Original Article

J Nepal Health Res Counc 2021 Apr-Jun;19(51): 396-401

DOI: https://doi.org/10.33314/jnhrc.v19i2.3623

Characteristics and Outcome of Patients with COVID-19 Undergoing Invasive Mechanical Ventilation for Respiratory Failure in a Tertiary Level Hospital in Nepal

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ABSTRACT

Background: Corona virus disease 2019 has become a global health issue. The goal of this study was to investigate the characteristics and outcomes of patients with corona virus disease 2019 undergoing invasive mechanical ventilation and identify factors associated with mortality.

Methods: Ninety four consecutive critically ill patients with confirmed corona virus disease 2019 undergoing invasive mechanical ventilation were included in this retrospective, single-center, observational study. The outcome variable was mortality of patients undergoing invasive mechanical ventilation and factors associated with it during intensive care unit stay.

Results: Seventy nine (84%) out of 94 patients with confirmed corona virus disease 2019 who underwent invasive mechanical ventilation didn't survive. Ninety four percent of patients who had Type 2 Diabetes Mellitus did not survive in comparison to 72 percent of patients who didn't have Type 2 Diabetes Mellitus. Similarly, 48 (94.1%) out of 51 patients with a positive C-reactive protein value didn't survive in comparison to 31 (72%) out of 43 patients with a negative C-reactive protein.

Conclusions: The presence of Type 2 Diabetes Mellitus and a positive C-reactive protein value were strongly associated with mortality. Patients with a Sequential organ failure assessment score of more than eight at intensive care unit admission and peak D-dimer level of more than or equal to two during intensive care unit stay didn't show significant association with mortality. These findings need further exploration through larger prospective studies.

Keywords: COVID-19; critically ill patients; invasive mechanical ventilation; Nepal; outcomes

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), a multisystem disease responsible for numerous deaths worldwide is caused by the highly contagious virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2). The first outbreak of COVID-19 was reported in Wuhan, China, at the beginning of December, 2019.[1] Patients with COVID-19 can belong to a wide range of age group, present with several co-morbidities and rapidly progress to respiratory failure mandating invasive mechanical ventilation (IMV).[2,3] The mortality rate among patients receiving IMV has been found in excess of 50% in various studies. Data from resource limited setting like ours in this regard is still limted and therefore necessitates a study. The findings from our study can be useful to effectively manage and prognosticate the outcome of patients with COVID-19

We therefore aimed to study the characteristics and outcome of patients undergoing IMV for respiratory failure in a tertiary level COVID intensive care unit (ICU) in Nepal.

METHODS

For this single center, retrospective observational study, we included 94 consecutive patients with confirmed COVID-19 undergoing IMV in Tribhuvan University Teaching Hospital (TUTH) COVID ICU from March 24, 2020 to December 15, 2020. A total of 130 patients had undergone IMV for respiratory failure due to COVID-19 in the pre specified period but only 94 patients were included in our study. Thirty six patients were excluded because of insufficient data and failure to meet inclusion

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criteria. Individual patient record was accessed from the medical records section and data was entered into pre-designed data entry forms.

The medical and nursing charts and laboratory findings of all the patients were reviewed and entered into pre-designed data collection forms. All patients with age more than or equal to 16 years were included if they had a laboratory confirmed COVID-19 through SARS CoV-2 polymerase chain reaction (PCR), were admitted to TUTH COVID ICU for respiratory failure due to COVID-19 and were receiving IMV. Patients less than 16 years of age, not having a laboratory confirmed COVID-19 through SARS CoV-2 PCR, not receiving IMV, receiving IMV for causes other than respiratory failure, patients with Do not Resuscitate (DNR)/Do not escalate (DNE) orders were not included in the study. Data were independently verified by two investigators to ensure accuracy. All relevant data regarding characteristics and outcome of patients with COVID-19 undergoing IMV during ICU stay, along with potential factors affecting mortality were recorded. This included age, sex, presence of co-morbidities, presence of Type 2 DM, presence of symptoms at hospitalization, duration of symptom onset to hospitalization, Partial pressure of oxygen (PaO2)/ Fraction of inspired oxygen (FiO2) [P/F] ratio at ICU admission, requirement of vasopressors/inotropes at ICU admission, Sequential Organ Failure Assessment (SOFA) score on ICU admission, P/F ratio immediately before intubation, duration from ICU admission to intubation, Peak levels of inflammatory markers [Ferritin, D-dimer, CRP, Lactate Dehydrogenase (LDH), Troponin I) during ICU stay and mortality of patients undergoing IMV during ICU stay. The upper and lower limit of laboratory values as per the institutional protocol of hospital X were taken as reference to label a particular investigation as elevated or decreased. If the values were between upper and lower limits then they were labeled as normal.

All admitted patients were managed based upon the institutional protocol of TUTH for management of COVID-19 patients. All Patients once admitted to ICU were placed on either non-invasive ventilation (NIV) or High Flow Nasal Cannula (HFNC) and subjected to at least 16 hours of self proning per day. Patients were intubated if the initial trial with NIV or HFNC failed and the decision for intubation was made by the treating physician. After intubation, patients were managed with lung protective ventilation according to Acute Respiratory Distress Syndrome Network (ARDSnet) protocol,[4] to minimize lung injury. Tidal volumes of 4-6 milliliters per kilogram (ml/kg) of predicted body weight (PBW) was set and a plateau pressure of < 30 centimeters of water (cm H_2O) was targeted during mechanical ventilation. All patients admitted to ICU received Dexamethasone 6 milligram (mg) daily for 10 days and Remdesivir 200 mg on day one followed by 100 mg daily for next 4 days. Antibiotics were administered if any evidence of infection was present and was decided by the treating physician. Prophylactic anticoagulation with Low Molecular Weight Heparin (LMWH) was started after dosage adjustment where not contraindicated. According to institutional protocol of TUTH, Plasma therapy was administered to all laboratory confirmed COVID-19 patients. All patient admitted to TUTH COVID ICU received plasmatherapy if they hadn't received it before ICU admission. Conservative approach for fluid management was adopted for all patients. Similar treatment strategy was used for patients in Non-survivor and survivor groups according to the COVID-19 management protocol of TUTH.

The characteristics of patients with COVID-19 undergoing IMV for respiratory failure were explored through various clinical variables patients presented with at the time of ICU admission. The outcome measures were mortality among patients undergoing IMV during ICU stay and factors associated with mortality in the non-survivor group. All the possible factors that could be associated with mortality as described above were compared between the survivor and non-survivor groups.

Other potential factors that could have a significant association with mortality were the use of supportive therapy and treatment like Remdesivir, Dexamethasone, Anticoagulation, Antibiotics, use of plasmatherapy and duration of prone positioning prior to and after placement on IMV. These factors were not explored because all patients were assumed to have received these treatments based on the institutional protocol of TUTH for admitted COVID-19 patients. The incidence of Ventilator Associated Pneumonia (VAP) in the survivor and Non-survivor groups could not be compared because of insufficient data. The cause of death among all the non-survivors were either refractory hypoxemia secondary to ARDS or multi organ dysfunction secondary to sepsis. No patients died due to oxygen or equipment failure during the study period. The 30 day mortality of survivor's could not be explored due to insufficient data.

This study received ethical approval from the Institutional Research Committee (IRC) of TUTH.

Continuous data were presented as mean or median, and categorical data were presented as number (%). Proportions for categorical variables were compared using the Chi-square (and Fisher's exact) test. The factors that were significantly different between the

groups on bivariate analysis using the Chi square test (P < 0.05) were further entered into multivariate model and analyzed with binary logistic regression method to find out the true factors associated with mortality. Fitness of model was tested using Hosmer and Lemeshow test (Chi square 3.13, Significance 0.92). Accuracy of model was 88.3% as shown by classification table. A two-sided α of < 0.05 was considered statistically significant.

All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 25.0.

RESULTS

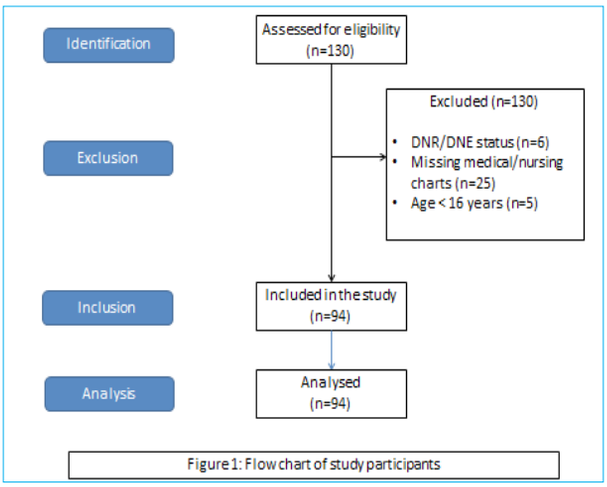

Figure 1. Flowchart of Study Participants.

A total of 94 COVID-19 confirmed patients were included in this study. The comparison between baseline characteristics of patients in the Survivor and Non-survivor groups are presented in (Table 1).

Table 1. Comparison of baseline characteristics among Non-survivors and survivors with COVID-19 undergoing IMV during ICU stay.

Baseline Characteristics	Total patients	Non-Survivors	Survivors	P value
Age				
Median (No), IQR	60 (7-87)	61 (7-87)	58 (18-77)	0.21
<=65 yrs	55	45	10	0.48
>65 yrs	39	34	5	
Sex				
Female (No, %)	31 (32.9)	23	8	0.06
Male (No, %)	63 (67.1)	56	7	
Presence of co-morbidities				
Yes (No, %)	75 (79.7)	64	11	0.49
No	19	15	4	
Presence of Type 2 DM				
Yes (No, %)	51 (54.2)	48	3	0.004
No	43	31	12	
Presence of symptoms at hospitalization				
Yes (No, %)	83 (88.3)	72	11	0.04
No	11	7	4	
Duration of symptom onset to hospitalization (Median, IQR)	4 (0-15)	4 (0-15)	5 (1-11)	0.22
P/F ratio at ICU admission				
<=100	79 (84)	65	14	0.55
101-200	14 (14.9)	13	1	
201-300	0	0	0	
>300	1 (1.1)	1	0	
Requirement of vasopressors at ICU admission				
Yes	28 (29.8)	28	0	0.006
No	66	51	15	

Statistical test used to calculate P value: Chi square (statistically significant: P value < 0.05)

The comparison between survivors and Non-survivor groups in terms of peak values of inflammatory markers during ICU stay is shown in (Table 2) and (Table 3) shows the binary logistic regression for detection of factors associated with mortality.

Table 2. Comparison of peak levels of inflammatory markers among Non-survivors and survivors with COVID 19 undergoing invasive mechanical ventilation during ICU stay.

Inflammatory markers	Total patients	Non-Survivors	Survivors	P value
Ferritin				
Elevated	82 (87.2)	70	12	0.36
Normal	12	9	3	
D-dimer				
<2	28	18	10	0.001
>=2	66	61	5	
CRP				
Positive	51 (54.2)	48	3	0.004
Negative	43	31	12	
Troponin I				
Positive	13 (13.8)	12	1	0.38
Negative	81	67	14	
LDH				
Elevated	88 (93.6)	74	14	0.96
Normal	5	5	1	

Test used for statistical significance: Chi square (Statistically significant: P < 0.05)

Table 3. Binary logistic regression for detection of factors associated with mortality.

Factors associated with mortality	Significance	Adjusted odds ratio	95% CI
Type 2 Diabetes Mellitus	0.02	6.06	0.03-0.81
Presence of symptoms	0.33	0.38	0.37-18.1
SOFA score at admission	0.49	0.48	0.25-16.49
Vasopressors at ICU admission	0.99	<0.001	0.00
D-dimer	0.10	0.28	0.78-15.35
CRP	0.03	5.26	0.04-0.91

CI- Confidence Interval

Twenty eight (29.8%) patients were on one or more vasopressors/inotropes at ICU admission. The requirement of vasopressors/inotropes on ICU admission was found to have a significant association with mortality using chi square test (P value 0.006) but this association was lost when further testing was done using binary logistic regression for multivariate model (Adjusted OR < 0.001, CI 0.00) .

Only 15 (16%) out of 94 patients survived and were discharged from ICU after successful extubation. The remaining 79 (84%) patients sustained mortality in ICU during the course of treatment. The outcome of patients receiving IMV during ICU stay is shown in (Table 4).

Table 4. Outcome of patients with COVID-19 receiving IMV.

	Total	Non-survivors	Survivors
Number of patients (No, %)	94	79 (84)	15 (16)
Duration of invasive mechanical ventilation (Median, IQR)	3 (1-27)	2 (1-14)	7 (1-27)
Duration of ICU stay(Median, IQR)	6 (1-27)	5 (1-19)	10 (3-27)

(No- number, IQR- Inter quartile range, %- percent)

DISCUSSION

In this study, the characteristics and outcome of 94 patients admitted to adult COVID ICU of TUTH were observed. A total of 79 (84%) out of 94 patients died during their ICU stay. The mortality rate for patients undergoing IMV was quite high but comparable to that observed from other studies.[5,6] In a study by Zhou et al.[5] in Wuhan, China, 31 (96.8%) out of 32 patients who underwent invasive mechanical ventilation (IMV) did not survive. Though the overall mortality for all patients admitted to hospital with COVID 19 irrespective of their ventilation status was only 28.2% in his study, the very high mortality rate for patients receiving IMV again suggests the very sick nature of patients in this cohort. In our center, we adopted the strategy of aggressive management of patients with COVID 19 with non-invasive measures like NIV and HFNC after admission to ICU. The choice of IMV was made only when all other non- invasive therapies failed. Around 36 percent patients were intubated within 24 hours of ICU admission in our study suggesting the extreme level of hypoxemia they were coping with before presentation to ICU. The comparison between P/F ratio immediately before intubation between the non-survivor and survivor groups was not statistically significant in our study. This result was however different from that found in few other studies where a significantly high mortality was observed in patients with P/F ratio below 100 immediately before intubation.[7,8]

There was no statistically significant association of age (P value 0.21) and sex (P value 0.06) with mortality in our study. Ninety four percent patients with a SOFA score more than eight at admission did not survive in comparison to 78.3% of patients with a SOFA score less than or equal to eight. This difference was not statistically significant when tested using binary logistic regression (Adjusted OR 0.48, CI 0.25-16.49). Findings different than ours was observed in a study done to validate SOFA score as a predictive tool for ICU mortality in patients with COVID-19.[9]

Another finding of our study was the significant association of Type 2 DM with mortality (Adjusted OR 6.06, CI 0.03-0.81). Multiple pathophysiological mechanisms can support the association between Type 2 DM and severity of COVID-19. Much of this knowledge is derived from SARS-COV infection rather than COVID-19. A compromised innate immune system due to chronic hyperglycemia, pro-inflammatory state characterized by inappropriate and exaggerated cytokine response and underlying pro-thrombotic hypercoagulable state have been implicated in this association.[10,11] A finding similar to ours was also demonstrated by numerous other studies showing an increase in COVID 19 associated mortality in patients with Type 2 DM.[12,13]

Biomarkers also have an important prognostic role in patients with confirmed COVID-19. Multiple studies have established a proven benefit of different biomarkers including ferritin, d-dimer, CRP and LDH in

prognostication of severity of illness in COVID-19.[14-17]

In our study a positive CRP had a significant association (Adjusted OR 5.26, CI 0.04-0.91) with mortality in COVID-19 confirmed patients receiving IMV. Similar finding of a positive correlation of high CRP levels with an increased mortality was also observed in multiple studies.[14-17]

In our study, 64.2 percent of patients with a D-dimer level less than two did not survive in contrast to 92.4 percent of patients with a D-dimer level more than or equal to two. This difference was not statistically significant (Adjusted OR 0.28, CI 0.78-15.35) using binary logistic regression. Findings different than ours was observed by Zhang et al, Soni et al and Yao et al in their studies.[18-20]

Our study has numerous limitations. Since it is a retrospective observational study, it is prone to numerous inherent biases. Retrospective studies are inferior level of evidence compared to prospective studies. Another limitation of our study is the presence of confounders which can affect mortality. Multivariate analysis and Binary logistic regression was therefore used to minimize the effect of confounders during identifying the true factors associated with mortality. Selection and measurement bias are another limitations of our study.

CONCLUSIONS

In this retrospective observational study, a number of important findings were observed.. The mortality rate of patients receiving IMV was significantly high and the presence of Type 2 DM and a positive CRP value were found to be significantly associated with mortality. Larger prospective studies are warranted to validate these findings.

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Competing interests: None declared

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