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Research Article

Evaluation of Risk Factors for Predicting Mortality in Critically Ill Adult COVID-19 Patients: A Retrospective Cohort Study

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I N F O

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A B S T R A C T

Background and Objective: Various risk factors have been evaluated to predict the mortality associated with COVID-19. We aim to explore and compare the clinical and laboratory risk factors with various outcomes of the disease between survivors and non-survivors amongst patients with moderate to severe COVID-19 disease.

Methods: All COVID-19 adult (≥ 18 years old) ICU in-patients with a definite outcome i.e. either death or discharge were included. The demographic, clinical, laboratory, treatment, and outcome data were retrieved. To explore the association between factors, univariate and multivariate logistic regression were done.

Results: A total of 163 patients were included out of which eight patients were shifted to other hospitals. Finally, a total of 145 patients were included in the study. Out of 145, 47 patients didn't survive and 98 survived. A significant proportion (85%) of non-survivors were current smokers and were observed to have COPD, HT, and CAD as comorbidities when compared to the survivors. The qSOFA score, CRP, and TLC counts were included in the multivariable logistic regression with the former being the independent risk factor.

Interpretation and Conclusion: Our study highlighted that older age, higher SOFA score, increased levels of total leucocyte count, and C-Reactive protein were independent risk factors affecting the clinical outcome in moderate to severe COVID-19 patients; however, qSOFA was found to be an independent risk factor predictor.

Keywords: COVID-19, Comorbidity, Mortality, Risk Factors, Outcomes

Introduction

In Wuhan, Hubei Province, China, a series of cases were reported of acute respiratory illness of unknown origin.[1,2] It was caused by a virus which was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2).[3] The World Health Organization officially named this disease as coronavirus disease 2019 (COVID-19) on February 11, 2020.

As far as the mortality is concerned, six (14.6%) patients worsened in a short duration of time and eventually expired due to multiple organ failure in a cohort study of 41 patients with COVID-19 pneumonia from Wuhan. In another cohort study of patients with COVID-19 pneumonia, the overall mortality of 4.3% (six out of 138) was reported.[4] Patient's clinical manifestations included fever with nonproductive cough, dyspnoea, myalgia, normal or decreased leucocyte counts, and evidence of pneumonia on chest radiograph imaging. Moreover, in severe cases, organ dysfunction and death were reported.[5,6] The results of single-arm meta-analysis by Li Q et al. showed that COVID-19 disease was seen more in the male gender. 60% of the total cases taken in the study were male. Also, it was found that the discharge rate of COVID-19 patients was 52%, and a fatality rate of 5% was observed.[7]

Various risk factors have been evaluated to predict the mortality associated with COVID-19 disease. Age ≥ 65 years with pre-existing concurrent cardiovascular or cerebrovascular diseases, CD3+ CD8+ T-cells ≤ 75 cells/ µL and cardiac troponin I ≥ 0.05 ng/ mL were found to be the four risk factors in a prospective cohort study which could predict higher mortality in patients with COVID-19 pneumonia.[4] Moreover, it was observed that there were increasing odds of in-hospital death of patients associated with older age (odds ratio 1.10), higher Sequential Organ Failure Assessment (SOFA) score ($p < 0.0001$), and d-dimer levels greater than 1.0 µg/mL ($p = 0.0033$) on admission in a retrospective cohort study done in adult patients in two hospitals of Wuhan, China. In addition to this, it was observed that the median duration of viral shedding was 20.0 days in survivors, but continued until death in patients who expired.[8]

However, on literature search, we could not retrieve any study exploring the risk factors predicting the mortality in critically ill COVID-19 patients admitted in the ICU in the Indian sub-continent. Different strains of the COVID-19 virus are prevalent; therefore, it is desirable to have a study exploring their fatality and risk factors in different geographical regions.

Here, we have presented details of all patients with laboratory-confirmed COVID-19 admitted to the various critical care units in a tertiary care institute in the city of Delhi with a definite clinical outcome (death or discharge) from 01st August till 30th September 2020. We aimed to explore and compare the clinical and laboratory risk factors between the deceased and survivors amongst patients with moderate to severe COVID-19 disease admitted in the ICU, and describe the clinical course of symptoms, and laboratory findings at the time of admission in ICU along with various outcomes of the disease. The primary outcome was risk factors predicting mortality and the secondary outcomes were demographic characteristics, comorbidities, laboratory investigations, and SOFA scoring.

Study Design: A Retrospective Study

This study was undertaken following approval from the Institutional Ethics committee - Human Research. The written informed consent from each patient was waived since the data were collected retrospectively. The case sheets were retrieved by names but files were subsequently coded to maintain anonymity. All adult (≥ 18 years old) in-patients admitted in the ICU in a tertiary care institute in the city of Delhi who were also diagnosed with COVID-19 according to the WHO interim guidance and had a definite outcome, i.e. either dead or discharged between 01 August 2020 till 30 September 2020 were included in the study. Paediatric, obstetric patients, and the ones who were shifted to other centres were excluded from the study. If the RT-PCR report was found to be positive on nasopharyngeal swab then only cases were diagnosed as COVID-19 pneumonia. The patient's information which was collected prospectively included demographic data, laboratory tests, clinical manifestations, and outcomes. To double-check the collected data, it was reviewed independently by two researchers.

The data were extracted manually after retrieving the case files from the Medical Record Department. All data were checked twice by the aforementioned two physicians; however, a third researcher (MM) adjudicated any difference in interpretation between the two primary reviewers. Demographic characteristics like age, sex, duration of stay in the hospital and in the ICU, history of contact, travel history, status of smoking, and existence of various co-morbidities such as hypertension (HT), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) etc. were recorded. Clinical manifestations, e.g. fever, cough, breathlessness, alteration in sense of smell and taste sensation, diarrhoea, and abdominal pain were recorded. The haemodynamic variables, i.e. systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation at the time of ICU admission were recorded from the case file. Laboratory procedures undertaken were also noted. The report of the repeat sample, if done, was also recorded. Routine blood examinations, e.g. complete blood count, total leucocyte count (TLC), coagulation profile, serum biochemical tests (including renal and liver function,

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creatine kinase, and electrolytes) were recorded from the case files. Chest radiographs and CT scans, if done, were also noted.

The disease severity of COVID-19 was defined according to the Clinical management protocol: COVID-19 by the Ministry of Health and Family Welfare, Govt. of India. Coagulopathy was defined as a 3-second extension of prothrombin time or 1.5 times increase in INR. Exposure history was defined as exposure to people with confirmed SARS-CoV-2 infection. ICU Scoring- Quick SOFA (qSOFA) scoring was done. Fever was defined as an axillary temperature of at least 37.3°C. Patients were labelled to have sepsis or septic shock according to the Definition for Sepsis and Septic Shock given by the Third International Consensus in 2016.[5] When there were clinical symptoms or signs of pneumonia or bacteremia and a positive culture of a new pathogen was obtained from lower respiratory tract specimens or blood samples after admission, then patients were diagnosed to have secondary infection.[5] Ventilator-associated pneumonia was diagnosed in our patients according to the clinical practice guidelines given by Infectious Diseases Society of America and the American Thoracic Society.[9] KDIGO clinical practice guidelines were used to diagnose acute kidney injury and Berlin Definition was used to diagnose acute respiratory distress syndrome (ARDS).[10] If serum levels of cardiac biomarkers were above the 99th percentile upper reference limit, or if electrocardiography and echocardiography revealed new changes, then only acute cardiac injury was diagnosed.[11] The various treatment patient had received was recorded retrospectively from their case files (Annexure-1). An evident cause of morbidity or mortality e.g. ARDS, heart failure, septic shock, coagulopathy or acute kidney injury was noted as perceived from the case file of the patient. The patient's outcome i.e. whether the patient was discharged or died, was recorded along with the number of days since the onset of illness, number of days on ventilator support etc. were recorded. The data from non-survivors such as the total number of days on ventilator, initial cardiac rhythm - shockable/ non-shockable, and whether the patient was on ionotropic support or not was also recorded from the case file.

Statistical analyses were done by using the SPSS software (version 20.0) IBM, Armonk, NY, USA). Descriptive variables were presented as mean, median (IQR), and proportion depending on the nature of data. Normally distributed continuous parameters were compared by unpaired t-test and skewed parameters were analysed by Mann-Whitney U test. Qualitative parameters were analysed by Chi-square test and Fisher's exact test. The row which contained more than two missing variables were omitted from analysis and the row with one or two missing variables were replicated with the mean, median (IQR), or mode depending upon the nature of data. To explore the association between factors such as clinical characteristics and laboratory parameterswith the risk of death, univariate and multivariate logistic regression was used.

Results

A total of 163 patients were admitted in the various ICUs of the institute during the aforementioned period. Eight patients subsequently left against the medical advice and were shifted to other hospitals. Finally, a total of 145 patients with moderate to severe disease in the various ICUs were included in the study. Out of 145, 47 patients didn't survive. The demographic characteristics of 145 patients are included in Table 1. The mean age of survivors has been observed to be younger than non-survivors. Similarly, amongst non-survivors, there were more males (68%). A significant proportion (85%) of non-survivors were current smokers. A significant proportion of non-survivors were observed to have COPD, HT, and CAD as comorbidities when compared to survivors. The mean time from onset of illness to hospital admission was observed to be 11.0 (7.0-14.0) days. qSOFA score at the time of ICU admission was used for risk stratification and was significantly higher amongst non-survivors when compared to survivors [4.0(4.0-6.0) vs 1.0(1.0-2.0)].

The laboratory investigations and treatment given to the patients are shown in Table 2. Serum creatinine > 133µmol/L was observed to be higher amongst non-survivors. All non-survivors were observed to have CRP > 20 at the time of ICU admission (Table 2).

Table 1.Demographic Characteristics of COVID-19 Patients

Variables		Total (N = 145)	Non-survivors (N = 47)	Survivors (N = 98)	P-Value
Age		57.0 (45.0-67.0)	65.0 (62.0-72.0)	58.0 (42.0-60.0)	< 0.001
Gender	Female	40.6% (n = 59)	31.1% (n = 15)	44.8% (n = 44)	-
	Male	59.3% (n = 86)	68.0% (n = 32)	55.1% (n = 54)	-
Exposure history		48.9% (n = 71)	44.6% (n = 21)	51.0% (n = 50)	-
Current smoker		42.0% (n = 61)	85.1% (n = 40)	21.4% (n = 21)	-
Comorbodity	COPD	40% (n = 58)	68.0% (n = 32)	26.5% (n = 26)	0.0007
	Diabetes mellitus	58.6% (n = 85)	34.0% (n = 50)	35.7% (n = 35)	0.0008

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	Hypertension	31.0% (n = 45)	21.0% (n = 31)	14.2% (n = 14)	< 0.0001
	CKD	1.37% (n = 2)	0%	2.01% (n = 2)	0.43
	CAD	12.4% (n = 18)	8.8% (n = 13)	5.1% (n = 5)	< 0.0001
	Autoimmune disease	2.0% (n =3)	0.6% (n = 1)	2.0% (n = 2)	< 0.0001
Time from onset of illness to admission (in days)		11.0 (7.0-14.0)	10.5 (8.0-15.0)	11.0 (8.0-14.0)	0.54
Disease severity	Moderate	35% (n = 51)	12% (n = 6)	53% (n = 51)	-
	Severe	30% (n = 44)	80% (n = 38)	9% (n = 6)	-
qSOFA		2.0 (1.0-3.0)	4.0 (4.0-6.0)	1.0 (1.0-2.0)	< 0.0001

Table 2.Laboratory Investigations and Treatment

Laboratory Investigations		**Total (N = 145)**	**Non-survivors (N = 47)**	**Survivors (N = 98)**	**P-Value**
Haemoglobin (g/dl)		12.6 (11.6-15.1)	12.7 (11.9-13.8)	12.7 (12.0-14.1)	0.3
Platelet count (10^4 cells/L)		20.6 (15.3-29.0)	16.95 (11.0-22.8)	23.1 (16.1-27.4)	-
Chest X ray PA view	B/L infiltrates	84 (68%)	35 (75%)	49 (51%)	0.0064
	Consolidation	110 (76%)	39 (84%)	71 (73%)	0.098
Serum creatinine (> 133µmol/L)		6% (n = 9)	9% (n = 4)	2% (n = 2)	0.050
Alanine transaminase (U/L)		24.0 (17.0-41.0)	38.0 (21.0-49.0)	25.0 (13.0-36.0)	0.005
Treatment		**n (%)**	**n (%)**	**n (%)**	**P-Value**
Antibiotics		139 (96)	46 (98)	93 (93)	0.18
Antiviral treatment		44 (30)	16 (31)	28 (30)	0.81
Corticosteroids		138 (95)	46 (98)	92 (93)	0.15
LMW Heparin		139 (96)	46 (98)	93 (93)	0.16
Tocilizumab		3 (2)	3 (6)	-	0.0054

Table 3.Outcomes amongst Both Survivors and Non-survivors

Outcomes	**Total (N = 145) n (%)**	**Non-survivors (N = 47) n (%)**	**Survivors (N = 98) n (%)**	**P-Value**
Sepsis	87 (60)	47 (100)	40 (41)	< 0.0001
Respiratory failure	80 (55)	47 (100)	33 (34)	< 0.0001
ARDS	58 (40)	46 (97)	12 (13)	< 0.0001
Septic shock	29 (20)	21(75)	8(0)	< 0.0001
Acute cardiac injury	44 (30)	28 (60)	16 (18)	< 0.0001
AKI	25 (17)	23 (51)	2 (2)	< 0.0001
Acidosis	9 (6)	9 (40)	0 (0)	< 0.0001
Coagulopathy	29 (20)	24 (52)	5 (5)	< 0.0001

Amongst the co-morbidities present during the course of stay, 100% of the non-survivors had sepsis and respiratory failure, followed by ARDS, sepsis, and AKI (Table 3).

The three factors qSOFA score (continuous), CRP (> 20, ≤ 20), and TLC count (> 11, ≤ 11) were included in the multivariable logistic regression (Table 4).The multivariable logistic regression revealed that amongst the aforementioned three factors, qSOFA was significantly associated with mortality. The significance of qSOFA score indicates that in its presence, there is no additional advantage of CRP and TLC in predicting mortality.

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Table 4.Multivariate Analysis

Variable Name	B (SE)	Odds Ratio (95% CI)	P-value
qSOFA score (per unit increase)	4.31 (1.19)	74.74 [7.22 to 773.33]	< 0.01
CRP > 20 (≤ 20 as reference)	2.67 (1.90)	14.44 [0.35 to 590.43]	0.160
TLC count > 11 (≤ 11 as reference)	1.83 (1.71)	6.23 [0.22 to 178.12]	0.285

The model correctly classifies 96.6% [99.0% non-survivor, 91.3% survivor], Cox-snell R-square 0.661

Discussion

In the present retrospective study on univariate analysis, three factors i.e. qSOFA score (continuous), CRP, and TLC counts were observed to be significantly higher amongst non-survivors and the multivariable logistic regression revealed that amongst the aforementioned three factors, only qSOFA was found to be significantly associated with mortality.

The clinical spectrum range is wide in cases of SARS-CoV-2 infection. Patients may have an asymptomatic infection or mild upper respiratory tract illness, and in severe viral pneumonia, respiratory failure may be observed and even death can occur.[8] The early reports of SARS-CoV-2-associated COVID-19 disease suggested that in SARS-like atypical pneumonia, 26 to 33% of patients required intensive care with mortality ranging from 4%-15%.[12,13]

Our study showed higher mortality in the old age group with more preponderance in males. A prospective cohort study showed that age ≥ 65 years was one of the risk factors predicting high mortality of COVID-19 pneumonia patients.[4] Moreover, in a single-centre study of 144 hospitalised patients with confirmed COVID-19 in North India, severe disease was seen more amongst male patients.[14]

Various comorbidities are known to influence the disease severity and patient outcome in COVID-19. In the present study, the most common comorbidity was COPD, followed by DM, HT, and CAD. In one of the multicentric, retrospective cohort studies, non-survivors were more frequently having diabetes, hypertension, and CAD.[8] Similar results were observed in a prospective study conducted on 179 COVID-19 patients.[4] In some previous studies, hypertension was observed to be the most common associated comorbidity followed by DM.[15,16] Similar to our observation, smoking was noted as a risk factor associated with severity of COVID-19 disease in many other studies as well.[17,18]

SOFA score has been observed to be a diagnostic marker for sepsis and septic shock, and also helps in assessing the state and degree of multi-organ dysfunction.[19,20] There was a good correlation between SOFA score and mortality as revealed in our study in line with a retrospective cohort study done in Wuhan, China.[8] In another study, SOFA score was one of the risk factors with poor prognosis in COVID-19 patients.[21]

Our study observed certain laboratory parameters which correlated significantly to mortality in these patients. We noted that patients with increased levels of TLC, C Reactive protein, and ALT had increased incidence of mortality. A preliminary study in India observed that 24 hr ICU mortality was 8.5%, and non-survivors had higher TLC along with a higher absolute neutrophil count, prothrombin time and INR (international normalized ratio).[13] Another study also stated that C-Reactive protein and total leucocyte count are strong predictors of mortality in COVID-19 patients.[4,22]

In concordance with our study, it was observed that alanine transaminase is also an associated risk factor with mortality among non-survivors in another research done in Wuhan, China.[8] In the present study, sepsis and respiratory failure were the most frequently observed outcome, followed by ARDS, heart failure, and septic shock.

Some limitations were observed in our study. First, the study design which was retrospective was a limitation. Moreover, few laboratory tests like lactate dehydrogenase, and serum ferritin were not done in all patients. Also, the lack of effective antivirals and use of high-dose corticosteroids might have also contributed to the poor clinical outcomes in some patients. Also, the study followed patients during the in-hospital course only, therefore, follow up details of survivors could not be done. Last but not least, interpretation of our findings might be limited by the sample size.

Conclusion

To conclude, our study highlighted that older age, higher SOFA score, increased levels of total leucocyte count, and C-Reactive protein were independent risk factors affecting the clinical outcome in critically ill COVID-19 patients.

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