Original article

Demographic features and outcomes in critically ill mechanically ventilated COVID-19 patients with respiratory failure in a resource limited ICU setting – Report from a tertiary care center in Karachi

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ABSTRACT

Background: Studies done on severe COVID-19 have revealed a wide heterogeneity in intensive care clinical outcomes across various countries. We aimed to identify the demographic features and outcomes of mechanically ventilated COVID-19 patients with respiratory failure in Pakistan in resource limited settings.

Methods: This was a cross-sectional study conducted at the COVID-19 Intensive care unit (ICU) of Jinnah postgraduate medical center in Karachi, Pakistan. 86 patients who received mechanical ventilation in a period of five months from 1/2/2021 till 30/6/2021 were included in the study. Patient demographic characteristics, comorbidities, clinical manifestations of COVID-19 infection, laboratory values at the time of presentation (hemoglobin, Neutrophil lymphocyte ratio, platelets, glomerular filtration rate, C-reactive protein, D-dimers, Ferritin, liver function tests and electrolytes) and mode and duration of ventilation, final outcome (survivor vs. non-survivor) and cause of death in non-survivors were recorded. Data was analysed using SPSS 26. Patient characteristics were compared among those who died early before 7 days with those who survived for more than 7 days using Pearson's Chi square test and Independent sample t-test.

Results: 86 patients, who required mechanical ventilation because of severe respiratory distress not alleviated by non-invasive methods of ventilation, were included in the study. 66.3% (n=57) were males and 33.7% (n=29) were females. Mean age was 59 (SD 12). The most common comorbidities were diabetes mellitus and hypertension 44.2% (n=38) each. Only 3 (3.4%) of mechanically ventilated patients were extubated and 1 patient was eventually discharged home on room air. The mortality rate was 98.8% and only one patient survived. The most common causes of death were respiratory failure (86%, n=74), renal failure (48.8%, n=42) and sepsis (18.6%, n=16).

Conclusion: Mortality in COVID-19 patients who require mechanical ventilation is very high in resource limited settings because of the lack of essential medications, specialized teams and established protocols of ICU management and is not related to the demographic characteristics and comorbidities of patients and severity of disease at presentation.

Keywords:

COVID-19, Intensive Care Unit, Mechanical Ventilation, Mortality

INTRODUCTION

The spectrum of SARS-CoV-2 infection (COVID-19 disease) ranges from asymptomatic to symptomatic disease[1,2]. Severe COVID-19 illness is characterized by SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%[3]. Among those who are critically ill, respiratory failure from acute respiratory distress syndrome (ARDS) is the dominant finding[4]. Studies have shown that patients that a up to 26% of hospitalized COVID-19 patients require ICU care[5].

Out of those that who require ICU care, up to 67% patients need invasive mechanical ventilation during the course of hospital stay[6]. The threshold of initiating invasive ventilation in COVID-19 patients varies in different hospitals across the world depending on the local clinical practices and availability of resources[7]. Hospital mortality rates in mechanically ventilated patients are high[8]. However, mortality data

Conflict of interest: The authors declared no conflict of interest exists.

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from different countries show significant variability[7]. In developed and developing countries studies have shown high mortality rates, up to 60-77% in mechanically ventilated patients[9-11].

Few studies have reported the outcome of mechanically ventilated patients in resource limited settings. Data regarding these patients is lacking from Pakistan. We carried out our study in the Intensive care unit of one of Pakistan's largest tertiary care public hospitals. Our hospital was under equipped in terms of medications including IL-6 inhibitors and antibiotics, as well as in terms of staff including a specialized anaesthesia or respiratory therapist team to manage mechanical ventilation. The study was designed to identify the demographic features and outcomes of mechanically ventilated COVID-19 patients with respiratory failure in resource limited settings.

PATIENTS AND METHODS

This was a cross-sectional study conducted at the COVID-19 ICU of a tertiary care government hospital of Karachi, Pakistan for a period of five months from 1/2/2021 till 30/6/2021. The COVID-19 ICU was an 80 beds facility set up at Jinnah postgraduate medical center. The center was under equipped in terms of medications, including IL-6 inhibitors and antibiotics, and specialized anaesthesia and respiratory therapist teams. The study was approved from the ethical committee of Jinnah postgraduate medical center. Patients, who required mechanical ventilation and fulfilled the inclusion and exclusion criteria, were included in the study. The Inclusion criteria set for the study were adult patients aged >18years, positive PCR test for covid-19 and need for mechanical ventilation. Patients with a history of recent major surgical procedure, recent stroke, recent acute coronary syndrome, active malignancy, pregnancy and hospital stay of less than 24 hours were excluded.

Blood samples of all the patients were collected within 24 hours of admission. Blood tests included arterial blood gas analysis, complete blood count, liver function tests, renal function tests, coagulation profile and inflammatory markers (C reactive protein, Lactate dehydrogenase, D Dimers and Ferritin). Chest X-ray of all patients was done within 24 hours of admission to determine the degree of lung involvement at the time of admission. Blood tests were serially repeated during the course of the hospital stay to monitor disease progression. The data collected from the reports of the above investigations was used in the study.

Demographic characteristics of patients; including age, gender and comorbidities, the mode of ventilation required by the patients during the course of ICU stay and the cause of death were recorded. Outcome was recorded as total duration of ICU stay, total duration of oxygen therapy, total duration of invasive or non-invasive ventilation and final status of the patient (alive, dead).

Data was analyzed using SPSS version 26. Mean and Standard deviation were calculated for Hemoglobin, Total leukocyte count, Neutrophil lymphocyte ratio, Platelets, Urea, Creatinine, Glomerular filtration rate, CRP, LDH and D-Dimers. Frequencies and percentages were used for gender and comorbidities. The rest of the data was organized into categorical variables, including PiO2/FiO2 ratio, oxygen requirement, duration of hospital stay, duration of oxygen therapy and duration of invasive and non-invasive ventilation. Patients were divided into two groups, those with duration of ICU stay of less than 7 days and those with duration of ICU stay of more than 7 days. Pearson's Chi square test was applied to compare the variation of categorical variables. Independent sample t test was used to compare the means of laboratory values amongst patient with a short and prolonged hospital stay, assuming normality. A confidence interval of 95% was taken and p-values less than 0.05 were considered as statistically significant.

RESULTS

A total of 372 COVID-19 positive patients were admitted in the Intensive care unit during the duration of the study. Out of them 108 (29%) received invasive ventilation. After applying the exclusion and inclusion criteria, 86 out of 108 were included in the study. Amongst the study participants, 66.3% (n=57) were males and 33.7% (n=29) were females. Mean age was 59 (SD 12), range 31- 80 years. The most common comorbidities among the study participants were diabetes mellitus and hypertension 44.2% (n=38) each. Table 1 shows the demographic characteristics and comorbidities of the 86 patients included in the study. The most commonly reported symptoms at the time of presentation were fever, cough, shortness of breath and diarrhea. Most of the patients, 59.3% (n=51), presented within 7 days of onset of symptoms and 97.7 % (n=84) presented within 7 days of onset of shortness of breath. Majority of the patients, 94.2% (n=81), were afebrile or had low grade fever (<38^{o}C) at the time of presentation in the Emergency Department. At the time of presentation 93% (n=80) of patients had MAP

>70mmHg and 57.0% (n=49) had respiratory rate ≤30. Oxygen saturation on room air at presentation was variable, 58.1% (n=50) patients had oxygen saturation less than 70% at presentation, 73.3% (n=63) patients had oxygen requirements more than 15L and 61.6% (n=53) patients had PO_2/FiO_2 ratio less than 100. During the course of ICU stay, 32.6% (n=28) patients developed severe renal failure and required dialysis. Continuous mode volume controlled ventilation was given to 97.7% (n=84) patients. 3.5% (n=3) patients received Pressure controlled continuous mode ventilation. Patients were also given trials of Synchronized intermittent mandatory ventilation and Spontaneous mode ventilation i.e. 22.1% (n=19) and 3.5% (n=3) respectively. Prior to receiving invasive ventilation, non-invasive ventilation was given to 89.5% (n=77) patients. The clinical manifestations of patients at presentation are shown in Table 2. Mean Neutrophil lymphocyte ratio at presentation was 13.5±12.9 and C-reactive protein 125.6 mg/l ±66.7. 25.6% (n=22) patients developed thrombocytopenia during the course of ICU stay. The t test analysis of all laboratory values was insignificant when compared on the basis of duration of hospital stay except for BUN, D dimers and lactate dehydrogenase, which were significantly higher in those with a short duration of ICU stay (less than 7 days) compared to those with duration of ICU stay more than 7 days, p=0.001, 0.009 and 0.004 respectively. The laboratory parameters of patients at presentation are shown in Table 3. All patients received IV methyl prednisolone or dexamethasone. Remdesivir was administered in 64.0% (n=55) and tocilizumab in 3.5% (n=3) patients. Anti-coagulant was given to 98.8% (n=85) patients One patient didn't receive anticoagulation because of hematuria. The treatment received by the patients is summarized in table 4. Out of 86 patients only 3 patients (3.4%) were extubated during the course of treatment. They were extubated after maintaining oxygen saturations on spontaneous mode of ventilation without respiratory distress. Out of those who were extubated, 2 patients died 2-3 days after extubation because of redeveloping respiratory distress. One patient was re-intubated again on day 2 of extubation and 1 patient was refused re-intubation by her family members. 1 patient, who was extubated, was eventually discharged home on room air. The patient who was discharged was a known case of Chronic Obstructive Pulmonary disease (COPD) and presented with severe type 2 respiratory failure and acute respiratory distress syndrome, PO2/FiO2 ratio of 180 and oxygen requirement of 5 L/min. He was extubated after 4 days of mechanical ventilation and discharged home after 12 days of ICU stay. The mortality rate was 98.8% (n=85). Out of the 86 patients who received mechanical ventilation, only one survived. The most common causes of death were respiratory failure (86.0% n=74), renal failure (48.8% n=42) and sepsis (18.6% n=16).

Other causes of death were cardiac arrest, acute coronary syndrome, heart failure and stroke. When

Table 1: Patient demographics and comorbidities

Clinical feature		n (%)	Duration of hospital stay (n)	
			0-7 days	>7days
Age	<40	8 (9.3)	6	2
	40-70	56 (65.1)	22	34
	70 and above	22 (25.6)	13	9
Gender	Male	57 (66.3)	26	31
	Female	29 (33.7)	15	14
Co-morbidity	Diabetes Mellitus	38 (44.2)	18	20
	Hypertension	38 (44.2)	20	18
	Ischemic heart disease	5 (5.8)	4	1
	Chronic kidney disease	4 (4.6)	3	1
	Chronic liver disease	2 (2.3)	2	0
	Asthma	2 (2.3)	0	2
	COPD	1 (1.2)	0	1
	Others	15 (17.4)	8	7

Table 2: Clinical manifestations of patients in number and frequencies

Symptoms	Fever	63 (73.3%)
	Cough	41 (47.7%)
	Sore throat	6 (7%)
	Shortness of breath	86 (100%)
	Diarrhea	7 (8.1%)
	Nausea/Vomiting	3 (3.5%)
	Fatigue/Generalized weakness	5 (5.8%)
	Others	3 (3.5%)
Days since symptoms	≤7	51 (59.3%)
	>7	35 (40.7%)
Days since onset of shortness of breath	≤7	84 (97.7.%)
	>7	2 (2.3%)
Temperature at presentation	37.3-38.0°C	81 (94.2%)
	38.1-39.0°C	5 (5.8%)
Blood pressure at presentation	MAP≤70mmHg	80 (93.0%)
	MAP>70mmHg	6 (7.0%)
Respiratory rate at presentation	≤ 30/min	49 (57.0%)
	>30/min	37 (43.0%)
Oxygen saturation at room air	>90	0 0(%)
	70-89%	36 (41.9%)
	<70%	50 (58.1%)
Need for oxygen in liters at presentation	1-5L/min	5 (5.8%)
	6-15L/min	18 (20.9%)
	>15L/min	63 (73.3%)
PO2/FiO2 ratio	<100	53 (61.6%)
	100-300	32 (37.2%)
	>300	1 (1.2%)
Need for mechanical ventilation during hospital stay	Non-invasive ventilation	77 (89.5%)
	Invasive ventilation	86 (100.0%)
Mode of ventilation received	CMV	84 (97.7%)
	SIMV	19 (22.1%)
	PCV	3 (3.5%)
	Spont.	3 (3.5%)
Predominant mode of ventilator	CMV	82 (95.3%)
	SIMV	2 (2.3%)
	PCV	2 (2.3%)
	Spont.	0 (0%)
Need for dialysis	Yes	28 (32.6%)

Table 3: Laboratory characteristics at presentation

Laboratory value at presentation	Duration of hospital stay (Mean ± SD)			p-value
	Overall	0-7 days	>7 days	
Hemoglobin (mg/dl)	12.4±1.9	12.4 ± 1.8	12.4 ± 2.0	0.879
Total leukocyte count	14.0±11.9	12.5 ± 5.3	15.4 ± 15.6	0.257
Neutrophil lymphocyte ratio	13.5±12.9	14.9 ± 15.1	12.2 ± 10.4	0.329
Platelets ($x10^9$)	233±98.4	225.8 ± 122.1	239.8 ± 71.0	0.515
Urea (mg/dl)	70.2±49.2	90.9±58.1	51.9 ± 29.9	0.001*
Creatinine (mg/dl)	1.9±2.5	2.5 ± 3.3	1.5 ± 1.2	0.052
Glomerular filtration rate (ml/min)	59.0±31.1	52.4 ± 31.4	65.0 ± 29.9	
C Reactive Protein (mg/l)	125.6±66.7	123.4 ± 56.0	127.4. ± 74.9	0.796
D Dimers (mcg/ml)	5.0±4.7	7.1 ± 4.4	2.8 ± 4.0	0.009*
Lactate Dehydrogenase (U/l)	889.2±476.7	1059.0 ± 500.1	751.1 ± 413.0	0.004*
Ferritin (mcg/l)	1083.1±657.1	1232.5 ± 626.3	500.1±413.0	0.138
International Normalized ratio	1.1±0.4	1.1±0.4	1.0 ± 0.4	0.173
Serum sodium (mmol/l)	137.9±6.8	137.8± 7.09	137.8± 7.01	0.985
Serum potassium (mmol/l)	4.0±0.8	4.2 ± 0.8	3.9 ± 0.6	0.061
Total bilirubin (mg/dl)	0.7±0.6	0.8 ± 0.6	0.6 ± 0.4	0.414
Direct bilirubin (mg/dl)	0.3±0.3	0.4 ± 0.3	0.2 ± 0.2	0.097
Alkaline phosphatase (U/l)	137.8±78.7	135.8 ± 89.8	142.1 ± 70.9	0.822
Alanine aminotransferase (U/l)	82.8±199.0	110.6 ± 281.6	57.5 ± 55.5	0.224

*statistically significant

Treatment received (n=86)

Treatment regimen	Number of Patients (percentages)
Remdesivir	55 (64.0%)
Dexamethasone	85 (98.8%)
Methylprednisolone	82 (95.3%)
Tocilizumab	3 (3.5%)
Anticoagulation	85 (98.8%)

Table 5: Outcome

	Outcome	n (%)
Duration of ICU stay	0-7 days	41 (47.7%)
	More than 7 days	45 (52.3%)
Duration of invasive ventilation	0-7 days	73 (84.9%)
	More than 7 days	13 (15.1%)
Extubation status	Extubated	3 (3.5%)
	Not extubated	83 (96.5%)
Outcome	Survivor	1 (1.2%)
	Non-survivor	85 (98.8%)
Cause of death	Respiratory failure	74 (86.0%)
	Renal failure	42 (48.8%)
	Sepsis	16 (18.6%)
	Cardiac arrest	6 (7%)
	Others	4 (4.7%)

compared with duration of ICU stay, there weren't any significant differences in age, gender or treatment received between patients who survived longer than 7 days than those who died within 0-7 days. Since 85 out of 86 patients died, there was no effect of age, gender or the presence of comorbidities on the mortality rate of patients. Table 5 shows the outcome of patients included in the study.

DISCUSSION

The study was conducted in a resource limited, tertiary care public hospital of Pakistan. The study revealed a high (98.8%) mortality rate amongst patients who receive mechanical ventilation at the hospital. Only 3.4% of patients were extubated and out of them only one recovered and was discharged home. The patient that recovered was a known case of Chronic Obstructive Pulmonary disease (COPD) and presented with severe type 2 respiratory failure and acute respiratory distress syndrome, PO2/FiO2 ratio of 180 and oxygen requirement of 5 L/min. He was extubated after 4 days of mechanical ventilation and discharged home after 12 days of ICU stay.

It has been identified that ICU mortality rate from COVID-19 is higher than other causes of pneumonia[12]. Two meta-analysis of 49 and 21 studies reported the characteristics and outcomes of COVID-19 patients who received ICU care and mechanical ventilation[13,14]. Both the analysis revealed a wide heterogeneity in clinical outcomes across various countries, with mortality ranging from 21-100%. The variation is hypothesized to be secondary to variations in ICU facilities, ventilator performance, experience of the ICU team, patient and demographic characteristics[15]. Studies from developed countries, including the USA and China, have also reported mortality rates of up to 76-92% in COVID-19 patients who received mechanical ventilation[16,17]. A similar study conducted in Pakistan in October 2020 reported a mortality rate of 93.6% in patients who received mechanical ventilation[18]. However, recently published data has shown that mortality rates amongst invasively ventilated COVID-19 patients have improved[19,20].

Our study did not show any significant effect of comorbidities on mortality rates. A meta-analysis by Bajgain concluded that the presence of one or more comorbidity is not associated with a higher fatality rate[21]. On the contrary, some studies have shown that

the presence of comorbidities increases the risk of mortality from COVID-19[22].

Several reasons could account for the high mortality seen in our study. Firstly IL-6 inhibitors were not easily available at our center and could not be afforded by most admitted patients. Only 3 out of 86 (3.5%) patients received tocilizumab during the course of hospital stay. Several trials have shown a mortality benefit of tocilizumab on severely ill COVID-19 patients [23,24] and several guidelines have endorsed the use of tocilizumab for patients who have progressively severe or critical COVID-19[25,26].

Additionally, there was a lack of a specialized and coordinated anesthesia team at the study setting. Most of the patients received continuous mode ventilation without proper regulation of PEEP (positive end-expiratory pressures). Pathological changes in the lungs in COVID-19 patients differ from typical ARDS and for this reason studies have advocated the need of protected ventilation in COVID-19 patients[27,28]. Protected ventilation in COVID-19 includes low tidal volumes, plateau pressures and careful PEEP titration[29].

Furthermore, only a few antibiotics were available in the unit and due to lack of resources and proper staff training, infection control protocols were not properly followed. 18.8% of invasively ventilated patients died because of sepsis. Studies have shown that the incidence of secondary infection and infection by antimicrobial resistant pathogens is very high in critically ill patients with Covid-19 and has a significant impact on prognosis[30].

Studies have shown that D-Dimers more than 1mcg/ml, CRP >100mg/l, LDH >245 U/l, ferritin >500, NLR >3.6, GFR <60, elevated liver enzymes and thrombocytopenia are associated with severe Covid-19 disease[31-39]. This was consistent with our study which showed a mean NLR of 13.5, GFR 59.0ml/min, CRP 125.6 mg/l, LDH 889.2 U/l, D-Dimers 5.0mcg/ml, and Alanine aminotransferase 82.2 IU/l. 25.6% patients developed thrombocytopenia during the course of the hospital stay.

Because of the variable outcomes of invasively ventilated COVID-19 patients, the question of whether or not to offer invasive ventilation to COVID-19 patients and when to offer it is presently highly debatable among medical professionals[40]. Our study showed very high mortality rates in invasively ventilated COVID-19 patients in resource limited settings, which has further raised the question of benefit of invasive ventilation in COVID-19 patients in such settings.

CONCLUSION

Mortality in COVID-19 patients who require mechanical ventilation is very high in resource limited settings because of the lack of essential medications, specialized teams and established protocols of ICU management and is not related to the demographic characteristics and comorbidities of patients and severity of disease at presentation.

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