different countries may be explained by the variability in the level of healthcare infrastructure, the burden of comorbid illness, and the restricted availability of effective therapeutic strategies at the early part of the pandemic. In our study, patients with multiple comorbidities have higher mortality rates, although when analyzed individually, only chronic liver disease was associated with poor outcomes. However, data were available for a minimal number of patients. Although data were available for a very small number of patients. Literature on the effect of comorbidities, especially on ICU patients, is scarce and conflicting. Petrilli et al.[16] found that age and comorbidities strongly predicted hospital admission and only a weak association was found with critical illness or death. However, the COVID-ICU group[2] found a significant correlation between diabetes, hypertension, and older age with mortality, not unlike our study.

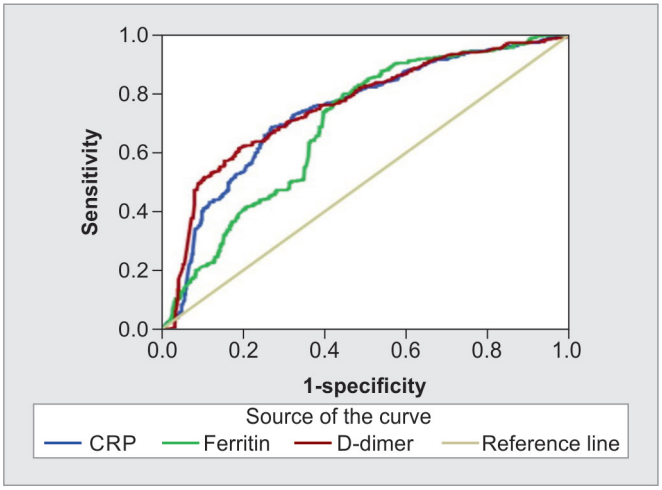


Fig. 2: ROC curve-prediction of invasive mechanics ventilation

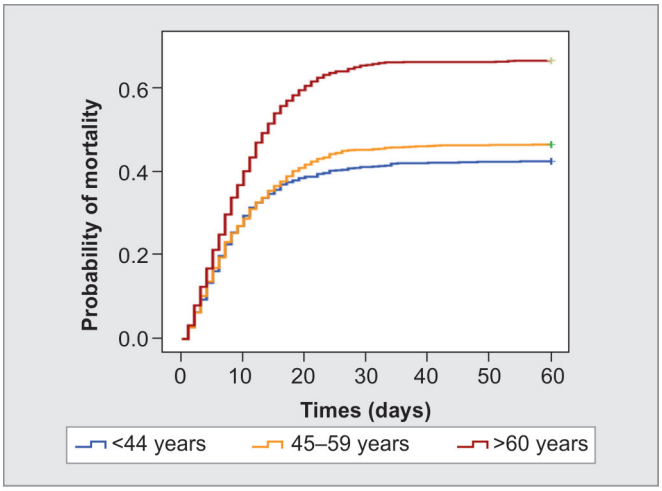
Among laboratory parameters, lower hemoglobin, low albumin, high D-dimers, and high creatinine were significantly more among non-survivors; however, only elevated D-dimer was found to be independently associated with mortality. COVID-ICU group[2] and many case series [7,17–20] also found D-dimers to be a significant contributor to mortality. This may reflect the underlying COVID-19-induced hypercoagulable state predisposing the patients to macro and microthrombosis of major organs, leading to multiorgan dysfunction and resultant mortality.

The elevated D-dimer warrants early administration of prophylactic anticoagulation to prevent the harmful effects of thromboembolism. Our study demonstrated better outcomes with prophylactic anticoagulation, while therapeutic anticoagulation was associated with increased mortality on univariate analysis. Although we did not have data regarding the bleeding/thromboembolic

Table 4: Results of binary logistic regression analysis

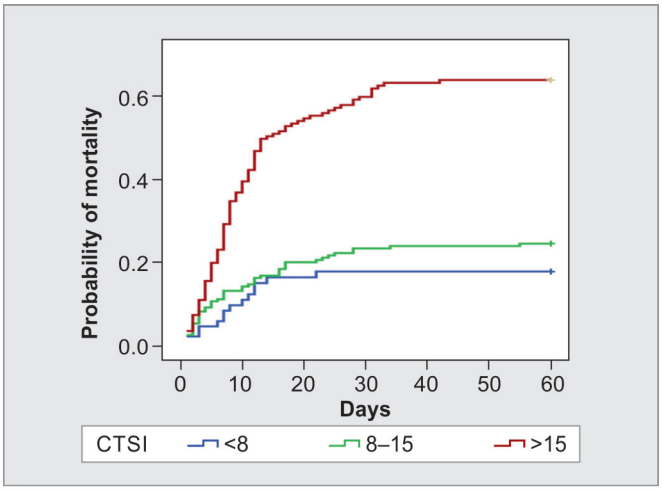
Predictors of invasive ventilation							
Univariable analysis				*Multivariate analysis*			
Parameter	*OR*	*95% CI*	*p-value*	*Parameter*	*Hazard ratio*	*95% CI*	*p-value*
Hemoglobin	0.97	0.94–1.00	0.056	CRP	1.008	1.006–1.010	<0.001
NLR	1.017	1.017–1.012	<0.001	D-dimer	1.089	1.065–1.113	0.000
ESR	1.011	1.008–1.015	<0.001				
CRP	1.005	1.004–1.007	<0.001				
aPTT	1.004	0.993–1.015	0.485				
Creatinine	1.106	1.06–1.15	<0.001				
Ferritin	1.001	1.00–1.001	<0.001				
Predictors of mortality							
Age	0.98	(0.97–0.98)	<0.001	Age	1.019	(1.001–1.038)	0.039
Use of dexamethasone	0. 63	(0.52–0.77)	<0.001	D-dimer	1.121	(1.072–1.172)	0.001
Use of remdesivir	0.71	(0.55–0.91)	0.008	Prophylactic LMWH	0.647	(0.527–0.794)	0.001
Prophylactic LMWH	0.71	(0.55–0.91)	<0.001				
Therapeutic LMWH	1.22	(1.09 –1.36)	<0.001				
HFNO	0.79	(0.65–0.97)	0.026				
CPAP	0.73	(0.57–0.92)	0.01				
Creatinine	1.08	(1.04–1.13)	0.001				
D-dimer	1.01	(1.0–1.03)	0.016				

AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; CPAP, continuous positive airway pressure CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HFNO, high-flow nasal oxygen NLR, neutrophil lymphocyte ratio



Age (years)	No. at risk	0	28	60
<44	1,342	1,305	889	876
45–59	1,881	1,829	1,196	1,180
>60	2,482	2,402	1,295	1,274

Fig. 3: Kaplan–Meier curve depicting probability of mortality with age



CTSI	No. at risk	0	28	60
<8	85	83	71	71
8–15	223	218	177	174
>15	274	265	152	144

Fig. 4: Kaplan–Meier curve depicting probability of mortality with CTSI

events, our results corroborate the finding of the ACTION trial that the use of therapeutic anticoagulation had no clinical benefit.[21]

Identifying the determinants of outcomes of critically ill patients is pertinent as this will help optimize the use of ICU care and other resources, especially in resource constraint countries like India. In our study, the predictors of mortality with acceptable sensitivity and specificity were age > 55 years, and CTSI > 13.5. Among these parameters, CTSI had the highest predictive accuracy. Tabatabaei et al.[22] have also reported CTSI as a predictor of mortality. However, their reported cut-off of 7.5 (sensitivity of 0.83, specificity of 0.87) is much lower. Non-availability of CTSI in all ICU patients at admission due to operational issues could be one of the factors associated with this discrepancy.

The European studies reported significantly higher intubation rates in ICU patients.[2] The COVID-ICU[2] study group reported that 63% of ICU patients were intubated within the first 24 hours, while overall 80% of patients received mechanical ventilation. In contrast, studies from China[23] reported a 47% intubation rate among critically ill patients. In a large multicenter study from America,[15] the overall rate of mechanical ventilation was 67%. Our study reports a relatively lower percentage (31%) of patients requiring invasive mechanical ventilation than in other countries. The discrepancy may be explained by the intensivist's reluctance to initiate mechanical ventilation due to limited resources and workforce at the peak of the pandemic. Lower intubation rates may have influenced this practice of delaying or avoiding early intubation in American or Chinese studies and could have been responsible for altering the mortality.

Apart from mortality, we also analyzed the predictors for invasive ventilation. High NLR, CRP, and D-Dimer at admission were independently associated with the need for invasive mechanical ventilation. Similar findings have been reported in a large number of cohort studies.[23,24] These findings support the importance of elevated inflammatory parameters in the disease progression. CRP of more than 75 mg/dL has been proposed as a parameter that predicts the progression of the disease, thus requiring not only an escalation of oxygen but also the need for more aggressive immunosuppression.[25]

In the initial phase of the COVID-19 pandemic, there was a paucity of reliable treatment options due to the novelty of the disease and the evolving treatment paradigms. As more data emerged, the efficacy of low-dose dexamethasone[26] and interleukin 6 inhibitors[27] was established. These agents were not initially part of therapeutic strategies; subsequently, these drugs were included in the treatment guidelines by the ICMR.[13] In our analysis, we did find reduced mortality with the use of dexamethasone and antiviral drug (remdesivir). In our study, IL6 inhibitor (tocilizumab) did not affect the outcomes, but this discrepancy could be due to a lack of data regarding the timing, dose, or mode of administration of the drug.

The study's strength is the detailed physiological, clinical, laboratory, radiological, and outcome data of more than 5870 critically ill patients admitted in multiple centers/ICUs across India. We recognize several limitations to our study. At the height of the pandemic, the medical facilities across India were severely overburdened. So uniformity in admission criteria and treatment modalities across different ICUs cannot be ascertained. Secondly, missing data due to many patients getting admitted and difficulty capturing all the details, especially during the peak of the crisis may have been a confounder. Thirdly, the data capture forms had been designed so as to reflect the commonly recorded parameters in all hospital case record forms. Absence of status of oxygenation at admission indices, such as the ratio of the partial pressure of arterial oxygen to fraction of inspired oxygen (PFR), the ratio of percentage oxygen saturation to the fraction of inspired oxygen (SFR), the ratio of oxygen saturation/fraction of inspired oxygen to respiratory rate (ROX index) could not be calculated due to the absence of data. Moreover, various scores for major organ dysfunction at admission like sequential organ function assessment (SOFA), acute physiology and chronic health evaluation (APACHE), simplified acute physiology score (SAPS II) score could not be computed due to a lack of data on some important variables. Data on ICU

complications, such as ventilator-associated pneumonia (VAP), central line-associated blood stream index (CLABSI), catheter-associated urinary tract infection (CAUTI), renal replacement therapy (RRT) could not be analyzed.

Conclusion

In this retrospective study of laboratory confirmed 5,865 COVID-19 patients admitted to ICU in India, overall mortality was 43.2%. Mortality was higher in older age and patients with multiple comorbidities. High D-dimer and high CT severity index at admission were significant predictors of mortality in critically ill patients treated in the ICU. Inflammatory markers such as CRP and D-dimer have independently predicted the need for invasive ventilation. This information may be valuable in early triaging and resource management in future outbreaks of similar kinds.

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This manuscript has been published as a preprint on Research Square (link:https://assets.researchsquare.com/files/rs-1740554/v1/6756b536-a7e8-41fe-afdb-5599ece604f5.pdf?c=1655413686) prior to its formal publication in Indian Journal of Critical Care Medicine peer-reviewed journal.

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