Barotrauma, invasive ventilation, and timing of tocilizumab as predictors of mortality along with inflammatory markers and comorbidities in critically ill COVID-19 patients: A retrospective study

INTRODUCTION

As of 12th April 2021, the novel coronavirus disease (COVID)-19 pandemic affected 135,646,617 individuals and caused 2,930,732 deaths globally.[1] In most of the affected individuals, the disease is known to be of mild to moderate severity. However, nearly one-third of those affected develop acute respiratory distress syndrome and require intensive care management.[2] The mortality in such critically ill patients is determined by multiple factors such as age, the severity of disease indicated by acute physiological and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA score), organ dysfunction, markers such as serum ferritin level, serum lactate dehydrogenase (LDH) level, the requirement of vasopressor, mechanical ventilation, and drugs such as steroids.[3-6] Invasive mechanical ventilation is one of the important parameters in predicting mortality.[7] Mechanically ventilated COVID-19 patients are at a higher risk of barotrauma. Barotrauma is also an independent predictor of mortality in such patients.[8] In this study, we explored the outcomes and factors associated with intensive care unit (ICU) mortality among critically ill COVID-19 patients.

METHODS

This was a single-centre, retrospective, observational study conducted in a tertiary level ICU in India. After approval of the hospital ethics committee, the data of COVID-19 patients requiring ICU admission between February 2020 and November 2020 were analysed. We extracted demographic, clinical and outcome data from patient record files and electronic databases. The presence of comorbidities such as diabetes, hypertension, ischaemic heart disease, hypothyroidism, respiratory ailments (asthma/chronic obstructive pulmonary disease), chronic kidney disease and malignancy was noted. Laboratory parameters including inflammatory markers such as C-reactive protein (CRP), D-dimer, etc., were captured. Outcomes of discharge or death during ICU stay were noted. Patients who were discharged against doctor's advice as well as those who were transferred to other care centres were considered as discharged.

The primary outcome of the study was to determine the factors associated with mortality during their stay in the ICU.

RESULTS

563 COVID-19 patients who required ICU admissions were analysed. Their mean age was 55.9 ± 14.0 years and 72.8% of them were males. Hypertension (39.6%) and diabetes (36.6%) were the major comorbidities observed. The mean total leukocyte count (TLC) was 9792.4 ± 5838.7 cells per mm^3. Median [interquartile range (IQR): 25–75] levels of CRP, D-dimer, ferritin, LDH and interleukin (IL)-6 were 6.3 mg/dl (1.9–14.6), 304.5 µg/mL (164.3–688.5), 343.7 µg/L (169.3–791.5), 393 U/L (279.5–560.5) and 42.7 pg/mL (15.2–110.4), respectively [Table 1]. Mean oxygen saturation at admission was 92.6 ± 9.0%. Tocilizumab was administered in 8% of the patients. Overall, 139 (24.7%) patients died and 424 (75.3%) were discharged [Figure 1].

Various factors were associated with different outcomes in ICU patients [Table 2]. Compared to survivors, the mean age of the non-survivors was significantly higher (53.6 ± 13.9 vs. 62.7 ± 12.2 years, $P < 0.0001$). A higher proportion of non-survivors were aged >60 years (56.1% vs. 32.1%, $P < 0.0001$). Diabetes mellitus ($P = 0.008$) and hypertension ($P = 0.001$)

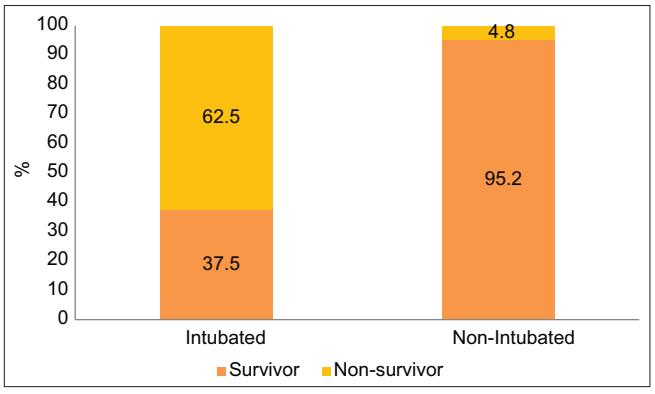

Figure 1: ICU outcome in tocilizumab treated patients with or without intubation

Table 1: Baseline characteristics

Parameters	Observation
Age (*n*=563)	
Mean age	55.9±14.0
Age >60 years	214 (38.0)
Gender (*n*=558)	
Male	410 (72.8)
Female	148 (26.3)
Comorbidities (*n*=563)	
Hypertension	223 (39.6)
Diabetes mellitus	206 (36.6)
Ischaemic heart disease	65 (11.5)
Hypothyroidism	30 (5.3)
Respiratory ailments (Asthma/COPD)	17 (3.0)
Chronic kidney disease	17 (3.0)
Malignancy	8 (1.4)
Inflammatory markers	
Total leucocyte count (*n*=559)	9792.4±5838.7
C-reactive protein (mg/dl) (*n*=429)	6.3 (1.9-14.6)
D-dimer (µg/ml) (*n*=468)	304.5 (164.3-688.5)
Serum ferritin (µg/L) (*n*=492)	343.7 (169.3-791.5)
Lactate dehydrogenase (U/L) (*n*=489)	393 (279.5-560.5)
Interleukin-6 (pg/ml) (*n*=474)	42.7 (15.2-110.4)
Procalcitonin (ng/ml) (*n*=72)	0.21 (0.07-0.90)
Blood biochemistry	
Serum creatinine (mg/dl) (*n*=525)	0.8 (0.7-1.2)
Serum total bilirubin (mg/dl) (*n*=520)	0.6 (0.4-0.9)
Alanine transaminase (IU) (*n*=533)	32.3 (21-53)
Aspartate transaminase (IU) (*n*=533)	38.6 (28-53)
Serum albumin (mg/dl) (*n*=520)	3.3±0.6
Oxygen saturation (%) (*n*=524)	92.6±9.0
Treated with Tocilizumab	45 (8.0)

COPD: Chronic obstructive pulmonary disease

were associated with higher mortality. Patients who required invasive ventilation (93.9%) had higher mortality whereas the mortality was lower with the use of non- invasive ventilation (NIV) (6.7%). We observed barotrauma in 12 (2.1%) patients. A higher proportion of non-survivors had barotrauma than surviving ones (4.3% vs. 1.4%, $P = 0.040$). Among inflammatory markers, significantly higher levels of TLC ($P = 0.001$), CRP ($P < 0.0001$), D-dimer ($P < 0.0001$), ferritin ($P < 0.0001$), LDH ($P < 0.0001$), IL-6 ($P < 0.0001$) and procalcitonin ($P = 0.007$) were observed in non-survivors than survivors. In addition, the median level of creatinine was significantly higher in non-survivors ($P < 0.0001$). Patients who succumbed in the ICU had significantly lower oxygen saturation at admission than survivors (88.7 ± 12.9% vs. 93.8 ± 7.02%, $P < 0.0001$).

We observed no significant difference in survivors and non-survivors with respect to the use of tocilizumab ($P = 0.078$) [Table 3]. However, its administration in patients without intubation was associated with significantly lower mortality than those who required mechanical ventilation (62.5% vs. 4.8%, $P < 0.0001$) [Figure 1]. The timing of administration from symptom onset as well as from admission did not differ significantly in survivors and non-survivors when stratified by intubation [Table 3].

Calculation of statistical power showed that it ranged from 75% to 100% for different variables such as age, sex, diabetes, hypertension and intubation requirement. For the barotrauma association with mortality, power was nearly 53%, probably because of a lesser proportion of patients that developed barotrauma. Nonetheless, the study identified reinforces the finding that the development of barotrauma should be avoided to improve the outcomes.

DISCUSSION

We observed an ICU death rate of 24.7% in critically ill COVID-19 patients. Studies from India in such critically ill patients have reported mortality varying from 16.7% to 38%.[9] Age is an important contributor to mortality. Among non-survivors, 56.1% of patients were above the age of 60 years. Rahim *et al*.[10] reported that mortality was higher for invasive mechanical ventilation (93.6%) and for over 60 years (87.3%). Increasing age affects arterial oxygen without impairing the elimination of carbon dioxide. A higher number of comorbidities in the elderly increases susceptibility to more severe disease. Inflammatory damage in COVID-19 is identified as one of the pathogenic features. Rapid viral replication and cellular destruction with subsequent recruitment of macrophages and monocytes induce the release of cytokines and chemokines. Such an inflammatory response is severe in the critically ill and may be even higher in non-surviving patients. A meta-analysis of 56 studies involving 8719 COVID-19 patients identified higher levels of white blood cell count, CRP, procalcitonin, erythrocyte sedimentation rate and IL-6 as predictors of mortality.[11]

In critically ill COVID-19 patients, refractory respiratory failure was the most common cause of ICU deaths. We observed that among non-survivors, the invasive mechanical ventilation rate was 93.3% compared to 44.3% in survivors. Alternatively, patients managed with NIV had significantly lower mortality. Rahim *et al*.[10] observed that invasive mechanical ventilation is an independent predictor of mortality. We observed barotrauma in nearly 2% of

Table 2: Predictors of in-hospital mortality outcome

Parameter	*n*, NS/S	Non-survivor (*n*=139)	Survivor (*n*=424)	*P*
Age	139/424	62.7±12.2	53.6±13.9	<0.0001
Age >60 years	139/424	78 (56.1)	136 (32.1)	<0.0001
Male sex	139/419	106 (76.3)	304 (72.6)	0.391
Diabetes mellitus	139/424	64 (46.0)	142 (33.5)	0.008
Hypertension	139/424	72 (51.8)	151 (35.6)	0.001
Ischaemic heart disease	139/424	19 (13.7)	46 (10.8)	0.367
Respiratory ailment	139/424	5 (3.6)	12 (2.8)	0.647
Hypothyroidism	139/424	5 (3.6)	25 (5.9)	0.295
Chronic kidney disease	139/424	5 (3.6)	12 (2.8)	0.647
Malignancy	139/424	3 (2.2)	5 (1.2)	0.397
Intubation required (*n*=127)	90/97	84 (93.3)	43 (44.3)	<0.0001
NIV only without intubation (*n*=60)		6 (6.7)	54 (55.7)	
Barotrauma	139/424	6 (4.3)	6 (1.4)	0.040
Total leucocyte count (u/l)	138/421	6643.8±556.6	5427.0±266.7	0.001
C-reactive protein (mg/ml)	96/333	10.9 (4.7-17.6)	5.7 (1.7-13.2)	<0.0001
D-dimer (ng/ml)	115/353	560 (288-1684)	249 (150.5-538.0)	<0.0001
Serum Ferritin (ng/ml)	116/376	645.2 (274-1023)	320.2 (138.8-628.2)	<0.0001
Lactate dehydrogenase (U/L)	110/370	501 (375-705)	355 (261-523.3)	<0.0001
Interleukin-6(pg/ml)	118/356	91 (223-235.2)	35.8 (12.7-91.0)	<0.0001
Procalcitonin (ng/ml)	27/45	0.63 (0.14-3.58)	0.15 (0.05-0.60)	0.007
Serum creatinine (mg/dL)	134/391	1 (0.8-1.8)	0.8 (0.7-1.1)	<0.0001
Serum total bilirubin g/dL)	127/392	0.6 (0.4-1.0)	0.6 (0.4-0.9)	0.585
Alanine transaminase (U/L)	135/398	32 (23-52)	33 (20-54)	0.848
Aspartate transaminase (U/L)	135/398	38 (30-54)	39 (28-63)	0.859
Serum albumin (*n*=520) (g/dL)	128/392	3.3 (2.9-3.6)	3.3 (3.0-3.7)	0.566
Oxygen saturation on admission	122/402	88.7±12.9	93.8±7.02	<0.0001

NS: non-survivors, S: survivor, NIV: non-invasive ventilation

Table 3: Tocilizumab administration, its timing, and outcomes with respect to intubation

Parameter	*n*, NS/S	Non-survivor (*n*=139)	Survivor (*n*=424)	*P*
Tocilizumab administration (*n*=45)	139/424	16 (11.5)	29 (6.8)	0.078
Time of administration - From symptom onset	16/29	8.5±4.8	7.6±3.6	0.493
Time of administration - From admission to ICU	16/29	4.6±3.7	3.9±3.6	0.506
Time of administration from symptom onset				
In intubated patients	15/9	8.3±5.0	7.8±4.1	0.779
In non-intubated patients	1/20	11	7.6±3.5	0.350
Time of administration - From admission to ICU				
In intubated patients	15/9	4.5±3.8	3.4±2.1	0.469
In non-intubated patients	1/20	7	4.1±4.1	0.496

ICU: Intensive care unit

invasively ventilated cases. Barotrauma significantly increased mortality risk. Kahn *et al*.[12] reported a mortality rate of 56% and 37% in patients with or without barotrauma, respectively. Higher positive-end expiratory pressure (PEEP) was reported as a risk factor for barotrauma.[8] These findings indicate that the use of mechanical ventilation should be restricted. NIV in properly selected patients can provide successful outcomes even in severe and critically ill COVID-19 patients. Our patients were either on weaning mode of ventilator or were spontaneously breathing, and hence, the probable mechanisms for barotrauma/spontaneous pneumothorax could include high minute ventilation (12.5 L/min) and high respiratory rate (29/min), higher high-resolution computed tomography (HRCT) score (18.07) indicating severity of illness, late stage of disease (20.5 days) and preceding events such as suctioning and bouts of cough.

The COVID-19 pandemic claimed many lives despite the fact that several measures including drugs such as azithromycin, favipiravir, remdesivir and 2-Deoxy-D-glucose were tried in the treatment of COVID-19 patients.[13,14] We observed no significant difference in mortality with tocilizumab administration. This is probably because of the higher number of intubations among those treated

with tocilizumab. The mortality rate was significantly lower in non-intubated patients with tocilizumab administration. The timing of tocilizumab administration plays an important role in determining the outcomes in critically ill patients. Moreno Diaz *et al*.[15] reported that the use of tocilizumab within 10 days of symptom onset is reported to significantly reduce the mortality at day 90 in severe COVID-19 cases. Although insignificant, we observed that in survivors, tocilizumab administration was a day earlier than in non-survivors. There is a rather large burden of COVID-19 patients in ICUs. Triaging based on risk factors and requirement of oxygen[16] is essential to allow adequate and appropriate allocation of resources in managing critically ill COVID-19 patients. The recovery and mortality data in critically ill COVID-19 patients with systemic comorbidities need to be closely audited.[17]

CONCLUSION

We conclude from the findings in our study cohort that higher age, the presence of comorbidities, increased levels of inflammatory markers, use of mechanical ventilation, barotrauma and the timing of tocilizumab are associated with an increased risk of in-hospital mortality in COVID-19 patients. We suggest that following lung-protective ventilation strategies, gentle suctioning of ventilated patients, close monitoring of respiratory rate and tidal volume during weaning, and the judicious use of cough suppressants may reduce the risk of barotrauma.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 12-Jul-2021
Revised: 22-Sep-2021
Accepted: 14-Oct-2021
Published: 29-Oct-2021

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Access this article online	
Quick response code	Website: www.ijaweb.org
	DOI: 10.4103/ija.ija_637_21

How to cite this article: Zirpe K, Gurav S, Deshmukh A, Wankhede P. Barotrauma, invasive ventilation, and timing of tocilizumab as predictors of mortality along with inflammatory markers and comorbidities in critically ill COVID-19 patients: A retrospective study. Indian J Anaesth 2021;65:755-9.