Original Article

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Factors Associated with Mortality among COVID-19 Patients Admitted in an Intensive Care Unit at a Tertiary Care Setting: A Retrospective Study from Mizoram, India

Anaesthesia Section

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ABSTRACT

Introduction: Characteristics of Coronavirus Disease-2019 (COVID-19) patients from different tertiary centres in India are beginning to be enumerated with limited data on critically ill patients admitted in Intensive Care Units (ICU), with low SpO_2 levels.

Aim: To describe clinical profile and identify the factors associated with mortality among COVID-19 positive patients admitted in ICU at a tertiary care setting in Mizoram, India.

Materials and Methods: A retrospective study was conducted in Zoram Medical College, Mizoram, India, among 55 confirmed COVID-19 patients admitted in ICU between March 2020 and March 2021. All the patients admitted in ICU during the period was included in the study. Demographic data, symptoms, co-morbidity, investigations, ventilation required, treatment given, duration of ICU stay, and outcomes were recorded from case sheets. The primary outcome was inpatient mortality. Secondary outcomes included length of ICU stays, SpO_2 levels, need for oxygen support. The p-value was set at <0.05 analysed using coGuide software.

Results: The mean age was 56.47±15.24 years, and 38 (69.1%) participants were males. Most of 45 (81.8%) participants survived, and 10 (18.2%) patients died in ICU. The mean length of ICU stay was 7 (4 to 13) days in the survival group and 13 (7.5 to 17) for non survivors. The mean SpO_2 levels at the time of admission were 95% (90 to 97) in survivors and 80% (72.25 to 95.50) among non survivors. Following admission to ICU, 16 (29.1%) patients required intubation, High Flow Nasal Cannula (HFNC) was given to 2 (3.6%), and oxygen support (non rebreather mask) was required in all 55 (100%) patients. Pharmacological treatment included empiric antibiotics in 51 (92.73%), antiviral in 30 (54.55%), steroids in 45 (81.8%), Ivermectin in 21 (38.2%), and low molecular weight heparin in 36 (65.5%) patients. Binary logistic regression analysis found low SpO_2 levels at the time of admission (CI:0.85-0.97, p-value=0.008), hypotension (p-value <0.001), tachycardia (p-value=0.001), use of remdesivir (odds ratio 14.82, 95% CI:1.72 to 127.52), use of tocilizumab (odds ratio 14.33, 95% CI: 2.14 to 95.85) and use of meropenem (odds ratio 8.00, 95% CI: 1.51 to 42.45) were significantly associated with in-hospital mortality.

Conclusion: Oxygen saturation below 90%, hypotension, and tachycardia, at the time of admission in ICU were considered as predictors of in-hospital ICU mortality in COVID-19 patients. The reason for low mortality among patients admitted in ICU can be attributed to early admission to ICU and care when SpO_2 reading has reached 94%.

Keywords: Coronavirus disease-2019, Critical care, Hypotension, Oxygen saturation, Tachycardia

INTRODUCTION

In 2019, more than 13 million people were diagnosed with Coronavirus Disease-2019 (COVID-19) worldwide, since it was first identified in China [1]. Almost one-third of the hospitalised patients with COVID-19 are admitted to the Intensive Care Units (ICU) [2]. The agent causing Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is COVID-19 and the disease is responsible for the largest pandemic since the Spanish flu pandemic in the early twentieth century. Optimised support is the most important factor in the patient's prognosis, as there is no specific antiviral treatment [3].

The first COVID-19 case in India was reported in January 2020, and gradually the incidence of disease increased extensively by May. By mid-October 2020, India has emerged as the second most affected country globally after the United States of America (USA) with 7.3 million cases and a mortality rate of 1.7% [4]. The infection in India is widely prevalent with predominant asymptomatic individuals. Lack of adequate health resources has caused complications to set in, thus increasing the admission of COVID-19 patients to ICU [5].

Patients with COVID-19 usually present with fever, myalgia, non productive cough, and progressive shortness of breath. In moderate to severe cases, signs of organ dysfunction, such as Acute Respiratory Distress Syndrome (ARDS), acute kidney injury, pulmonary oedema, myocarditis, septic shock, and deaths, can occur [6]. Based on the clinical symptoms and laboratory test results, patients are categorised as mild, moderate, severe, and critical. Mild/moderate cases include most of the affected patients (81%). Although, severe and critical ones comprise only 14% and 5% of infected subjects, they require hospitalisation. Almost 20% of hospitalised patients need ICU. The mortality rate of ICU admitted COVID-19 patients are reported to be relatively high. Nearly, 61.5% die due to many different reasons [7].

A previous single-center retrospective study among proven COVID-19 pneumonia admitted to Dubai hospital, United Arab Emirates, by Nadeem R et al., reported that survivors spent more days in the ICU and the hospital than non survivors {median 18 (6.5-29.5) vs. 11 (4-18), p-value 0.003} [8]. Another retrospective study among COVID-19 ICU patients by Anudeep A et al., in India concluded that patients treated with antivirals had a better outcome [9]. The mean length of ICU stay was 9.2±3.7 days, and the mortality rate was 38%.

Current evidence-based literature was conducted only on epidemiological characteristics, clinical profile, and preventive measures of COVID-19. However, studies on clinical profiles and outcomes of critically ill COVID-19 patients admitted to ICU in India are very limited.

Coronavirus disease-2019 fatality rates might be significantly different, prompting researchers to seek more information about the characteristics and treatments of COVID-19 patients in ICUs. An in-depth analysis of related data may help develop more effective treatment protocols for future severe patients. Here we described clinical characteristics, treatments, and outcomes of confirmed COVID-19 patients admitted to the ICU of a tertiary hospital.

During the period from March 2020 to March 2021, Mizoram has recorded the least COVID-19 deaths in whole of India. Hence, it is of utmost importance to study the clinical profile and reasons for low mortality among COVID-19 patients admitted in ICU.

Objectives:

1. To determine the clinical profile of acutely ill COVID-19 positive patients admitted in an ICU at a tertiary care setting.
2. To identify factors associated with mortality among COVID-19 patients admitted in ICU.

MATERIALS AND METHODS

A retrospective study was conducted in the Department of Anaesthesiology and Intensive Care of Zoram Medical College, Mizoram, India. The study was conducted for a period of one year, from March 2020 to March 2021. Institutional Ethics Committee approval was obtained from the Institutional Ethical Committee board of concerned tertiary care setting (No.F.20016/1/18-ZMC/IEC). As the data was collected retrospectively, patient's consent form was not needed. COVID-19 positive patients were the source population, and patients admitted in the COVID-19 ICU were selected as the study population.

Sample size calculation: The proportion of ICU admission in COVID-19 patients was assumed as 58% as per the study by Grasselli G et al., [10]. Absolute precision was 15% and 95% confidence level. The formula was used for sample size as per the study by Daniel WW [11].

$$N=\frac{Z^2p(1-P)}{d^2}$$

Where, n=sample size

Z=statistic for a level of confidence level=1.960

P=Expected prevalence/proportion of outcome=0.58

d=Precision=15

As per the calculation mentioned above, the required sample size was 42. Considering non participation rate of about 20%, eight subjects were added. With this, the final sample size was 50. Total 55 samples were considered in the final study. A convenient sampling technique was used.

Inclusion criteria

- COVID-19 positive patients age ≥18 years of both genders.
- COVID-19 Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive and Rapid Antigen Test (RAT) positive.
- High-Resolution Computed Tomography (HRCT) chest which was suggestive of COVID-19.
- Acutely ill COVID-19 patients admitted in ICU.

Exclusion criteria

Non COVID-19 patients admitted with respiratory problems were excluded from the study.

Data Collection

Case sheets of COVID-19 patients admitted to the ICU between March 2020 to March 2021 from the medical records division were used to collect data. Demographic data, symptoms on presentation, vitals on presentation, co-morbidities, investigations, ventilation required, treatment given, complications, procedures, duration of hospital stay and course of ICU stay, and outcomes were recorded. Baseline Electrocardiogram (ECG), COVID-19 RT-PCR, HRCT-Chest, and Computed Tomography (CT) severity, {COVID-19 Reporting and Data System (CO-RADS) for use in the standardised assessment of pulmonary involvement of COVID-19 on unenhanced chest CT images} were done in all the cases. All laboratory tests, including RT-PCR for confirming COVID-19, were performed at the concerned tertiary care setting [12].

Pharmacological treatment included empiric antibiotics, antiviral, steroids, Ivermectin, and low molecular weight heparin in COVID-19 patients. The therapy was followed as per pharmaco-immunomodulatory therapy in COVID-19 and the treatment protocol followed in COVID-19 Dexamethasone (CoDEX) randomised clinical trial in Brazil [13,14].

Study variables: The primary outcome was inpatient mortality. Secondary outcomes included length of ICU stays, SpO_2 levels, need for oxygen support.

STATISTICAL ANALYSIS

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. For normally distributed quantitative parameters, the mean values were compared between study groups using an independent sample t-test (2 groups), and non normally distributed parameters were compared between study groups using the Mann-Whitney U test. Wilcoxon rank test was used to compare SpO_2 between admission and discharge. Uni variate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. An unadjusted Odds ratio along with 95% Confidence Interval (CI) was presented. p-value <0.05 was considered statistically significant. IBM Statistical Package for the Social Sciences (SPSS) was used for statistical analysis version 26 (IBM Corp., Armonk, NY, USA) [15].

RESULTS

The study included 55 COVID-19 positive patients, with a mean age of 56.47±15.24 years (ranging 25-93 years), and included 38 (69.1%) males. Upon presentation, 19 (34.5%) had a high fever, and 41 (74.5%) participants had low SpO_2 levels. Out of 55 patients, 45 (81.8%) survived, and 10 (18.2%) patients died in ICU [Table/Fig-1].

Parameter	n (%)
Age (Mean±SD) in years	56.47±15.24 (25 to 93)
Gender	
Male	38 (69.1%)
Female	17 (30.9%)
Reason for admission	
Low SpO_2	41 (74.5%)
High fever	19 (34.5%)
Atrial fibrillation	3 (5.5%)
Bradycardia	16 (29.1%)
Drowsiness	5 (9.1%)
Co-morbidity	43 (78.2%)
Chronic Obstructive Pulmonary Disease (COPD)	1 (1.82%)
Diabetes	28 (50.9%)
Hypotension	12 (21.82%)
Hypertension	14 (25.5%)
Tachycardia	17 (30.9%)
Others	14 (25.5%)
Computed Tomography (CT) chest score	
Normal	2 (3.64%)
Mild	8 (14.55%)
Moderate	17 (30.91%)
Severe	12 (21.82%)

Tuberculosis	1 (1.82%)
Not done	15 (27.27%)
Days in ICU (Mean±SD) (N=55)	10.96±9.31 (2.0, 44.0)
Oxygen saturation (SpO_2)	
Admission (Mean±SD) (N=45)	91.82±8.21 (60.0, 100.0)
Discharge (Mean±SD) (N=45)	98.29±2.80 (93.0, 100.0)
Outcome	
Survived	45 (81.8%)
Expired	10 (18.2%)

[Table/Fig-1]: Descriptive analysis of baseline parameters in the study population (N=55).

Following admission to ICU, 16 (29.1%) patients required Intubation, HFNC was given to 2 (3.6%), and oxygen support (non rebreather mask) was required in all 55 (100%) patients. Pharmacological treatment included empiric antibiotics in 51 (92.73%), antiviral in 30 (54.55%), steroids in 45 (81.8%), Ivermectin in 21 (38.2%), and low molecular weight heparin in 36 (65.5%) patients [Table/Fig-2].

Parameter	n (%)
Antibiotics	51 (92.73%)
Antiviral	30 (54.55%)
Steroids	45 (81.8%)
Sedatives	17 (30.91%)
Mucolytic	22 (40%)
Oxygen therapy by non rebreather mask	55 (100%)
Hydroxychloroquine	1 (1.8%)
Ecosprin	7 (12.7%)
Ivermectin	21 (38.2%)
Vitamin C	53 (96.4%)
Vitamin B complex	53 (96.4%)
Paracetamol	41 (74.5%)
Insulin	24 (43.6%)
Vitamin D	29 (52.7%)
Low molecular weight heparin	36 (65.5%)
Intubation	16 (29.1%)
High Flow Nasal Cannula (HFNC)	2 (3.6%)
Prone position	42 (76.4%)
Noradrenaline	12 (21.8%)

[Table/Fig-2]: Descriptive analysis of medications and treatment given in the study population (N=55).

Overall inpatient mortality was 10 (18.2%) in the present study. The median length of ICU stay was 7 (4 to 13) days for survivors and 13 (7.5 to 17) for non survivors. The median SpO_2 levels on admission were 95% (90 to 97) in survivors and 80% (72.25 to 95.50) among non survivors. Binary logistic regression analysis found low SpO_2 levels at the time of admission (CI:0.85-0.97, p-value 0.008), hypotension (p-value <0.001), tachycardia (p-value 0.001), use of remdesivir (odds ratio 14.82, 95% CI:1.72 to 127.52), use of tocilizumab (odds ratio 14.33, 95% CI:2.14 to 95.85) and use of meropenem (odds ratio 8.00, 95% CI:1.51 to 42.45) were significantly associated with in-hospital mortality [Table/Fig-3,4].

Parameters	Outcome		Odds ratio (95% CI)	p-value
	Survivors (n=45)	Non survivors (n=10)		
Age (years)	54.82±14.29	63.9±17.86	1.04 (0.99, 1.09)	0.096*
Days in ICU (n=54)	7 (4 to 13)	13 (7.5 to 17)	1.01 (0.94, 1.09)	0.713†
SpO_2 on admission (%)	95 (90 to 97)	80 (72.25 to 95.50)	0.91 (0.85, 0.97)	0.008†
Sex				
Female (Baseline)	15 (33.33%)	2 (20%)	2.00 (0.38, 10.61)	0.416‡
Male	30 (66.67%)	8 (80%)		
Co-morbidities	33 (73.33%)	10 (100%)	-	0.999‡
Low SpO_2	31 (68.89%)	10 (100%)	-	0.999‡
High fever (Baseline=No)	14 (31.11%)	5 (50%)	2.21 (0.55, 8.89)	0.263‡
Hypotension	3 (6.67%)	9 (90%)	-	**<0.001**
Tachycardia	8 (17.78%)	9 (90%)	-	**0.001**

[Table/Fig-3]: Binary logistic regression of baseline parameters in predicting outcome (N=55).
Binary logistic regression could not be performed due to the small sample size
*Independent sample t-test, †Mann-Whitney u test, ‡Chi-square test
Significant p-values are mentioned in bold

Treatments		Outcome		Odds ratio (95% Confidence interval)	p-value
		Survivors (n=45)	Non survivors (n=10)		
Steroids	Dexamethasone (Baseline=No)	28 (62.22%)	6 (60%)	0.91 (0.22, 3.70)	0.896
	Methyl prednisolone (Baseline=No)	7 (15.56%)	4 (40%)	3.62 (0.81, 16.22)	0.093
Antiviral	Favipiravir (Baseline=No)	4 (8.89%)	0 (0%)	-	0.999
	Remdesivir (Baseline=No)	17 (37.78%)	9 (90%)	14.82 (1.72, 127.52)	0.014
Antibiotics	Doxycycline (Baseline=No)	22 (48.89%)	4 (40%)	0.70 (0.17, 2.81)	0.612
	Piperacillin plus tazobactam (Baseline=No)	8 (17.78%)	4 (40%)	3.08 (0.70, 13.52)	0.135
	Meropenem (Baseline=No)	15 (33.33%)	8 (80%)	8.00 (1.51, 42.45)	0.015
Ivermectin (Baseline=No)		18 (40%)	3 (30%)	0.64 (0.15, 2.82)	0.558
Low molecular weight heparin (Baseline=No)		27 (60%)	8 (80%)	2.67 (0.51, 14.03)	0.247
Prone position (Baseline=No)		41 (91.11%)	1 (10%)	0.01 (0.00, 0.11)	**<0.001**
Tocilizumab (Baseline=No)		2 (4.44%)	4 (40%)	14.33 (2.14, 95.85)	0.006

[Table/Fig-4]: Comparison of medications given in predicting outcome (N=55).
Binary logistic regression could not be performed due to 0 in one of the cells
Significant p-values are mentioned in bold. Chi-square test was used

DISCUSSION

According to the author's knowledge, this is the first study from their tertiary care centre that reported the clinical profile of COVID-19 positive patients admitted in the ICU.

The mean age was 56.47±15.24 years in this study, and 38 (69.1%) participants were males. The finding can be compared to a single-center, retrospective, observational study by Yang X et al., in China, where the mean age was 59 years, 27 (52%) were older than 60 years, and 35 (67%) patients were men out of 52 [16]. The present study observed that non survivors 63.9±17.86 years were more senior than survivors 54.82±14.29 years. Based on previous studies, evidence suggests that older male patients are the most susceptible to COVID-19, which present study data supports [17].

Following admission to ICU, 51 (92.73%) received antibiotic treatment, 45 (81.8%) received steroids, 30 (54.55%) received antiviral, 16 (29.1%) patients required Intubation, and all 55 patients support of oxygen needed (non rebreather mask). These findings were following retrospective manual medical record review by Argenzian MG et al., in New York, where overall, 64.9% (552/850) of patients required in-hospital antibiotic treatment, 543 (63.9%) out of 850 patients received hydroxychloroquine, 222 (94.1%) out of 236 of patients

received vasopressors, 220 (93.2%) were intubated at least once, and 174/236 (73.7%) required supplemental oxygen [18].

The majority of 45 (81.8 %) survived, and 10 (18.2%) patients died in ICU. The median length of ICU stay was 7 (4 to 13) days in the survival group and 13 (7.5 to 17) days for non survivors. This finding was similar to a cross-sectional study by Kokoszka-Bargieł I et al., in Poland, where 27 out of 32 patients completed their ICU stay during the observation period [19]. The mean ICU stay was 12.7 (9.7) days (1 h to 41.4 days). ICU mortality was 67%. Hospital mortality and those disqualified were 70% and 79%, respectively. The present study's survival rate was 80%, similar to a recent study by Weiss P, where the survival rate was nearly 70% [20].

During stay in ICU, the COVID-19 patients had high fever 19 (34.5%), bradycardia 16 (29.1%), drowsiness 5 (9.1%), atrial fibrillation 3 (5.5%), and 41 (74.5%) participants had low SpO_2. The majority of 28 (50.9%) participants had diabetes, and 14 (25.5%) were hypertensive. These findings can be related to a retrospective study by Aggarwal S et al., in the United States where out of 42, fever was reported by 15 (94%) patients, 9 (56.3%) had a history of hypertension, 3 (19%) had a history of coronary artery disease, 3 (19%) had a history of congestive heart failure, and 2 (13%) had a history of stroke, 5 (31%) patients were tachycardic, 6 (38%) patients were hypoxemic, and none of the patients were hypotensive [21].

In the present study, the mean SpO_2 levels on admission were 91.82±8.21% which increased to 98.29±2.80% during discharge among patients who survived. The median SpO_2 levels on admission were 95% (90 to 97) in survivors and 80% (72.25 to 95.50) among non survivors. The finding was following a retrospective cohort study by Mejía F et al., in Peru, where oxygen saturation (SaO_2) on admission was generally low with a median of 87% (IQR: 77-92) and (28.46%), patients were admitted with oxygen saturation (SaO_2) below 80% [22]. The oxygen saturation (SaO_2) levels on admission was less in deceased patients than discharged patients (78% vs. 91%, p-value <0.001). The findings suggest that a maximum of patients were hospitalised too late after developing significant hypoxaemia, resulting in higher mortality. The challenging context of the "silent hypoxaemia" that many COVID-19 patients experience early in the disease should be recognised faster in the community setting for timely management of patients [23].

As previously studied in children [24], the importance of hypoxaemia as a predictor of mortality includes other lower respiratory infections elsewhere COVID-19. Timely detection of hypoxaemia, strategies such as use of pulse oximeters to monitor for hypoxaemia, is needed. These pulse oximeters are now relatively inexpensive and widely available in primary and community care facilities [25].

Exploratory analysis showed that for settings where pulse oximeter use in the community would not be feasible, measuring tachypnoea could be an alternative predictive factor on mortality, which is also inexpensive and straight forward [26]. As this is a matter of concern involving the public's health, more hospital beds and increased availability of supplemental oxygen should be upgraded to meet the expected increase in demand for the early care of hypoxaemia. Patients with alarm signs should be quickly identified and transferred to the hospital with the help of a robust call centre and ambulance system.

Patient characteristics across different regions are required to enable better clinical awareness and allocation of medical resources. There is paucity in literature describing the clinical features of ICU hospitalised patients infected with COVID-19, especially outside of major metropolitan areas. The present study will encourage other hospitals to publish their experiences, not only from significant university hospitals but also from smaller and middle-sized community institutions. The main strength is that population and setting are both representatives of care for COVID-19 patients. The data added evidence to existing literature and can help in timely management of COVID-19 patients at a referral centre.

Limitation(s)

As the study was the retrospective study, results should be interpreted cautiously. It was a single-centre study, and the findings cannot be generalised to the overall population. Further, extensive prospective multicentric studies are needed to support the present study's findings to provide insights into this ongoing pandemic globally.

CONCLUSION(S)

In conclusion, the mortality of critically ill patients with COVID-19 is high. The survival time of the non survivors was likely to be within two weeks after ICU admission. The median SpO_2 levels on admission were more in survivors compared to non survivors. Identifying risk factors associated with non survivors could help in risk-stratification and in-time management of COVID-19 positive patients. The key to successful management of COVID-19 patients is to admit the patients in ICU when SpO_2 reading reaches the level of 94% and start early treatment.

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