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Early Intubation Reduces the Risk of Death Among COVID-19 Patients: An Observational Study

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The objective of this study was to find the association of invasive mechanical ventilation, non-invasive mechanical ventilation (N.I.V) and high flow nasal canula (HFNC) with mortality in COVID 19 pneumonia patients with ARDS. This is an observational cohort study conducted among patients those who were infected with COVID19 infection and received ventilator support. This study was a single centred, conducted among COVID19 patients, who came to a tertiary hospital in Bhubaneswar, Odisha. All patients admitted with COVID19 infection and received mechanical ventilation in between August 2020 to November 2020 was included in this study. As this is an observational cohort study, any intervention not required. Only, data collectors collected all relevant patient data using an android-based data collection platform. 398 patients were found to be eligible for this study. Among them, only 24.47% patients received invasive mechanical ventilation and rest were on N.I.V (62.77%) and HFNC support (12.77%). 26 patients died among the 92 invasively ventilated patients, whereas the mortality rate among N.I.V group of patients (78.7%) was significantly higher. Increased TLC count, C-Reactive, Protein, Urea, Creatinine, Heart rate, Respiratory rate were mostly associated with increased mortality among non-invasively ventilated patients. Early intubation may decrease the risk of mortality in patients infected with severe COVID19 infection.

Keywords: COVID19 Mortality; High Flow Nasal Cannula (HFNC) oxygen therapy; Invasive mechanical ventilation; N.I.V.

In this pandemic situation, the entire world examines the cause, severity, diagnostic approach, treatment strategies and outcome of this dreaded infection, especially those undergoing mechanical ventilation. From late 2019 to date, globally; the mortality associated with resultant of the disease has exceeded 2.6 million of the population.[1] Most patients with COVID19 infections present with respiratory complaints; with majority of them having hypoxia of variable severity and thus end up needing some kind of mechanical ventilation.[2] It was found that most of the clinicians were confused regarding the timing of intubation, even if there was an indication for the same. A recently published questionnaire-based survey on the timing of intubation in COVID19 ARDS patients included 292 clinicians, 34.2% observed that there was higher mortality in patients intubated early and around 82% clinicians felt intubation might increase the risk of nosocomial infections.[3]

Intubation and invasive mechanical ventilation directly being the cause of mortality are still questionable. There was much discrepancy in outcomes for invasively ventilated patients with COVID19, as has been reported from different countries. Initially, an UK newspaper claimed higher mortality, of around 65% in those who have received mechanical ventilation. In support of that, an article published in JAMA also reported that around 88% mortality in patients who were intubated and put on mechanical ventilation.[4] However, later on Hannah Wunsch contradicted the above findings citing that the denominator used might not be correct as it excluded those patients still on ventilator in the ICU.[5] China and Italy have reported higher mortality in ventilated patients,[6–8] whereas, several studies conducted in the UK[9] reported lung-protective ventilation with low tidal volume[10], low driving pressure[11], high positive end-expiratory pressure (PEEP)[12,13], prone positioning[12] and extracorporeal membrane oxygenator (ECMO)[14,15] (ECMO) have aided in reducing the mortality in patients with acute respiratory distress syndrome (ARDS). But still it is not clear whether it can be applied in the routine practice of managing ARDS in patients infected with COVID19.

So, this study was planned to find out the association of invasive or non-invasive mechanical ventilation with mortality in patients with ARDS due to COVID19 infections. Various laboratory parameters, vitals [Heart Rate, Mean arterial pressure, Respiratory rate and Oxygen saturation (SpO2)] and arterial blood gas (ABG) parameters along with different ventilation strategies and their association with mortality were also analysed.

METHODOLOGY

Study design and participants

This is a single centred, observational cohort study conducted in an Intensive care unit (I.C.U) of a tertiary care hospital of eastern India. This study was conducted after getting approval from the institutional ethical committee. Need for individual informed consent was waived off because of observational nature of the study. The data collectors were trained and the study coordinators ensured the integrity and timely completion of the data collection.

Patients aged 18 years or more were eligible for this study. Patients who were admitted to the I.C.U with COVID19 infection and received ventilatory support were included. COVID19 infection was confirmed by either positive RT-PCR test or on the basis of typical abnormality in chest C.T. in the absence of other alternative diagnosis. To ensure the quality of the study, RT-PCR was confirmed from microbiologists and chest C.T. findings were confirmed from the radiologists. We have excluded the patients who were transferred to other hospitals with in 1 hour of ventilatory support and those in oxygen support with a face mask or Non-rebreather mask (NRBM). Ventilatory support is defined as those patients were received either Invasive mechanical ventilation (I.M.V.) or Non-invasive mechanical ventilation (N.I.V), or High-flow Nasal cannula (HFNC). Time period across which the data were collected was August 2020 to November 2020. We also followed up patients included during the above said time frame for extra one month to avoid outcome bias. No new patient data were recorded in that extra one-month period of time.

Procedure

Data collectors and doctors obtained the demographic variables including Age, available disease severity score like Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) score. Apart from demographic variables other relevant laboratory parameters (like Complete Blood Count (C.B.C), Liver Function Test (L.F.T), Renal Function Test (R.F.T), C-reactive protein (C.R.P), Serum Ferritin and Serum Procalcitonin), Vital parameters (Heart rate, Mean arterial pressure (M.A.P), Respiratory rate, SpO2) and ABG parameters (pH, PaCO2, PaO2, Bicarbonate, Lactate) were also collected for each individual.

We had initially developed an android platform-based application where all the above parameters were incorporated. Data collectors were trained about the use of the application. Only APACHE II and SOFA score were calculated for each eligible individual with the help of doctors. After the end of data collection, all the recorded data were incorporated into a Microsoft excel chart. Before analysis, the study coordinators screened all data for potential errors and incomplete recordings. The error or incomplete recordings were corrected with the help of doctors and data collectors. Further, all data were verified for appropriateness. After data cleaning, data analysis was started.

Outcomes

The primary outcome of our study was to compare mortality rate in those undergoing invasive or non-invasive mechanical ventilation or HFNC. Secondary outcome of our study was to study the laboratory parameters, vital parameters and ABG parameters among different types of ventilation. We have included patients who are still on ventilatory support after completion of study period into alive group to avoid observational bias.

Statistical analysis

We have presented the primary outcome as a binary variable. A convenience sampling technique was applied for the analysis. We did not adjust any multiplicity across the analysis. So, these findings should be interpreted as exploratory as we do not claim confirmed statistical evidence.

Continuous variables are presented as median [IQR] and categorical variables as frequency percentage. To find out the association of different types of ventilation with mortality, chi-square test was used. Kruskal Wallis test was used to find the association of laboratory parameters, vital parameters and ABG parameters with different types of ventilation. Furthermore, Mann-Whitney U non-parametric test was performed to find the association of all the above parameters with mortality.

The p value was set at 0.05 for the level of significance, which means a p value less than 0.05 was considered as statistically significant. Data were analysed with the SPSS version 25.0 statistical software.

RESULTS

Between August 2020 to November 2020, 398 patients were included in this study as per the eligibility criteria, but 22 patients were transferred to another hospital. Among 376 included patients, 198 (52.7%) were confirmed by RT-PCR and 178 (47.3%) confirmed by chest C.T. scan. 92 (24.5%) were received invasive mechanical ventilation, 236 (62.7%) received Non-invasive mechanical ventilation, and the rest 48 (12.8%) undergoing HFNC support. The mortality rate among the included patients was 39.9%. In our analysis, it was observed that the mortality rate was significantly higher in the patients who received Non-invasive mechanical ventilation (78.7%) as compared to the invasive mechanical ventilation group (17.3%) and HFNC group (4.0%) and also found a statistically significant association (p-value <0.001).

We did a separate analysis to find out the risk factors for patients undergoing mechanical ventilation. The analysis observed that there was no significant distribution of Age among different types of ventilated patients. The Median Age of patients in the Invasive and Non-invasive mechanical ventilation group was 45 years, whereas, in the HFNC group, it was 42.5 years. The average SOFA and APACHE II score in the Invasive ventilated group were 4 (IQR 3 - 5) and 8 (IQR 6 - 11), respectively, which is observed significantly higher from Non-invasive ventilated (Median of SOFA score 1 [IQR 0 – 3], Median of APACHE II score 5 [IQR 4 – 8]) and HFNC group of patients (Median of SOFA score 1 [IQR 0 – 2], Median of APACHE II score 3 [IQR 2 – 4.5]) with p-value <0.001. Among laboratory parameters, S.G.P.T, C.R.P and potassium values were significantly associated with different ventilation types with a p-value of 0.041, 0.002 and 0.009, respectively. The median heart rate in the Non-invasively ventilated patient group was 98 (IQR 86 - 113), which is comparatively higher than other groups (92 [IQR 77 – 106] in the Invasive group vs 81 [IQR 71 – 90] in the HFNC group) and also found statistically significant with p-value <0.001. Likewise, respiratory rate, SpO2 and temperature also found a statistically significant association with different types of ventilation with p-value 0.019, <0.001 and 0.029, respectively. In ABG, it was found that invasively ventilated patients had developed severe hypoxia, hypercapnia, and lactic acidosis compared to Non-invasive mechanical ventilation and HFNC (p-value 0.010, <0.001 and <0.001 respectively in between groups). *Table 2*

In another subgroup analysis, the median Age of patients observed to be higher in those died (48 [36 – 56] in death patients vs 43 [27 – 53] in the survivor group, p-value <0.001). The non-survivors were severely infected with a high APACHE II score (6 [4 – 10] in non-survivor vs 5 [4 – 8] in the survivor group, p-value 0.016). Other laboratory parameters also like T.L.C, C.R.P, Urea, Creatinine and Sodium levels increased in the non-survivor

Table 1. Association of different ventilator groups with outcome

	Outcome		
	Non-survivor (N%)	Survivor (N%)	*p* Value
I.M.V	26 (17.3%)	66 (29.2%)	< 0.001*
N.I.V	118 (78.7%)	118 (52.2%)	< 0.001*
HFNC	6 (4.0%)	42 (18.6%)	< 0.001*

*Showing statistically significant association.
All parameters were represented as frequency percentage (N%) and hypothesis testing was performed by using Chi - square test.
I.M.V – Invasive Mechanical Ventilation, N.I.V – Non-invasive mechanical ventilation, HFNC – High Flow Nasal Canula.

Table 2. Analysing risks associated with patients undergoing different types of ventilation.

	I.M.V Median [IQR]	N.I.V Median [IQR]	HFNC Median [IQR]	*p* Value
AGE	45[32-55]	45[34-56]	42.5[29-50]	0.194
SOFA	4[3-5]	1[0-3]	1[0-2]	<0.001*
APACHE II	8[6-11]	5[4-8]	3[2-4.5]	<0.001*
Haemoglobin	12.4 [11.20-13.50]	12.15 [10.2-13.4]	11.45 [8.90-12.8]	0.128
T.L.C	13.15 [7.73-17.33]	12.9 [8.76-16.2]	8.24 [6.52-15.30]	0.200
Platelet	211[122-335]	215[176-266]	201[153-233]	0.456
Neutrophil	91.5 [89.35-93.20]	89.4[82.6-93.7]	88.15[76.4-91.15]	0.084
Lymphocyte	6.15[4.75-8.10]	7.9[3.5-12.3]	9.9[7.1-21.1]	0.022*
S.G.O.T	59.5[50.0-348]	46[33.5-72]	65[36-94]	0.052
S.G.P.T	77.5[43.0-110.0]	39[24.5-61]	43[24-47]	0.041*
Ferritin	677.7 [265.80-2231.00]	563.4[349.4-829.4]	564.3[238.5-1900.0]	0.700
C.R.P	110[61-151]	70.5[34-110]	68[39-90]	0.002*
Urea	46.35[36.6-61.1]	42.1[34.6-64.7]	38.15[27.1-54.7]	0.268
Creatinine	0.85[0.6-1.1]	0.7[0.6-1.05]	0.7[0.7-1.3]	0.696
Sodium	141[138-145]	141[137.75-144.0]	139.5[137-142]	0.062
Potassium	4.4[3.8-4.8]	4.8[4.25-5.40]	4.6[4.0-5.1]	0.009*
Porcalcitonin	0.25[0.25-0.25]	0.15[0.15-0.45]	0.29[0.22-5.33]	0.185
M.A.P	94[48-100]	92[75-116]	93[73-104]	0.934
Heart Rate	92[77-106]	98[86-113]	81[71-90]	<0.001*
Respiration Rate	26[22-32]	26[22-29]	22[20.5-27.5]	0.019
SpO_2	95[93-98]	94.5[91-98]	97.5[96.5-99]	<0.001*
Temperature	98.2[98.0-98.6]	98.4[98.05-98.6]	98.4[98.4-98.6]	0.029*
pH	7.42[7.34-7.45]	7.43[7.38-7.46]	7.39[7.38-7.43]	0.117
pCO_2	36.3[33.0-39.9]	33.65[30.85-39.00]	99.7[87.1-123.0]	0.010*
pO_2	75[63.9-96.4]	71.8[58.84-90.85]	99.7[87.1-123.0]	<0.001*
Bicarbonate	23.7[21.4-26.2]	23.35[21.45-25.15]	22.1[20.8-23.6]	0.129
Lactate	2.05[1.5-3.85]	1.6[1.2-2.0]	1.6[1.2-1.7]	<0.001*

*Showing statistically significant association.
All parameters were represented as Median [IQR] and hypothesis testing was performed by using Kruskal Wallis test.
I.M.V – Invasive Mechanical Ventilation, N.I.V – Non-invasive mechanical ventilation, HFNC – High Flow Nasal Canula, SOFA – Sequential Organ Failure Assessment score, APACHE II - Acute Physiology and Chronic Health Evaluation II score, T.L.C – Total Leukocyte Count, S.G.O.T - Serum glutamic-oxaloacetic transaminase, S.G.P.T - Serum glutamic-pyruvic transaminase, C.R.P – C-reactive Protein, M.A.P – Mean Arterial Pressure, pH – Potential of Hydrogen, pCO2 – Partial pressure of Carbon Dioxide, pO2 – Partial pressure of Oxygen.

group and also found statistically significant with mortality (p-value 0.001, 0.006, <0.001, <0.001 and <0.001, respectively). Among vital parameters, increased heart rate (98 [86 – 118] in non-survivor vs 88 [76 – 105] in survivor, p-value <0.001), increased respiration rate (26 [23 – 31] in non-survivor vs 24 [22 – 29] in survivor, p-value 0.002) and decreased SpO2 (94 [91 – 97] in non-survivor vs 96 [93 – 98] in survivor, p-value 0.002) also observed to be associated with increased risk of mortality. Likewise, pH also found to be significantly associated with above; it was found that among non-survivors, most of them had low pH with a median value of 7.39 [7.33 – 7.44] and p-value <0.001.

DISCUSSION

This is a largest Indian observational study conducted among patients with COVID19 infections and received ventilator support. After analysis, it was observed that only 17.3% of patients died among invasively ventilated patients, whereas, 78.7% died among patients those were

Table 3. Analysing risks associated with mortality

	Non-Survivor Median [IQR]	Survivor Median [IQR]	*p* Value
AGE	48[36-56]	43[27-53]	<0.001*
SOFA	2[0-4]	2[0-3]	0.150
APACHE II	6[4-10]	5[4-8]	0.016*
Haemoglobin	11.6 [10.2-12.8]	12.45 [10.7-13.4]	0.065
T.L.C	14.81 [9.45-18.29]	11.09 [7.03-14.96]	0.001*
Platelet	209[146-258]	216.5[166-310]	0.112
Neutrophil	92.8[87.9-95.9]	88.95[82.2-92.5]	0.007
Lymphocyte	5.3[3.5-12.3]	8.9[5.75-14.6]	0.003*
S.G.O.T	63[39-79]	48[36-72]	0.239
S.G.P.T	45[26-91]	42[25-61.5]	0.297
Ferritin	734[375.5-1086.5]	502.8[265.8-684.0]	0.082
C.R.P	90[51-132]	70.5[31-110]	0.006*
Urea	54.7[39.1-86.1]	39.9[29.7-50.9]	<0.001*
Creatinine	0.9[0.7-1.4]	0.7[0.6-0.9]	<0.001*
Sodium	143[141-148]	140[137-142]	<0.001*
Potassium	4.6[4.1-5.5]	4.7[4.25-5.20]	0.450
Porcalcitonin	0.29[0.25-0.51]	0.22[0.15-0.45]	0.187
M.A.P	93[80-110]	96[84-100]	0.825
Heart Rate	98[86-118]	88[76-105]	<0.001*
Respiration Rate	26[23-31]	24[22-29]	0.002*
SpO_2	94[91-97]	96[93-98]	0.002*
Temperature	98.4[98.1-98.6]	98.4[98-98.6]	<0.809
pH	7.39[7.33-39.9]	7.43[7.39-7.46]	<0.001*
pCO_2	35.95[32.3-39.9]	34.8[31.6-39.5]	0.125
pO_2	74.55[60.9-97.8]	76.7[64.4-99.4]	0.553
Bicarbonate	22.5[20.0-24.9]	23.55[21.65-25.80]	0.043*
Lactate	1.7[1.4-2.6]	1.7[1.3-2.2]	<0.468

*Showing statistically significant association.

All parameters were represented as Median [IQR] and hypothesis testing was performed by using Mann Whitney - U test.

SOFA – Sequential Organ Failure Assessment score, APACHE II - Acute Physiology and Chronic Health Evaluation II score, T.L.C – Total Leukocyte Count, S.G.O.T - Serum glutamic-oxaloacetic transaminase, S.G.P.T - Serum glutamic-pyruvic transaminase, C.R.P – C-reactive Protein, M.A.P – Mean Arterial Pressure, pH – Potential of Hydrogen, pCO2 – Partial pressure of Carbon Dioxide, pO2 – Partial pressure of Oxygen.

on N.I.V support. There were observed various factors like SOFA score, APACHE II score, T.L.C, C.R.P, Urea, Creatinine, H.R., Respiratory rate, pH, pCO2 and lactate responsible for increased risk of mortality and I.M.V.

The clinical decision making for the ventilator support among COVID19 patients, which always varied, even if there was an indication for mechanical ventilation.[3] In Lung safe study, even if strong evidence and everyone were meeting the criteria for mechanical ventilation, 15% received N.I.V support and mortality among them found to be higher.[16] In another study, even if the clinicians preferred mechanical ventilation, most of them were not agreed with Invasive mechanical ventilation, although there was strong clinical evidence for above, like persistent hypoxia, tachypnoea, N.I.V failure.[17] In some dictum, they have mentioned the procedure associated with invasive mechanical ventilation such as preoxygenation, bag-mask ventilation and suctioning of airways increases the risk of Health Care associated pneumonia (HCPs) and mortality.[18] Secondly, availability of adequate resources played a major role for not preferring I.M.V in management of COVID19 patients.[19–21] A study published by Wang Y et al. included 344 patients, reported a 97% mortality rate among intubated patients, and the median duration of ventilator day was four days.[22] Grasselli G et al. also reported a 64% mortality rate among intubated patients in another Italian study.[8] This higher mortality rate in the above studies might be due to the non-availability of adequate resources because those patients who were receiving invasive mechanical ventilation required a longer duration of hospital stay.[23] In other words, a longer duration of hospital stays required a large number of beds and ventilators. Data collected from other regions like England, Northern Ireland and wales demonstrated 47.6% of died among 13020 intubated patients.[24] In support, a very recently published study by Auld SC et al. reported lower mortality among intubated patients (35.7%).[25] Our findings also demonstrated that 17.3% of patients died among 92 invasively ventilated patients.

In our cohort analysis, there was increased mortality, which is 78.7% among Non-invasively ventilated patients than invasively ventilated patients. It was also observed that even if there was a higher SOFA and APACHE II score in invasively ventilated patients, the mortality rate was much less compared to those who were received N.I.V support. This less mortality might be due to early decision-making for intubation because initial lung injury increases the capillary leakage, leading to the impairment of gaseous exchange and a vicious circle of self-inflicted lung injury.[26,27] N.I.V increases the fluctuation of pleural pressure that might trigger patient self-inflicted lung injury (P-SILI), which leads to worsening of pulmonary oedema and clinical outcome of patients.[26] The lung safe study showed higher mortality in N.I.V patients when there was a PaO2/FiO2 ratio <150 mm of Hg.[16]

In our analysis, increased C.R.P, respiration rate, pCO2 and decreased SpO2, pO2 was significantly associated with increased risk of invasive mechanical ventilation. In severe form of the disease, there were observed increased inflammatory markers, tachypnoea and persistent hypoxia. So, as per the severity of the disease, the risk of invasive mechanical ventilation also increases. In assessing the risk of mortality, it was observed that the median age was higher in patients who died than survivors. These findings also supported other studies conducted in different regions. A study conducted by Wang et al observed elevated W.B.C count (4.7 [3.4 – 6.4] vs 7.8 [4.7 – 11.9], p-value <0.001), C.R.P level (11.4 [2.2 – 27.9] vs 88.6 [59.7 - 118], p-value <0.001), D-dimer (0.2 [0.1 – 0.3] vs 0.5 [0.4 – 1.4], p-value <0.001) often associated with increased risk of mortality.[28] Another study conducted among 663 included patients, 25 of them died, and they had increased W.B.C count (p-value <0.001) and C.R.P level (p-value 0.014) compared to the survivors.[29] Our study also reported similar results. There were observed elevated T.L.C count (14.81 [9.45 – 18.29] in non-survivor vs 11.09 [7.03 – 14.96] in survivor, p-value 0.001), C.R.P (90 [51 – 132] in non-survivor vs 70.5 [31 – 110] in survivor, p-value 0.006), Urea (54.7 [39.1 – 86.1] in non-survivor vs 39.9 [29.7 – 50.9] in survivor, p-value <0.001), Creatinine (0.9 [0.7 – 1.4] in non-survivor vs 0.7 [0.6 – 0.9] in survivor, p-value <0.001) and sodium levels (143 [141 – 148] in non-survivor vs 140 [137 – 142] in survivor, p-value <0.001) in non-survivor group compared to survivors and also found to have statistically significant. Likewise, increased heart rate (98 [86 – 118] in non-survivor vs 88 [76

– 105] in survivor, p-value <0.001), respiratory rate (26 [23 – 31] in non-survivor vs 24 [22 – 29] in survivor, p-value 0.002) and SpO2 (94 [91 – 97] in non-survivor vs 96 [93 – 98] in survivor, p-value 0.002) which were predictors of severity of disease also significantly associated with mortality in patients with COVID19 infections.

CONCLUSION

In a cohort of critically ill patients with COVID19 infection, we reported although, invasively ventilated patients were more severely infected, mortality rate was significantly lower than Non-invasively ventilated patients due to early intubation when indicated. So, it may be recommended for early intubation rather than wait for more time with N.I.V support.

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Conflict of Interest

The authors declare that, there is no conflict of interest among them.

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