



Predictors of Mortality among Hospitalized Patients in a Tertiary Care Center across Three COVID-19 Waves

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ABSTRACT

Background: Several studies conducted across the globe have stated the most frequent risk factors linked to increased severity and death related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite the huge impact SARS-CoV-2 had on India, there is a lack of adequate research on the epidemiology and predictors of mortality due to coronavirus disease 2019 (COVID-19). The study aims to assess the predictors of mortality among COVID-19 patients admitted to a tertiary healthcare hospital in central India across the first, second, and third COVID-19 waves.

Materials and methods: This record-based cross-sectional study was conducted using secondary data of patients hospitalized with SARS-CoV-2 between September 2020 and October 2022 in a designated COVID-19 treatment center.

Results: Data on 861 adult patients were analyzed. The mean age of the patients was 52.87 ± 14.21 years, with the majority of them being females (573, 66.6%). Results showed no significant difference between men and women infected with COVID-19. During the complete course of the pandemic age patients, a history of hypertension, cough, dyspnea, myalgia, loss of taste, loss of smell, computed tomography (CT) score, and invasive ventilation was significantly associated with mortality of COVID-19 patients. Among the COVID-19 approved pharmacotherapy, steroids significantly (p -value < 0.000) lowered the risk of mortality [adjusted odds ratio (aOR): 0.134; 95% confidence interval (CI): 0.071–0.255] in COVID-19 hospitalized patients.

Conclusion: Various sociodemographic and clinical profile predictors were associated with COVID-19 infection among pharmacotherapies. Steroid use helped lower the risk of mortality associated with COVID-19. More studies will help us to understand the various characteristics of the SARS-CoV-2 virus more elaborately, so as to ensure the proper preparedness of the healthcare system for future COVID-19 impacts.

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INTRODUCTION

There was a devastating impact brought by the coronavirus disease 2019 (COVID-19) pandemic, and nearly all parts of the world and societies were affected. It was caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in China late in 2019.¹ COVID-19 has different prevalence and mortality rates depending on variables such as geographical location, transmission rate, vulnerability of the population, effectiveness of preventive measures, and the strength of the healthcare system.^{1,2} According to the statistics released by the Ministry of Health and Family Welfare in India, the country logged over 44 million cases of COVID-19, with a mortality rate of 1.19%.²

The COVID-19 pandemic has brought immense challenges to mankind in that there is limited knowledge regarding disease pattern, genetic susceptibility, risk factors for mortality, long-term side effects, and the absence of an effective cure.³ A wide range of studies carried out worldwide have reported several common risk factors for

severe illness and death with SARS-CoV-2, including elderly age, male sex, hypertension, diabetes, smoking, and a history of heart disease. Elevated concentrations of certain biomarkers, such as C-reactive protein (CRP), serum ferritin, lactate dehydrogenase (LDH), D-dimer, and prothrombin time (PT), have also been associated with a higher severity and mortality of COVID-19.⁴ Despite the significant milestones in the understanding of COVID-19, most studies provided a general outline of the pandemic. The nature of the disease and its effects on societies should be understood further by a more detailed elaboration of its characteristics for future management of the disease.

Other studies have been carried out within the country^{3–5} and abroad^{6–13} on COVID-19 mortality and its risk factors. However, the predisposing factors to mortality among populations with different demographic and clinical characteristics vary significantly, and, most importantly, the resilience of the health system plays an enormous role in determining outcomes.⁵ Given that COVID-19 has a significant impact

on India, there are not adequate studies on the epidemiology and predictors of mortality in the country.

Therefore, this research tries to assess predictors of mortality among patients admitted into a central Indian tertiary care hospital during the first, second, and third waves of the COVID-19 pandemic.

Objectives

To assess the clinical profile and the predictors of mortality among patients admitted with COVID-19 in a tertiary care hospital.

MATERIALS AND METHODS

It is a record-based cross-sectional study which was carried out at a tertiary healthcare center in Central India, a superspecialty hospital at Gondia district in Maharashtra, which turned into a designated COVID-19 treatment center under the policies released by the government during the time of the COVID-19 pandemic. In the present study, inclusion was made of all patients above 18 years, who were admitted for >1 day in this hospital for the treatment of COVID-19. Hospital records were used for the analysis of all individuals hospitalized with SARS-

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CoV-2 [RT-PCR positive or COVID-19 antigen (Ag) positive] between January 2020 and April 2022 ($N = 861$). The abovementioned inclusion criteria were used to enroll patients into the study, as it depicted the time period of the three COVID-19 pandemic waves within the country. Rapid antigen COVID-19 testing kits used for the cases in the study were J Mitra, Merrill, SD Biosensor, and MyLab. All of which were approved by Indian Council of Medical Research (ICMR) for testing. Kits used for interleukin 6 (IL-6), ferritin, D-dimer, and C-CRP were Croma II and Snibe Co., Erba reg, Avecon, Delta, Coral, and DiaSys. The number of patients under treatment or undergoing testing depended upon the severity of the COVID-19 infection, and this has been denoted as "N" in the table. Computed tomography (CT) was used to assess grading in COVID-19 positive patients and was scored out of 45 ($N = 53$) and 24 ($N = 234$). This change in scoring was because of an alteration in the grading of CORADS score as suggested by the COVID-19 Task Force. Steroids used for patient management were methylprednisolone and dexamethasone.

A universal sampling technique was utilized and included 861 participants: wave I-408, wave II-422, and wave III-31. The hospital record sheets were used to document patients' demographic characteristics, detailed histories, any underlying morbidities, clinical presentations, investigations done, treatments performed, and health outcomes.

Statistical Analysis

Data were entered in Microsoft Excel sheets. For the purpose of analysis, SPSS version 27.0 and Strata statistical analysis software were used in this study. In this study, data were analyzed wave-wise, which comprises three waves: wave I ($n = 408$), wave II ($n = 422$), and wave III ($n = 31$). A combined analysis of the three waves was also done. For all the variables, descriptive statistics were obtained. The categorical variables were presented by percentages, while the continuous variables, such as mean, median, and standard deviation, were calculated. Cutoff levels for IL-6, Ferritin, D-dimer, and CRP kits were 0–7 ng/mL, 10–322 ng/mL, 0–500 ng/dL, and 6 mg/dL, respectively. Analysis concerning laboratory parameter values was done in two groups: laboratory parameters above the mean levels and other laboratory parameters below the mean levels. To check predictors of outcome (mortality), "0" was coded for no death, while "1" was given for death. The second objective-attempted to see the association of independent variables and outcome (death) using the Chi-squared tests for categorical variables and independent t -test for those

continuous variables (IL-6, ferritin, D-dimer, CRP). Comparisons for CT score using medians were done since the CT score was rated using two different methods, and the Mann–Whitney test was employed for associating the median score. For assessing the third objective as far as the effectiveness of pharmacotherapy on mortality of COVID-19 is concerned, all variables (pharmacotherapy) with 0.2 on univariate analysis were considered for further analysis using logistic regression. A $p < 0.05$ was considered statistically significant.

In view of the confidentiality, all identifying details were made available for use by the investigators only in a single data sheet that is password accessed. All data have been deidentified prior to analysis. All methods complied with the Declaration of Helsinki regulations and guidelines.

RESULTS

Sociodemographic and Clinical Profile

In total, the hospital records of 861 admitted patients were analyzed. The mean (SD) age of the patients was 52.87 ± 14.21 years. The majority of the patients hospitalized were females, $n = 573$ (66.6%). The clinical characteristics of the study participants across the three COVID-19 waves are summarized in Table 1. The maximum number of participants was in wave II ($n = 422$), followed by wave I ($n = 408$), then wave III ($n = 31$). The median age varied for all three waves; the youngest patients were noted in wave II (25 years), followed by wave I (39 years), and then wave III (57 years). More female patients were admitted than males across all three waves. Hypertension and diabetes were the commonest comorbidities present, followed by congestive heart disease, chronic kidney disease, and chronic obstructive pulmonary disease (COPD); similar presentation was noted in all three waves. Fever and cough were the commonest symptoms across all three waves. In the second wave, higher proportion of fever, dyspnea, and cough were seen, whereas symptoms of loss of taste and smell were commonly seen in the third wave.

Table 2 shows a comparison of laboratory parameters. A blood test was done only if recommended by the physician. The mean values of heart rate (HR), respiratory rate (RR), and mean arterial pressure (MAP) were almost similar in all three waves. CRP and ferritin were higher in the second wave, IL-6 in the first wave, and D-dimer in the third wave. Table 3 represents the treatment used across all three waves. High-flow nasal oxygen was used more in the second wave, remdesivir was used more in the first and second waves, and

Favipiravir was used more in the second wave. In contrast, tocilizumab was equally used across all three waves. Only 40 patients in the second wave received bevacizumab. Steroid was the most common drug used in all three waves. Death outcome was higher in wave II ($n = 59/422$; 13.98%) than in wave I ($n = 22/408$; 5.39%) and wave III ($n = 2/31$; 6.45%), total $n = 83/861$ (9.63%).

Association of Demographic and Clinical Profile Characteristics with Mortality across Three Waves of COVID-19

In wave I, patients with the following characteristics were associated with a higher risk of mortality—dyspnea, increased RR, increased HR, high D-dimer, and IL-6. In wave II, patients with the following characteristics were associated with a higher risk of mortality—diabetes, hypertension, dyspnea, cough, loss of smell, myalgia, raised white blood cell (WBC) count, and raised CT score. No variable was found to be significant in the third wave, but when combined, all three waves of patients with the following risk factors were found to have a risk of mortality; age, hypertension, dyspnea, cough, loss of taste and smell, myalgia, increased RR, high IL-6, and D-dimer score (univariate analysis to assess predictors of mortality across three waves of COVID-19 is shown in Table 4).

Assessing the Effect of Pharmacotherapy on Mortality in COVID-19 Patients

In wave I, steroid use significantly lowered the risk of mortality [adjusted odds ratio (aOR): 0.055; 95% confidence interval (CI): 0.015–0.195] with a p -value < 0.000 . Tocilizumab was not significant, with a p -value of 0.393 and an odds ratio of 4.7 (95% CI: 0.132–173.2).

In wave II, steroid use significantly (p -value < 0.000) reduced mortality (aOR: 0.125; 95% CI: 0.055–0.281). Remdesivir and bevacizumab were also found to be significantly associated with p -value of 0.013 (aOR: 15.349; 95% CI: 1.795–131.2) and p -value < 0.000 (aOR: 5.036; 95% CI: 2.294–11.058), respectively. Tocilizumab and favipiravir were not significantly associated with a p -value of 0.419 and 1.0, respectively.

In wave III, invasive ventilation was significantly associated (p -value < 0.001) with reduced mortality (aOR: 0.144; 95% CI: 0.088–0.265).

Combining all waves, steroid use was found to significantly (p -value 0.000) reduce mortality (aOR: 0.134; 95% CI: 0.071–0.255). Remdesivir and bevacizumab

were also significant, with a p -value of 6.856–3.270, respectively. The higher odds ratio in remdesivir and bevacizumab in patients with severe symptoms received these medications. Whereas favipiravir and p -value < 0.000 (aOR: 6.856; 95% CI: wave II and combined waves suggests that and tocilizumab were not significantly

Table 1: Comparison of clinical presentation of patients admitted with COVID-19 across three consecutive waves

Variable	Wave I (N = 408)	Wave II (N = 422)	Wave III (N = 31)	Waves I + II + III (N = 861)
Sociodemographic				
Age (median) (years)	39 (13–87)	25 (4–88)	57.4 (25–83)	52.87 (4–88)
Gender				
Male	121 (29.65)	154 (36.49)	13 (41.93)	288 (33.40)
Female	287 (70.35)	268 (63.51)	18 (58.07)	573 (66.60)
Comorbidities				
Hypertension	201 (49.26)	170 (40.28)	21 (67.74)	392 (45.53)
Diabetes	137 (33.74)	119 (28.19)	16 (51.61)	272 (31.60)
CHD	67 (16.42)	42 (9.95)	9 (29.03)	118 (13.70)
CKD	10 (2.4)	3 (0.7)	2 (6.45)	15 (1.74)
COPD	1 (0.2)	4 (0.94)	0	5 (0.58)
Symptoms				
Fever	329 (80.63)	366 (86.72)	17 (54.83)	712 (82.70)
Dyspnea	186 (45.58)	227 (53.79)	11 (35.48)	424 (49.25)
Cough	313 (76.71)	374 (88.62)	8 (25.80)	695 (80.72)
Cold	193 (47.3)	216 (51.18)	1 (3.22)	410 (47.62)
Loss of taste	72 (17.64)	32 (7.58)	6 (19.35)	110 (12.78)
Loss of smell	79 (19.36)	23 (5.45)	9 (29.03)	111 (12.89)
Chest pain	24 (5.88)	19 (4.5)	0	43 (4.99)
Myalgia	55 (13.48)	56 (13.27)	12 (38.70)	123 (14.29)
Headache	49 (12.01)	47 (11.13)	2 (6.45)	98 (11.38)
Dizziness	56 (13.72)	33 (7.8)	1 (3.22)	90 (10.45)
Others*	64 (15.6)	68 (16.11)	3 (9.6)	135 (15.6)

*Others include nausea, vomiting, and diarrhea; The number in parentheses represents row-wise percentages

Table 2: Comparison of laboratory results of patients admitted with COVID-19 across three consecutive waves

Variable	Wave I (Mean \pm SD)	Wave II (Mean \pm SD)	Wave III (Mean \pm SD)	Waves I + II + III (Mean \pm SD)
RR (breaths per minute)	23 \pm 3.9 (n = 408)	24.5 \pm 5.4 (n = 422)	25 \pm 6.5 (n = 31)	23.8 \pm 4.8 (n = 861)
HR (beats per minute)	89.46 \pm 16.3 (n = 408)	93.6 \pm 15.1 (n = 422)	92 \pm 14 (n = 31)	91.6 \pm 15.8 (n = 861)
MAP (mm Hg)	94.1 \pm 9.3 (n = 408)	93.4 \pm 10 (n = 422)	91.2 \pm 7.4 (n = 31)	93.7 \pm 9.6 (n = 767)
WBC ($\times 10^9$ /L)	8.3 \pm 4.13 (n = 236)	8.9 \pm 4.7 (n = 381)	9.3 \pm 3.4 (n = 30)	8.7 \pm 4.4 (n = 647)
Platelets ($\times 10^9$ /L)	243 \pm 100 (n = 237)	223 \pm 96.5 (n = 379)	246 \pm 80.7 (n = 30)	232 \pm 98 (n = 646)
CRP (mg/dL)	31.9 \pm 35.6 (n = 290)	44.9 \pm 45.8 (n = 218)	18 \pm 18.8 (n = 24)	36.6 \pm 40.2 (n = 532)
Ferritin (ng/mL)	423 \pm 763 (n = 370)	452 \pm 910 (n = 363)	305.6 \pm 340 (n = 7)	436 \pm 835.7 (n = 740)
IL-6	78.4 \pm 219 (n = 287)	71.4 \pm 154 (n = 95)	22 \pm 42 (n = 14)	74.7 \pm 201.2 (n = 396)
D-dimer (ng/mL)	812 \pm 1721 (n = 370)	760 \pm 1406 (n = 223)	2524 \pm 3654 (n = 16)	841 \pm 1717 (n = 609)
CT score*	18 (0–38) (n = 171)	17 (0–25) (n = 164)	17 (0–22) (n = 21)	17 (0–38) (n = 356)

*Median values

Table 3: Comparison of treatment of patients admitted with COVID-19 across three consecutive waves

Variable	Wave I N (%)	Wave II N (%)	Wave III N (%)	Waves I + II + III N (%)
High-flow nasal cannula	144 (35.29)	108 (25.59)	1 (3.22)	253 (29.38)
Invasive ventilation	70 (17.15)	108 (25.59)	4 (12.90)	182 (21.14)
Mechanical ventilation	1 (0.24)	4 (0.94)	0	5 (0.58)
Remdesivir	327 (80.14)	321 (76.06)	12 (38.70)	660 (76.66)
Bevacizumab	0	40 (9.47)	0	40 (4.65)
Favipiravir	17 (4.16)	43 (10.18)	0	60 (6.97)
Tocilizumab	2 (0.5)	2 (0.47)	2 (6.44)	6 (0.70)
Steroids	351 (86.02)	386 (91.46)	21 (67.74)	758 (88.04)

Table 4: Univariate analysis to assess predictors of mortality among patients admitted with COVID-19 across three consecutive waves

Variable	Wave I (p-value)	Wave II (p-value)	Wave III (p-value)	Waves I + II + III (p-value)
Age (years)	0.203	0.149	0.367	0.000
Gender	0.933	0.057	0.811	0.215
Diabetes	0.914	0.047	0.157	0.114
Hypertension	0.115	0.000	0.313	0.001
CHD	0.897	0.318	0.350	0.871
CKD	0.545	0.483	0.701	0.684
COPD	0.814	0.523	NA	0.427
Fever	0.000	0.113	0.185	0.888
Dyspnea	0.017	0.000	0.657	0.000
Cough	0.491	0.037	0.419	0.007
Cold	0.419	0.286	0.790	0.490
Loss of taste	0.085	0.065	0.474	0.003
Loss of smell	0.061	0.047	0.350	0.001
Myalgia	0.489	0.016	0.066	0.049
Other symptoms	0.570	0.036	NA	0.141
Respiratory rate*	0.010	0.162	0.278	0.00
Heart rate*	0.006	0.149	0.321	0.21
Mean arterial pressure*	0.423	0.386	0.939	0.151
White blood cell count*	0.632	0.005	0.695	0.20
Platelets*	0.813	0.738	0.854	0.461
C-reactive protein*	0.614	0.980	0.977	0.562
IL-6*	0.000	0.805	0.203	0.000
D-dimer*	0.000	0.601	0.206	0.000
Ferritin*	0.934	0.166	0.021	0.213
CT score*	0.011	0.006	NA	0.001
High-flow nasal cannula	0.319	0.000	NA	0.220
Invasive ventilation	0.000	0.000	0.000	0.000
Mechanical ventilation	0.807	0.037	NA	0.022
Remdesivir	0.506	0.004	0.735	0.021
Bevacizumab	NA	0.000	NA	0.000
Favipiravir	0.303	0.018	NA	0.029
Tocilizumab	0.006	0.141	0.701	0.051
Steroids	0.000	0.000	0.312	0.000

*Independent t-test was used for continuous variables; NA, not applicable if there was an absence of the respective variables

associated with a *p*-value of 1.00 and 0.719, respectively.

DISCUSSION

In our study, age of the patients was not a significant parameter affecting their outcome in individual waves; however, when all the waves were considered together, increasing age was found to be a significant parameter. Similar results were also found in studies conducted by Lalani et al.³ and Gayam et al.¹⁰ In a letter to the editor by Ruan et al.,¹³ there was also a significant difference in age-groups between the death group and the discharge group. In a study by Nguyen et al.,¹⁴ male gender was a predictor of higher mortality among hospitalized adults with COVID-19. Total deaths (9.6%) reported in our study during the COVID-19 pandemic were lower than the study by Baruah et al.⁵ and higher than the study by Vig et al.⁴ The difference in death rates is a known aspect of COVID-19 infection, and it has been attributed to several factors such as local COVID-19 containment strategies, mitigation policies and healthcare capacity and delivery, and patient factors such as population age structure, ethnicity, geography, and socioeconomic status.^{11,12,15} The death rate in the third wave was very low across the country. In our study, two individuals in the third wave were reported dead, of which one was diagnosed with a mass lesion in a CT scan, suggesting neoplasm. Both these patients were around 80 years of age and admitted for <24 hours with multiple comorbidities.

Dorjee et al.¹⁵ stated that among the COVID-19 deaths reported in their study, 27% were suffering from hypertension. History of diabetes mellitus, COPD, and malignancy were found to be the significant predictors of mortality among COVID-19 patients in a study by Corona et al.¹⁶ A study by Beltramo et al.¹⁷ found that COVID-19 patients with chronic respiratory diseases developed significantly more ventilator-associated pneumonia. However, in the present study, among the various comorbidities, a history of hypertension and malignancy was only found to significantly affect the outcome of the patients. In the meta-analysis performed, Corona et al.¹⁶ discovered dyspnea, fatigue, and myalgia to be the significant predictors of mortality among COVID-19 patients. In the present study, dyspnea and myalgia were the predictors of outcome, along with cough and neurological manifestations—loss of taste and smell. Decreased lymphocyte counts, lower platelet counts, and elevated ferritin and D-dimer levels were found to be significant lab parameters affecting COVID-19

mortality in various studies.^{8,10,16} Raised ferritin levels, D-dimer, and IL-6 levels were the laboratory parameters significantly related to mortality in the present study. CT scores of the patients were found to be significantly associated with treatment outcomes in the present study. The use of mechanical and invasive ventilation in treating patients significantly reduced mortality in our study. Studies by Khamis et al.⁸ conducted in Oman also found that the majority of the patients admitted with COVID-19 were on mechanical ventilation during their hospital stay.

Studies conducted in various parts of the world have proved that treatment with steroids is an important predictor in reducing mortality among COVID-19 patients, whereas other studies have not established this association.^{18–20} Various meta-analyses and systematic reviews conducted have shown a significant reduction in deaths of COVID-19 patients in the steroidal group as compared to the nonsteroidal group.^{21–23} The current study also revealed a significant association of COVID-19 mortality among patients on remdesivir therapy as well as steroid treatment. This suggests that patients with severe signs and symptoms would likely receive these treatment measures. Meta-analyses and systematic reviews by Hariyanto et al.²⁴ and Elsayah et al.²⁵ have also stated similar findings. Other treatment modalities that were found to be significant predictors associated with the mortality rate among COVID-19 patients in the present study were bevacizumab and favipiravir.

Strengths and Limitations

The strength of the study is that it is a single-center study where records were electronically maintained. It was one of the first COVID-19-designated hospitals in the district. It received a large number of patients in all waves across the COVID-19 pandemic. Limitations could be that the results may not be generalizable as it is a single-center study, and the current study design may not be ideal to infer causal association.

CONCLUSION

In this record-based cross-sectional study of hospitalized patients with COVID-19 infection, each wave of COVID-19 represented a different sociodemographic and clinical profile of patients. On assessing the COVID-19 pandemic as a whole, characteristics such as age, presence of symptoms such as dyspnea, cough, myalgia, and a few neurological manifestations were found to be significantly affecting COVID-19 mortality along with laboratory and treatment factors

such as CT score, invasive ventilation, and steroids use. Being a newer strain of the virus, these data are helpful to understand various characteristics of SARS-CoV-2 and to ensure better preparedness of the healthcare system for the future.

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