RESEARCH ARTICLE

Predictors of mortality among hospitalized patients with COVID-19: A single-centre retrospective analysis

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Background: The severity of disease and mortality due to coronavirus disease (COVID-19) was found to be high among patients with concurrent medical illnesses. Serum biomarkers can be used to predict the course of COVID-19 pneumonia. Data from India are very scarce about predictors of mortality among COVID-19 patients.

Methodology: In the present retrospective study of 65 RT-PCR confirmed COVID-19 patients, we retrieved data regarding clinical symptoms, laboratory parameters, and radiological grading of severity. Further, we also collected data about their hospital course, duration of stay, treatment, and outcome. Data analysis was done to compare the patient characteristics between survivor and non-survivor groups and to assess the predictors of mortality.

Results: The mean age of the study population was 56.23 years (SD, 12.91) and most of them were males (63%); 81.5% of patients survived and were discharged, whereas 18.5% of patients succumbed to the disease. Univariate analysis across both groups showed that older age, diabetes mellitus, higher computed tomogram (CT) severity score, and raised levels of laboratory parameters viz, D-dimer, CPK-MB (creatine kinase), and lactate dehydrogenase (LDH) were associated with increased mortality among hospitalized patients. On multivariate analysis, elevated levels of serum D-dimer (odds ratio, 95% CI: 10.98, 1.13–106.62, $p = 0.04$) and LDH (odds ratio, 95% CI: 19.15, 3.28–111.87, $p = 0.001$) were independently associated with mortality.

Conclusion: Older patients, diabetics, and patients with high CT severity scores at admission are at increased risk of death from COVID-19. Serum biomarkers such as D-dimer and LDH help in predicting mortality in COVID-19 patients.

Key Words: *COVID-19; mortality; predictors; inflammatory markers; comorbidity*

INTRODUCTION

In December 2019, a new virus that causes pneumonia spread out in Wuhan, Hubei province. Later on, it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) [1]. On 11 March 2020, WHO declared coronavirus disease 2019 (COVID-19) a pandemic [2]. As of 1 February 2021, a total of 100.2 million confirmed cases of COVID-19, including 2.2 million deaths reported to WHO and 10.7 million confirmed cases of COVID-19 with 154,392 deaths in India [3]. In India, the initial mortality rate was 30.77% which decreased to 1.4% later on [4]. Mortality was high, especially in critically ill patients. Also, the mortality was high among patients with comorbid illnesses like hypertension, diabetes mellitus, chronic lung diseases, hypo/hyperthyroidism, cardiovascular diseases, and cerebrovascular disease [5].

The standard diagnostic test is real-time polymerase chain reaction (RT-PCR), which detects viral nucleotides via oropharyngeal and (or) nasopharyngeal swab. Radiological findings of the chest are very crucial with a high degree of diagnostic accuracy that can suggest COVID-19 pneumonia; hence, chest computed tomography has an important role in the diagnosis and prognosis of COVID-19 infection [6]. Several inflammatory markers like white blood cell count, D-dimer, lactate dehydrogenase (LDH), and serum ferritin are used as supporting tools for prognostication of COVID-19 infection [7]. Various studies that emphasize co-morbid illnesses and inflammatory markers have been carried out to predict mortality among COVID patients [1, 6, 8–10]. There are only a few studies from India that evaluated the predictors of mortality in COVID patients [11], so we conducted a retrospective analysis of hospitalized COVID patients to identify the risk factors associated with mortality among them.

METHODS

Study design

This retrospective study included patients from a dedicated COVID hospital in the southern part of Rajasthan, India. All adult patients who were hospitalized for COVID-19 disease and those who were either discharged from the hospital or died in the hospital were included in the study. The hospitalized patients were categorized to receive the inpatient care based on their oxygen requirement and the presence of any comorbid condition necessitating advanced care. We admitted the

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patients to the general ward with oxygen requirement at 1–4 L/min; high dependency unit (HDU) with oxygen requirement at 4–15 L/min using a face mask or non-rebreathing mask (NRBM) and no other comorbid condition necessitating intensive care unit (ICU) stay; and ICU admission if the patient required high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), or mechanical ventilation (MV) support in addition to conditions necessitating ICU stay. This was as per our institute's policy for the management of COVID-19 patients. We excluded the patients who either transferred to another care center or who died within 48 h of hospital admission. Patients were considered as a case of COVID-19 illness if they tested positive using the RT-PCR method. The present study was approved by the institutional ethics committee.

Data collection

We extracted data regarding the patient's demographic details, clinical symptoms and signs, laboratory parameters, treatment details including oxygen requirement, and requirement of non-invasive and invasive ventilatory support. Further, we also obtained outcome data of the patients, either discharged or deceased. Data collection was done by accessing hospital records (patient files and electronic records) and a standard data collection form was used to extract the data. Data extraction was done by two researchers (KP and RA) and was further cross-checked by a third researcher (AK). Any discrepancies in interpreting the data were determined by the third researcher.

The laboratory record includes complete blood counts, total leukocyte count, platelet counts, and lymphocyte counts; D-dimer level; Interleukin-6 (IL-6) levels; creatinine; liver enzymes; and LDH ferritin, and electrolyte levels. Every patient had a high-resolution computed tomography (HRCT) scan to quantify the severity of the illness and to rule out other possible causes of respiratory failure.

We collected data on the total length of hospital stay, days in the ICU, days of non-invasive/invasive ventilatory support, and days on high-frequency nasal canula (HFNC) oxygen or oxygen with mask/nasal prong. Data on the use of antiviral drugs (favipiravir or remdesivir) and systemic corticosteroids (dexamethasone, methylprednisolone) were also collected.

Statistical analysis

The data were analyzed using a statistical package for social sciences (SPSS version 21.0). Quantitative data were presented as mean and standard deviation and qualitative data were presented as frequency and percentage. Univariate analysis was carried out to find out any association between various parameters and mortality among COVID patients. Parameters that have a statistically significant association ($p < 0.05$) on univariate analysis subjected to multivariate analysis to determine independent risk factors for mortality.

RESULTS

A total of 108 patients were admitted to our hospital from 1 June to 31 August 2020. We excluded 43 patients who either tested negative using the RT-PCR or had incomplete data; 65 patients were included in the final analysis. Among these 65 patients, 53 were discharged and 12 died during hospitalization.

The comparison of clinical and demographic characteristics, laboratory tests, and treatment among survivors and non-survivors are shown in Tables 1 and 2. The mean age of the study population was 56.23 years (standard deviation (SD): 12.91) and most were males (63%). The mean age of the patients who died of COVID-19 was significantly higher compared to survivors (63.11 vs 54.66, respectively; $p = 0.04$). Comorbidities were present in 52.30% of the patients with hypertension and diabetes mellitus being the most common (32.3%) followed by cardiovascular disease and thyroid disorder (6.15%). The presence of diabetes mellitus was significantly higher among non-survivors than that of survivors (58.33% vs. 26.41%, respectively; $p = 0.04$).

On admission, the most common symptoms were fever (83%), shortness of breath (61.53%), and cough (49.23%). Patients with cough as their predominant symptom had significantly better outcomes ($p < 0.05$). The mean peripheral arterial oxygen saturation was 88.95% (SD, 11.40) on admission. Patients who died during their hospital course had significantly higher respiratory rate, higher pulse rate, and lower spO_2 at the time of admission than those who survived (Table 1).

TABLE 1

Baseline characteristics of the hospitalized patients

Parameters	Survivors (*n* = 53)	Non-survivors (*n* = 12)	*P*
Age (years), mean (SD)	54.66 (13.11)	63.16 (9.69)	0.04
Sex			0.18
Male, *n* (%)	31 (47.7%)	10 (15.4%)	
Female, *n* (%)	22 (33.8%)	2 (3.1%)	
Hypertension, *n* (%)	16 (30.18%)	5 (41.66%)	0.50
Diabetes mellitus, *n* (%)	14 (26.41%)	7 (58.33%)	0.045
Chronic lung disease, *n* (%)	1 (1.88%)	1 (8.33%)	0.338
Chronic kidney disease, *n* (%)	1 (1.88%)	1 (8.33%)	0.338
Cardiovascular disease, *n* (%)	4 (7.54%)	0	1.00
Hypothyroidism, *n* (%)	3 (5.66%)	2 (16.66%)	0.227
Clinical symptoms on admission			
Fever, *n* (%)	44 (83.01%)	10 (83.33%)	1.00
Cough, *n* (%)	30 (56.6%)	2 (16.66%)	0.023
Fatigue, *n* (%)	1 (1.88%)	0	1.00
Shortness of breath, *n* (%)	30 (56.6%)	10 (83.33%)	0.11
Sputum, *n* (%)	6 (11.32%)	1 (8.33%)	1.00
Body ache, *n* (%)	2 (3.77%)	0	1.00
Chest pain, *n* (%)	5 (9.43%)	0	0.58
Sore throat, *n* (%)	1 (1.88%)	0	1.00
Vital parameters on admission			
Systolic blood pressure, mean (SD)	129.6 (15.21)	133.5 (31.10)	0.53
Diastolic blood pressure, mean (SD)	80.96 (10.19)	77.66 (13.79)	0.35
Pulse rate, mean (SD)	93.35 (13.07)	104.5 (19.19)	0.02
SPO_2 on admission (with or without O2), mean (SD)	90.83 (9.52)	80.66 (15.40)	0.004
Respiratory rate, mean (SD)	24.94 (4.88)	32.16 (7.60)	<0.001

Note: SD = standard deviation.

Patients underwent HRCT scans of the thorax for quantification of the disease at the time of admission. Patients with higher computed tomogram severity scores (CTSS) at the time of admission had significantly poor outcome (18.91 vs. 13.26; $p = 0.001$). Inflammatory markers like D-dimer, ferritin, creatinine phosphokinase-MB (CPK-MB), LDH, and Interleukin-6 (IL-6) were assessed at the time of admission and serially thereafter. We took the values of these parameters at admission, their highest value during the disease course, and the average value. Serum ferritin, CPK-MB, and LDH were significantly higher among non-survivors as compared to survivors. IL-6 and D-dimer were also higher in non-survivors, but it didn't reach statistical significance.

We conducted a univariate analysis of all the parameters that were found to be statistically significant among survivors and non-survivors. We found that older age, diabetes mellitus, higher CTSS, and raised levels of inflammatory markers like D-dimer, CPK-MB and LDH were independently associated with mortality among hospitalized patients (Table 4). Parameters that were significantly associated with poor outcome were included in multivariate logistic regression analysis. We found that elevated levels of serum D-dimer (odds ratio, 95% confidence interval (CI): 10.98, 1.13–106.62, $p = 0.04$) and serum LDH (odds ratio, 95% CI: 19.15, 3.28–111.87, $p = 0.001$) during illness were independently associated with mortality.

DISCUSSION

This retrospective cross-sectional study was conducted at a dedicated COVID treatment facility in western India to determine the predictors of mortality in COVID-19. In the present study, the mean age of the study population was 56 years. The non-survivors were significantly older as compared to survivors (mean age 63 vs. 55 years, respectively; $p = 0.04$).

TABLE 2

Laboratory parameters

Parameters, mean (SD)	Survivors (*n* = 53)	Non-survivors (*n* = 12)	*P*
White blood cells, cells/mm^3, mean (SD)	9489 (4743)	12542 (6373)	0.06
Neutrophils, cells/mm^3 mean (SD)	7625 (4634)	10644 (6049)	0.06
Lymphocytes, cells/mm^3 mean (SD)	1385 (747)	1456 (2224)	0.85
Platelet count, per microliter mean (SD)	2.55 (0.97)	2.17 (0.88)	0.22
D-Dimer, ng/mL, mean (SD)			
Baseline	2662 (5014)	4799 (4278)	0.18
High	3046 (5233)	5985 (4023)	0.07
Average	2447 (3825)	5017 (4172)	0.04
Serum ferritin, µg/L, mean (SD)			
Baseline	355 (341)	674 (527)	0.01
High	362 (339)	752 (579)	0.003
Average	350 (333)	715 (563)	0.004
IL-6, pg/mL, mean (SD)			
Baseline	152 (535)	175 (340)	0.89
High	153 (534)	182 (337)	0.86
Average	127 (462)	178 (338)	0.72
CPK-MB, IU/L, mean (SD)			
Baseline	23 (12)	37 (11)	<0.001
High	23 (12)	39 (11)	<0.001
Average	22 (12)	38 (11)	<0.001
LDH, IU/L, mean (SD)			
Baseline	510 (217)	969 (421)	<0.001
High	520 (223)	1022 (381)	<0.001
Average	497 (214)	1016 (383)	<0.001
CT severity score, mean (SD)	13 (4.95)	19 (4.35)	0.001

Note: SD = standard deviation, IL-6 = Interleukin-6, CPK-MB = creatinine phosphokinase-MB, LDH = lactate dehydrogenase, CT = computed tomography.

TABLE 3

Treatment and hospital course of patients with COVID-19 in a hospital

Parameters	Survivors (*n* = 53)	Non-survivors (*n* = 12)	*P*
Antiviral used, *n* (%)			
Favipiravir	36 (67.92%)	7 (58.33%)	0.52
Remdesivir	18 (33.96%)	4 (33.33%)	1.00
Corticosteroids, *n* (%)			
Dexamethasone	19 (35.8%)	2 (16.6%)	0.309
Methylprednisolone	39 (73.5%)	11 (91.6%)	0.267
Hydrocortisone	0	1 (8.3%)	0.185
Plasma transfusion, *n* (%)	3 (5.66%)	4 (33.33%)	0.018
Requirement of stay in ICU, *n* (%)	23 (43.39%)	12 (100%)	0.08
Oxygen therapy (nasal prong/mask/NRBM)	22 (41.5%)	5 (41.66%)	1.00
HFNC use,	4 (7.54%)	5 (41.66%)	0.013
Duration of hospital stay, days, mean (SD)	11.5 (9.11)	7.7 (4.86)	0.04

Note: NRBM = non rebreathing mask, HFNC = high-frequency nasal canula, ICU = intensive care unit, SD = standard deviation.

Yanez et al. [12] found that 86.2% of the deaths occurred in those who were 65 years or older. In their study, individuals aged 55–64 years had an 8.1 times higher COVID-19 mortality rate than individuals younger than 55 years of age, and those aged 65 or older had a 62 times higher rate compared to the youngest group. Persons aged 65 or older had 7.7 times higher COVID-19 death rates than those between the ages of 55 and 64 years. Such an age-related vulnerability to an infection in the elderly could be explained by the one of the several mechanisms called immune-senescence. In simple terms, immune-senescence means impairment of innate immunity due to decreased production of naïve T and B cells as well as defective adaptive immunity due to reduced activation. Ultimately, these culminate in an ineffective clearance of viral pathogens and dysregulated immune response resulting in a cytokine storm [13]. Aging is also responsible for diminished levels of co-stimulatory molecules critical for production of T-cell primed anti-viral interferon production by alveolar macrophages and dendritic cells in response to influenza virus infection [14].

In our study, more than half of the patients had at least one comorbid illness. Hypertension and diabetes mellitus were most common with an equal preponderance (32.3%). Our results suggested that the odds of mortality among COVID-19 patients with diabetes mellitus were 3.9 times (95% CI: 1.06–14.3) higher than non-diabetics. However, in multivariate analysis, this was not confirmed to be an independent risk factor for mortality in COVID-19. A meta-analysis by Huang et al. [15] showed that diabetes was associated with severe COVID-19, and higher mortality though the exact mechanism has not been elucidated. Diabetics are predisposed to pulmonary dysfunction viz decreased lung volume, reduced pulmonary diffusing capacity, as well as ventilation control, bronchomotor tone, and noradrenergic innervation impairment. Higher susceptibility to severe COVID-19 in diabetics may be attributable to lymphopenia and the exaggerated cytokine storm associated with an increased renin-angiotensin system activation in several tissues [15].

We found that a higher CTSS at the time of admission was significantly associated with mortality (18.9 vs. 13.3, $p = 0.001$). Masoomeh Raoufi et al. [16] tried to correlate CT chest findings and COVID-19 mortality and found that higher CTSS was significantly associated with mortality. As per their findings, lower CTSS and lower pulmonary artery CT diameter were indicative of lower mortality [16]. Several other studies also correlated the CTSS and prognosis of the disease and found that a CTSS ≥ 18 was associated with a significant higher risk of death [6, 17, 18].

In our study, we observed that the use of plasma transfusion was found to be associated with poorer outcome (33.33% of non-survivors and 5.33% of survivors) was statistically significant ($p = 0.018$) (Table 3). Convalescent plasma was considered to be beneficial in COVID-19 as a source of antiviral neutralizing antibodies. Despite its postulated therapeutic effect on multiple immune pathways, such as antibody dependent cellular cytotoxicity, complement activation, or phagocytosis, trials could not prove the same. A multicenter randomized controlled trial from India demonstrated that administration of plasma therapy neither blocks the progression to severe disease nor leads to a reduction in mortality [19].

The role of various biomarkers in predicting the severity, prognosis, and mortality was explored in numerous studies. In our study, we evaluated the value of biomarkers like D-dimer, CPK-MB, LDH, ferritin, IL-6, absolute neutrophil count, and absolute lymphocyte count and their usefulness in predicting mortality in COVID-19. As per our study, elevated D-dimer was independently associated with mortality in COVID-19. He et al. [20], explored the role of D-dimer in prognosticating COVID-19 cases and found that elevated D-dimer levels were found in severe and critically ill patients [20]. D-dimer levels were significantly higher among those who had died as compared to those who survived. A meta-analysis by Zhan et al. [21] looked at the diagnostic value of D-dimer in predicting mortality in COVID-19 and found that pooled sensitivity of D-dimer in mortality prediction was 75% (95% CI: 65%–82%). These studies are in agreement with our finding. "Thrombo-inflammation"—the loss of normal antithrombotic and anti-inflammatory functions of the endothelial cells—leads to widespread dysregulation of coagulation, inadvertent complement, and platelet activation leading to a milieu of inflammatory thrombosis.

Among other biomarkers, our study demonstrated that higher levels of serum LDH are independently associated with mortality. In a pooled analysis, Brandon et al. [22] analyzed the link between LDH levels and COVID disease outcomes. They found that elevated LDH led to a 6-fold increased

TABLE 4

Univariate and multivariate regression analysis results

Parameters	Univariable odds ratio (95% CI)	*P*	Multivariable odds ratio (95% CI)	*P*
Age	3.8 (1.03–14.67)	0.05	—	—
Sex	0.28 (0.05–1.41)	0.12	—	—
Hypertension	1.65 (0.45–5.99)	0.44	—	—
Diabetes mellitus	3.9 (1.06–14.3)	0.04	—	—
CLD	4.7 (0.27–81.48)	0.29	—	—
CKD	4.7 (0.27–81.48)	0.29	—	—
CT severity score	5.29 (1.03–25.99)	0.05	—	—
Absolute neutrophil counts	2.3 (0.64–8.26)	0.19	—	—
Absolute lymphocyte counts	4.1 (0.96–17.09)	0.06	—	—
D-dimer (high)	15.5 (1.86–128.97)	0.01	10.98 (1.13–106.62)	0.04
Ferritin (high)	3.07 (0.84–11.21)	0.08	—	—
IL-6	1.9 (0.33–11.34)	0.47	—	—
CPK-MB	16.7 (3.29–84.57)	0.01	—	—
LDH (high)	24.44 (4.56–131.03)	0.00	19.15 (3.28–111.87)	0.001

Note: CI = confidence interval, CLD = chronic liver disease, CKD = chronic liver disease, IL-6 = Interleukin-6, CPK-MB = creatinine phosphokinase-MB, LDH = lactate dehydrogenase.

odds of developing severe disease and a 16-fold increased odds of mortality in COVID-19 patients [22]. LDH catalyzes the conversion of pyruvate to lactate in the glucose metabolic pathway. In SARS Cov-2, necrosis of the cell membrane triggers the release of LDH into the serum. In their study of 171 patients, Zhou et al. [23] demonstrated that odds of mortality were higher among those with elevated LDH levels [23].

LIMITATIONS

The present study has several important limitations. Firstly, the retrospective nature of the study might preclude us to collect more data that might have affected the patient's outcomes. Further, we excluded nearly 40% of the patients either because of negative RT-PCR reports or missing data. This could have led to selection bias. Secondly, being a single-center study, our results lack external validation and widespread use to other populations. Thirdly, the small sample size of the present study could be responsible for some non-significant differences in patient's baseline characteristics. Furthermore, it could have led non-significance of factors independently responsible for mortality.

Our findings suggest that older age, diabetes mellitus, higher CTSS, and raised levels of D-dimer, CPK-MB, and LDH conferred an increased risk of mortality in COVID-19. On multivariate analysis, only elevated D-dimer and LDH levels demonstrated an independent relationship with increased mortality. These findings could help us to identify those at the highest risk of death and prioritize them for aggressive management in resource-limited settings.

CONCLUSION

In conclusion, older patients (>65 years) and diabetics are at increased risk of death from COVID-19. Raised levels of serum D-dimer and LDH help in predicting adverse outcome in COVID-19 patients. Specific predictors like the presence of comorbidities and biomarker cut-offs should alert the physicians to triage these patients as they are the more vulnerable group to optimize the resource allocation.

AUTHOR DISCLOSURES

Contributors

All authors contributed to the conception or design of the work, the acquisition, analysis, or interpretation of the data. All authors were involved in drafting and commenting on the paper and have approved the final version.

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Competing interests

All authors declare no conflict of interest.

Ethical approval

This study was approved by our institutional ethical committee.

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