Original Research Article

Barotrauma, timing of Tocilizumab and Invasive ventilationas predictors of mortality with inflammatory markers and comorbidities in critically ill COVID-19 patients: A retrospective study

B. Srinivasa Rao[1*], B Sai Kumar[2], A. Uma[3]

[1]Consultant, Medicover Hospitals, Srikakulam, Andhra Pradesh, India
[2]Consultant, Medicover Hospitals, Srikakulam, Andhra Pradesh,, India
[3]Consultant, Medicover Hospitals, Srikakulam, Andhra Pradesh,, India

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Abstract

Background-Invasive mechanical ventilation is one of the important parameters inpredicting mortality.Mechanically ventilatedCOVID-19 patients are at a higher risk of barotrauma. **Objectives-** to determine we the outcomes, factors and predictors associated withintensive care unit (ICU) mortality among critically illCOVID-19 patients. **Methods-** A retrospective, observational study conducted in a tertiary level ICU.After approval of the hospital ethics committee, thedata of COVID-19 patients requiring ICU admissionbetween February 2020 and November 2020 wereanalysed. A total of 563 patients were admitted and included in the study. Universal sampling was done. SPSS (version 22.0) was used for analysis. **Results-**563 COVID-19 patients who required ICU admissionswere analysed. Their mean age was 55.9 ± 14.0 yearsand 72.8% of them were males. Hypertension (39.6%)and diabetes (36.6%) were the major comorbiditiesobserved.We observedbarotrauma in 12 (2.1%) patients. A higher proportionof non-survivors had barotrauma than survivingones (4.3% vs. 1.4%, P = 0.040).we observed no significant difference in survivorsand non-survivors with respect to the use oftocilizumab (P = 0.07). **Conclusion-**higher age, the presence of comorbidities, increasedlevels of inflammatory markers, use of mechanicalventilation, barotrauma and the timing of tocilizumabare associated with an increased risk of in-hospitalmortality in COVID-19 patients. It is recommended thatfollowinggentlesuctioning of ventilated patients, close monitoring ofrespiratory rate and tidal volume during weaning, andthe judicious use of cough suppressants may reducethe risk of barotrauma.

Keywords- COVID-19, barotrauma, invasive ventilation, tocilizumab, inflammatory markers, comorbidities.

Introduction

As of 12th April 2021, the novel coronavirus disease(COVID)-19 pandemic affected135,646,617 individualsand caused 2,930,732 deaths globally[1]. In most ofthe affected individuals, the disease is known tobe of mild to moderate severity. However, nearlyone-third of those affected develop acute respiratorydistress syndrome and require intensive caremanagement[2]. The mortality in such critically illpatients is determined by multiple factors such as age,the severity of disease indicated by acute physiologicaland chronic health evaluation (APACHE) II score,sequential organ failure assessment (SOFA score),organ dysfunction, markers such as serum ferritinlevel, serum lactate dehydrogenase (LDH) level, therequirement of vasopressor, mechanical ventilation,and drugs such as steroids[3.4,5]. Invasive mechanicalventilation is one of the important parameters inpredicting mortality. Mechanically ventilatedCOVID-19 patients are at a higher risk of barotrauma.Barotrauma is also an independent predictor ofmortality in such patients[6]. In this study, weexplored the outcomes and factors associated withintensive care unit (ICU) mortality among critically illCOVID-19 patients.

Materials and Methods

This was a single-centre, retrospective, observationalstudy conducted in a tertiary level ICU.After approval of the hospital ethics committee, thedata of COVID-19 patients requiring ICU admissionbetween February 2020 and November 2020 wereanalysed. A total of 563 patients were admitted and included in the study. Universal sampling was done. We extracted demographic, clinical andoutcome data from patient record files and electronicdatabases. The presence of comorbidities such asdiabetes, hypertension, ischaemic heart disease, hypothyroidism, respiratory ailments (asthmachronic obstructive pulmonary disease), chronickidney disease and malignancy was noted. Laboratoryparameters including inflammatory markers such asC-reactive protein (CRP), D-dimer, etc., were captured.Outcomes of discharge or death during ICU stay werenoted. Patients who were discharged against doctor'sadvice as well as those who were transferred to othercare centres were considered as discharged.

Statistical Analysis

All the collected data was entered in Microsoft Excel sheet and then transferred to SPSS software version 17 for analysis. Qualitative data was presented as frequency and percentages and analyzed using chi-square test of fisher's exact test. P-value < 0.05 was taken as level of significance.

*Correspondence
Dr. B. Srinivasa Rao
Consultant, Medicover Hospitals, Srikakulam, Andhra Pradesh, India

Results

Table 1- Demographic details and Predictors of Hospital Outcomes of the patients

Age (*n*=563)		**p-value**
Mean age	55.9±14.0	**0.001***
Age >60 years	214 (38.0)	**0.001***
Gender (*n*=558)		
Male	410 (72.8)	0.345
Female	148 (26.3)	
Comorbidities (*n*=563)		
Hypertension	223 (39.6)	**0.001***
Diabetes mellitus	206 (36.6)	**0.001***
Ischaemic heart disease	65 (11.5)	0.213
Hypothyroidism	30 (5.3)	0.92
Respiratory ailments (Asthma/COPD)	17 (3.0)	0.234
Chronic kidney disease	17 (3.0)	0.123
Malignancy	8 (1.4)	
Inflammatory markers		
Total leucocyte count (*n*=559)	9792.4±5838.7	**0.001***
C-reactive protein (mg/dl) (*n*=429)	6.3 (1.9-14.6)	**0.001***
D-dimer (µg/ml) (*n*=468)	304.5 (164.3-688.5)	**0.001***
Serum ferritin (µg/L) (*n*=492)	343.7 (169.3-791.5)	**0.001***
Lactate dehydrogenase (U/L) (*n*=489)	393 (279.5-560.5)	**0.001***
Interleukin-6 (pg/ml) (*n*=474)	42.7 (15.2-110.4)	**0.001***
Procalcitonin (ng/ml) (*n*=72)	0.21 (0.07-0.90)	**0.001***
Blood biochemistry		
Serum creatinine (mg/dl) (*n*=525)	0.8 (0.7-1.2)	**0.01***
Serum total bilirubin (mg/dl) (*n*=520)	0.6 (0.4-0.9)	0.221
Alanine transaminase (IU) (*n*=533)	32.3 (21-53)	0.231
Aspartate transaminase (IU) (*n*=533)	38.6 (28-53)	0.245
Serum albumin (mg/dl) (*n*=520)	3.3±0.6	0.256
Oxygen saturation (%) (*n*=524)	92.6±9.0	**0.001***

As per table 1 563 COVID-19 patients who required ICU admissions were analysed. Their mean age was 55.9 ± 14.0 yearsand 72.8% of them were males. Hypertension (39.6%)and diabetes (36.6%) were the major comorbiditiesobserved. The mean total leukocyte count (TLC) was 9792.4 ± 5838.7 cells per mm3. Tocilizumab was administered in 8% of the patients. Overall,139 (24.7%) patients died and 424 (75.3%) weredischarged.Compared tosurvivors, the mean age of the non-survivors wassignificantly 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). Diabetesmellitus (P = 0.008) and hypertension (P = 0.001)Patients whorequired invasive ventilation (93.9%) had highermortality whereas the mortality was lower with the useof non- invasive ventilation (NIV) (6.7%). We observedbarotrauma in 12 (2.1%) patients. A higher proportionof non-survivors had barotrauma than survivingones (4.3% vs. 1.4%, P = 0.040). Among inflammatorymarkers, 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) wereobserved in non-survivors than survivors. In addition, the median level of creatinine was significantlyhigher in non-survivors (P < 0.0001). Patients whosuccumbed in the ICU had significantly lower oxygensaturation at admission than survivors (88.7 ± 12.9%vs. 93.8 ± 7.02%, P < 0.0001).

Table 2-Administration, timing, and outcomes with respect to intubation of Tocilizumab

Parameter	***n*, NS/S**	**Non-survivor (*n*=139)**	**Survivor (*n*=424)**	***P***
Tocilizumab administration (*n*=45)	139/424	16 (11.5)	29 (6.8)	0.07
Time of administration - From symptom onset	16/29	8.5±4.8	7.6±3.6	0.49
Time of administration - From admission to ICU	16/29	4.6±3.7	3.9±3.6	0.50
Time of administration from symptom onset				
In intubated patients	15/9	8.3±5.0	7.8±4.1	0.77
In non-intubated patients	1/20	11	7.6±3.5	0.35
Time of administration - From admission to ICU				
In intubated patients	15/9	4.5±3.8	3.4±2.1	0.46
In non-intubated patients	1/20	7	4.1±4.1	0.49

as per table 2 we observed no significant difference in survivorsand non-survivors with respect to the use oftocilizumab (P = 0.07). The timing ofadministration from symptom onset as well as fromadmission did not differ significantly in survivors andnon-survivors when stratified by intubation.

Discussion

Studies from India in such critically ill patients have reported mortalityvarying from 16.7% to 38%[7]. Age is an importantcontributor to mortality. Among non-survivors,56.1% of patients were above the age of 60 years. Rahim et al[8], reported that mortality was higherfor invasive mechanical ventilation (93.6%) and forover 60 years (87.3%). Increasing age affects arterialoxygen without impairing the elimination of carbondioxide. A higher number of comorbidities in theelderly increases susceptibility to more severe disease.Inflammatory damage in COVID-19 is identified asone of the pathogenic features.A meta-analysisof 56 studies involving 8719 COVID-19 patientsidentified higher levels of white blood cell count,

CRP,procalcitonin, erythrocyte sedimentation rate and IL-6as predictors of mortality[9]. In critically ill COVID-19 patients, refractoryrespiratory failure was the most common cause ofICU deathsWe observed barotrauma in nearly 2% ofinvasively ventilated cases. Barotrauma significantlyincreased mortality risk. Kahn et al[10]. reported amortality rate of 56% and 37% in patients with orwithout barotrauma, respectively. Higher positive-endexpiratory pressure (PEEP) was reported as a riskfactor for barotrauma. These findings indicate thatthe use of mechanical ventilation should be restricted.NIV in properly selected patients can providesuccessful outcomes even in severe and criticallyill COVID-19 patients.We observed nosignificant difference in mortality with tocilizumabadministration. This is probably because of thehigher number of intubations among those treatedwith tocilizumab. The mortality rate was significantlylower in non-intubated patients with tocilizumabadministration. The timing of tocilizumabadministration plays an important role in determiningthe outcomes in critically ill patients. MorenoDiaz et al[11]. reported that the use of tocilizumabwithin 10 days of symptom onset is reported tosignificantly reduce the mortality at day 90 in severeCOVID-19 cases. Although insignificant, we observedthat in survivors, tocilizumab administration was aday earlier than in non-survivors. There is a ratherlarge burden of COVID-19 patients in ICUs. Triagingbased on risk factors and requirement of oxygen[12] is essential to allow adequate and appropriateallocation of resources in managing critically illCOVID-19 patients. The recovery and mortality datain critically ill COVID-19 patients with systemiccomorbidities need to be closely audited[13].

Conclusion

In the present study the cohort thathigher age, the presence of comorbidities, increasedlevels of inflammatory markers, use of mechanicalventilation, barotrauma and the timing of tocilizumabare associated with an increased risk of in-hospitalmortality in COVID-19 patients. It is recommended thatfollowinggentlesuctioning of ventilated patients, close monitoring ofrespiratory rate and tidal volume during weaning, andthe judicious use of cough suppressants may reduce the risk of barotrauma.

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