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Invasive versus non-invasive ventilation in patients with COVID-19 pneumonia: A retrospective study

Abhijit Nair[1]✉, Jacob Paul[1], Ajay Yadav[1], Khalid Al Sawafi[2]

[1]*Department of Anaesthesiology, Ibra Hospital, Ministry of Health-Oman, Sultanate of Oman*

[2]*Hospital Administration, Ibra Hospital, Ministry of Health-Oman, Sultanate of Oman*

ABSTRACT

Objective: To compare the survival and length of stay of invasive ventilation (IV) with those of non-invasive ventilation (NIV) in patients with COVID-19 acute respiratory distress syndrome in a single hospital from May 2020 to March 2021.

Methods: After obtaining approval from the Hospital Director, the data of COVID-19 patients including demographics, type of respiratory support (non-invasive ventilation or invasive ventilation), duration of ventilation, length of stay, discharge, and death were collected and analyzed.

Results: Out of the 152 patients identified, 134 patients were analyzed. The median intubation days were 10.0 (Q1: 3.5, Q3: 13.5) in the IV group and 0.0 (Q1: 0.0, Q3: 0.0) days in the NIV-only group. Out of the 101 patients who received NIV, 43 patients were subsequently intubated due to failure of NIV. Of the 63 patients (47.01%) who died, 22 (66.66%) were from the IV group and 40 (92.02%) were from the NIV-followed-by-intubation group, and 1 (1.72%) were from the NIV-only group. Multivariate analysis showed that the presence of a respiratory comorbidity (*OR*=16.56, 95% *CI*=1.56-175.48, *P*=0.02) was an independent predictor of survival.

Conclusions: Respiratory co-morbidity is a significant adverse predictor of survival outcome. The decision on the type of respiratory support should be made on a patient-to-patient basis.

KEYWORDS: Acute respiratory distress syndrome; COVID-19; Intensive care unit; Invasive ventilation; Morbidity; Mortality; Non-invasive ventilation

1. Introduction

Mechanical ventilation with low tidal volume (less than 6 mL/kg of ideal body weight) and low airway pressures (plateau pressure less than 30 cm water) is considered a standard of care for patients with acute respiratory distress syndrome (ARDS) of any etiology, especially when the PaO_2/FiO_2 (P/F) ratio is less than 150[1]. During the COVID-19 pandemic, the surge of sick patients with ARDS in the hospital posed a dilemma for clinicians. Many hospitals offered non-invasive ventilation (NIV) and high-flow nasal oxygenation (HFNO) in high-dependency areas due to a shortage of beds in the intensive care unit (ICU). There was no clarity at the beginning regarding the efficacy of early intubation, continuing NIV for an extended period to avoid endotracheal intubation, and admitting

Significance

Non-invasive ventilation can be offered to patients with COVID-19 pneumonia. However, the criteria are not well-defined. In this retrospective study, mortality was higher in patients on invasive ventilation than that of non-invasive ventilation. This study shows that the presence of respiratory co-morbidity is a significant adverse predictor of survival outcome.

✉To whom correspondence may be addressed. E-mail: abhijitnair95@gmail.com

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COVID-19 ARDS patients in high-dependency units[2,3].

Several societies over the world provided recommendations regarding when to initiate NIV, HFNO, and when to offer invasive ventilation (IV) to patients with COVID-19 ARDS[4-7]. Even before the pandemic, based on the data from the Large observational study to UNderstand the global impact of severe acute respiratory FailurE (LUNG SAFE) study, NIV was recommended in patients with ARDS according to the clinician's assessment, regardless of the severity[8]. During the pandemic, many clinicians supported the early IV strategy over NIV. However, the verdict is not out yet[9,10].

In our hospital, the anesthesiologists were involved in the care of COVID-19 patients who could not maintain oxygenation even with supplemental oxygen through a non-rebreathing mask, were tachypnoeic (respiratory rate >30/min), were in shock, had comorbidities, and had worsened inflammatory markers as well as radiological picture. The type of respiratory support was at the discretion of the anesthesiologist attending to the patient.

2. Patients and methods

2.1. Study design and setting

In this retrospective study, data were retrieved from electronic medical records (Al Shifa system, Ministry of Health, Oman) from May 2020 to March 2021 in a single hospital. The data retrieved included a total of 503 SARS-CoV-2 positive patients *via* reverse-transcriptase polymerase chain reaction test who were admitted to the ICU. Among these patients, 152 were referred for respiratory support.

2.2. Ethical approval

As this was a retrospective study, informed consent was not applicable, and as we do not have an ethical committee, relevant permission was obtained from the hospital administration (permission from Executive Director, Ibra Hospital, Ibra, Sultanate of Oman) on 14th May 2021.

2.3. Inclusion criteria

For this study, we included patients referred for respiratory support. Of the 503 patients, 152 patients with IV or NIV indicated in the electronic medical records were included. The patients who were managed with oxygen therapy using simple face mask or nasal canula were excluded. Out of these 152 patients, 18 patients were transferred to a higher-level center and were therefore excluded from analysis.

2.4. Grouping

Once a patient was referred for respiratory support, we ordered a baseline arterial blood gas estimation to assess the acid-base status and P/F ratio to quantify acute lung injury. NIV settings were titrated based on the severity and the trend of the P/F ratio. To facilitate NIV over a mask interface, sedoanalgesia in the form of intravenous

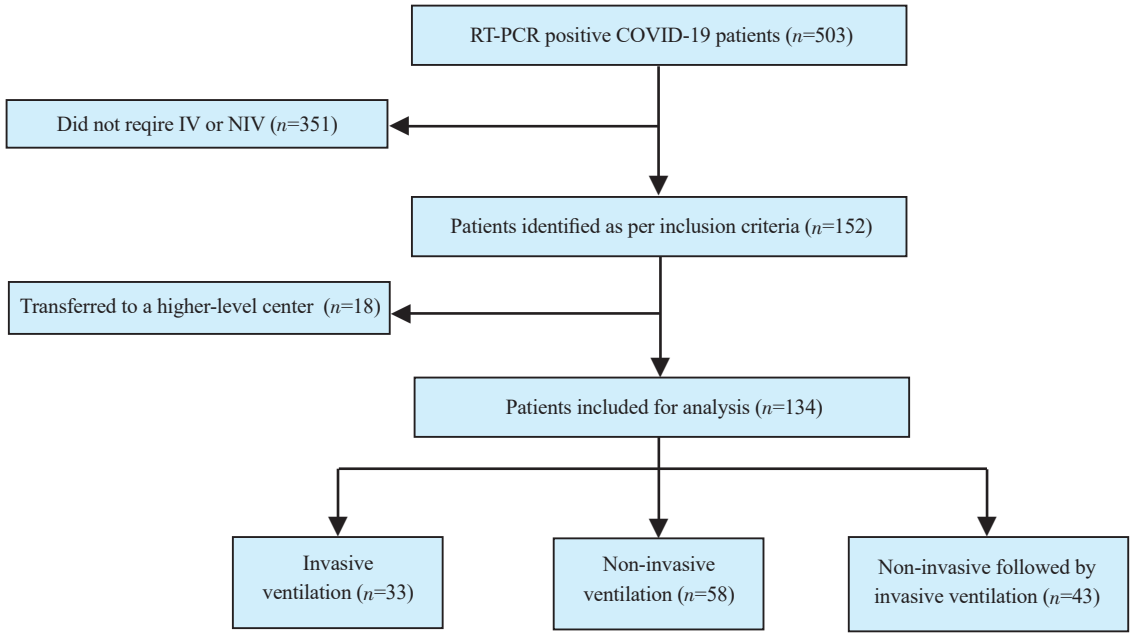

Figure 1. Flowchart of patients in different arms (invasiveventilation, non-invasive ventilation only, non-invasive followed by invasive ventilation).

fentanyl 0.5 μg/kg/h and midazolam (a maximum of 1 mg/h) was administered for all patients and titrated for an optimal response after carefully considering age and comorbidities. The patients on NIV with sedation were arousable and with intact mentation.

The decision to continue NIV even after having a trend of P/F ratio around 100 and at times even less than 100 was based on clinical correlation such as lack of worsening of respiratory distress, stable radiological picture, improving inflammatory markers, hemodynamic stability, and no signs of secondary pulmonary infection. The decision for IV was taken based on persistent tachypnoea, P/F ratio less than 100 with the highest positive end-expiratory pressure, worsening radiological picture and inflammatory markers, and persistent irritability suggestive of hypoxemia.

Unless clinically indicated, we continued NIV for at least 3 d because all the medication used for the disease (steroids, antivirals, broad-spectrum antibiotics) along with NIV would take some time to manifest in clinical improvement. After 3 d of NIV, if the patient did not improve clinically with ongoing pharmacotherapy, it was considered a failure of NIV. IV was then considered along with sedation, nasogastric tube insertion, urinary catheterization, invasive vascular lines as necessary, and prone ventilation based on the existing P/F ratio (less than 150). All patients who were intubated within 3 d of NIV initiation were considered in the IV group and those intubated after 3 d were considered eventually in the NIV-followed-by-intubation group (NIV-IV).

2.5. Primary and secondary outcomes

The primary outcome was a comparison of the overall survival between the IV, NIV-only, and NIV-IV groups. The secondary outcomes were a comparison of demographic characteristics, comorbidities, length of stay (LOS), duration of ventilation, and complications due to the chosen ventilatory strategy.

2.6. Statistical analysis

Demographics, NIV and IV details (duration of ventilation, timing of intubation), weaning details (extubation), discharge, and death of the patients were entered into a Microsoft Excel sheet (version: 16051.15726.20202.0) for analysis. Continuous variables were presented as mean ± standard deviation (if data were normally distributed) and median and interquartile range values (if data were not normally distributed). Categorical variables were depicted as frequency rates and percentages. Means for continuous variables were compared by the paired *t*-tests or the analysis of variance test. Proportions of categorical variables were compared using the Chi-squared test. Univariate and multivariate analyses were performed to determine the factors responsible for survival in these patients. All relevant analyses were performed using the Jeffreys's Amazing Statistics Program statistical program. A *P*-value <0.05 at a 95% confidence interval was considered statistically significant. Variables that have a *P*-value <0.10 at a 95% confidence interval in the univariate analysis were considered for multivariate analysis.

3. Results

Figure 1 demonstrates the flowchart of patients in different groups (IV, NIV-only, NIV-IV) and the outcomes. Table 1 summarizes the demographics, comorbidities, intubation days, LOS, and mortality across the three groups. The various comorbidities were comparable, except for pre-existing renal failure (*P*=0.012).

Out of the 134 patients who fulfilled the inclusion criteria, 33 patients (24.62%) were in the IV group who were either intubated immediately or on the second or the third day. The median number of intubation days for the IV patients was 10 (3.5, 13.5) d. A total of 58 patients (43.28%) received NIV only for a median of 6 (5, 9) d.

Table 1. Demographics and ventilation details of all patients.

Variables	IV (*n*=33)	NIV–only (*n*=58)	NIV–IV (*n*=43)	$F/H/\chi^2$	*P*
Age, years, mean±SD	65.2±16.2	54.3±15.7	54.3±15.7	20.964[F]	<0.001
Sex, *n*, %					
Male	21 (63.63%)	31 (53.45%)	30 (69.77%)	2.879[C]	0.237
Female	12 (36.36%)	27 (46.55%)	13 (30.23%)		
Comorbidities, *n*, %					
Hypertension	19 (57.33%)	33 (56.89%)	26 (60.46%)	0.136[C]	0.934
Diabetes mellitus	16 (48.48%)	22 (37.93%)	23 (53.48%)	2.564[C]	0.277
Respiratory	4 (12.12%)	1 (1.72%)	4 (9.30%)	4.305[C]	0.116
Renal	7 (21.21%)	2 (3.44%)	9 (20.93%)	8.768[C]	0.012
Neurological	3 (9.09%)	1 (1.72%)	3 (6.97%)	2.698[C]	0.259
Coronary artery disease	7 (21.21%)	10 (17.24%)	10 (23.25%)	0.586[C]	0.746
Others	7 (21.21%)	7 (12.06%)	8 (18.60%)	1.502[C]	0.472
NIV days, median, Q1, Q3	1.0 (0.5, 2.0)	6.0 (5.0, 9.0)	7.0 (5.0, 11.0)	68.910[H]	<0.001
Intubation days, median, Q1, Q3	10.0 (3.5, 13.5)	0.0 (0.0, 0.0)	4.5 (2.0, 12.0)	103.717[H]	<0.001
LOS, days, median, Q1, Q3	16 (11, 20)	12 (8, 18)	15 (9, 27)	7.648[H]	0.022
Mortality, *n*, %	22 (66.66%)	1 (1.72%)	40 (93.02%)	89.414[C]	<0.001

[F]Analysis of variance test; [C]Chi-squre test; [H]Kruskal Wallis *H* test; IV: invasive ventilation; NIV: non-invasive ventilation; NIV-IV: NIV followed by intubation; LOS: length of stay.

Table 2. Univariate analysis of variables associated with survival.

Variables	Survived (*n*=73)	Died (*n*=61)	$t/U/\chi^2$	*P*
Type of ventilation, *n*, %				
IV	13 (39.39%)	20 (60.61%)	5.966[C]	0.051[*]
NIV	31 (53.45%)	27 (46.55%)		
NIV-IV	29 (67.44%)	14 (32.56%)		
Age, years, mean±SD	62.5±15.3	62.0±18.0	−0.177[t]	0.859
Sex, *n*, %				
Male	47 (57.32%)	35 (42.68%)	0.687[C]	0.407
Female	26 (50.00%)	26 (50.00%)		
NIV days, median, Q1, Q3	5 (2, 7)	5 (3, 8)	2031.000[U]	0.381
Intubation days, median, Q1,Q3	1 (0, 9)	1 (0, 6)	2134.000[U]	0.666
LOS, days, median, Q1, Q3	14 (8, 19)	14 (10, 20)	1984.000[U]	0.279
Hypertension, *n*, %				
Yes	42 (56.76%)	32 (43.24%)	0.346[C]	0.556
No	31 (51.67%)	29 (48.33%)		
Diabetes mellitus, *n*, %				
Yes	38 (61.29%)	24 (38.71%)	2.160[C]	0.142
No	35 (48.61%)	37 (51.39%)		
Respiratory comorbidity, *n*, %				
Yes	1 (11.11%)	8 (88.89%)	7.316[C]	0.007[*]
No	72 (57.60%)	53 (42.40%)		
Renal comorbidity, *n*, %				
Yes	9 (47.37%)	10 (52.63%)	0.451[C]	0.502
No	64 (55.65%)	51 (44.35%)		
CNS comorbidity, *n*, %				
Yes	5 (62.5%)	3 (37.5%)	0.221[C]	0.638
No	68 (53.97%)	58 (46.03%)		
Coronary artery disease, *n*, %				
Yes	15 (55.56%)	12 (44.44%)	0.016[C]	0.900
No	58 (54.21%)	49 (45.79%)		
Other comorbidity, *n*, %				
Yes	13 (48.15%)	14 (51.85%)	0.546[C]	0.460
No	60 (56.08%)	47 (43.92%)		

[C]Chi-squre test; [t]the paired *t*-test; [U] Mann-Whitney *U* test; CNS: central nervous system; [*]*P*<0.10, varibles considered for multivariate analysis.

Table 3. Multivariate logistic regression analysis of significant risk factors of mortality.

Variables	Beta coefficient	Standard error	Wald statistic	*P*	Odds ratio (95% *CI*)
Type of ventilation, *n*, %					
IV	Reference	-	-	-	-
NIV	0.57	0.47	1.48	0.22	1.77 (0.71-4.43)
NIV-IV	1.17	0.51	5.31	0.02	3.21 (1.19-8.67)
Respiratory comorbidity, *n*, %					
No	Reference	-	-	-	-
Yes	−2.81	1.21	5.43	0.02	16.56 (1.56-175.48)

The median day to intubation for the remaining 43 NIV-IV patients was 7 (5, 11) d. The median LOS in days was 16 (11, 20), 12 (8, 18), and 15 (9, 27) in the IV, NIV-only, and NIV-IV groups respectively and the difference among the groups were statistically significant (*P*=0.022). The number of deaths was 22, 1, and 40 in the IV, NIV-only, and NIV-IV groups respectively and there was a statistically significant difference among the groups (*P*<0.001).The mortality in patients who were offered early intubation was 66.66% and in patients who were intubated after 3 d of NIV, the mortality was 93.02% (Table 1).

Univariate analysis of the risk factors in COVID-19 patients showed that the type of ventilation (*P*=0.051), and the presence of respiratory comorbidity (*P*=0.007) were responsible for predicting survival. Further multivariate analysis found that the presence of respiratory comorbidity was independently responsible for predicting survival if LOS and type of ventilation remained constant (*OR*=16.56, 95% *CI*=1.56-175.48, *P*=0.02) (Table 2, 3).

4. Discussion

In a multicenter, observational study involving 25 ICUs, Boscollo *et al* investigated the outcomes of COVID-19 patients intubated after the failure of NIV. On analysis of the data gathered from 280

patients who fulfilled the inclusion criteria, the authors concluded that the in-hospital mortality of ICU patients intubated after NIV failure was 43%, and the days on NIV before ICU admission and age were the potential risk factors of greater in-hospital mortality[11]. In a retrospective study, Daniel *et al* analyzed data gathered from 222 patients. The authors compared all-cause 30-day mortality for hospitalized COVID-19 patients with respiratory failure who underwent intubation first, intubation after NIV, or NIV only. The overall mortality of enrolled patients was 77.5% with patients in the intubation first group having a mortality of 82%, in intubation after NIV having a mortality of 84%, and the NIV-only group having a mortality of 69%. The mortality rate of patients who were intubated first and who were intubated after NIV was comparable[12].

In a prospective study by Chacko *et al*, the authors had a total of 286 patients who received NIV, and 47 patients underwent mechanical ventilation due to severe ARDS as they were unsuitable for NIV. NIV was initiated if the P/F ratio on admission was 100-300 and was tachypneic (respiratory rate more than 24 with increased work of breathing and use of accessory muscles). Out of the 286 patients, 204 patients (71.3%) were managed on NIV only, and out of which, 22 patients (10.8%) died. The remaining 82 (28.7%) patients underwent endotracheal intubation subsequently and 64 patients (78%) died. The overall mortality was 33.1% (30.1% in the NIV group and 59.6% in the IV group)[13]. In a retrospective study by Menzella *et al*, the authors analyzed the outcomes of 79 patients admitted with COVID-19 acute respiratory failure who were initiated on NIV. NIV was successful in 38 (48.1%) patients, and NIV failure in 41 patients (51.9%). Out of the 41 patients who failed NIV, 20 patients (25.3%) died[14]. In a retrospective study by Copolla *et al*, the authors started continuous positive airway pressure (CPAP) ventilation on 156 patients with a 100-200 P/F ratio. Out of the 156 patients, 93 were successfully managed on CPAP and 63 patients were managed with either NIV (45 patients) or IV (18 patients) depending on the clinical condition. Out of the 45 patients managed with NIV, NIV was successful in 16 patients, and 29 patients required IV and out of which 13 patients (28.9%) died eventually. Out of the 18 CPAP-failed patients, 14 patients (77.8%) eventually died[15]. In another retrospective, multicenter study by Zhou *et al*, the authors identified 68 patients who were initially started on HFNC or NIV. Out of this, 51 recovered and 17 patients required IV. Out of the 17 IV-required patients, 9 recovered, 4 received extracorporeal membrane oxygenation treatment, and 4 died[16].

There exists ambiguity in the choice of type of ventilation in COVID-19 pneumonia patients. Several researchers are proponents of early intubation. Hyman *et al* published their study with 755 COVID-19 ARDS patients that showed out of which 121 patients (16%) were mechanically ventilated and discharged home, 512 (68%) had died, 113 (15%) were discharged for rehabilitation, and 9 (1%) continued to stay in the hospital for medical reasons. The authors concluded that early intubation may be associated with improved survival[17]. Rola *et al* were of the opinion that early intubation could predispose to ventilator-associated pneumonia, hemodynamic issues due to sedation, barotrauma, critical illness polyneuropathy, and myopathy as results of muscle relaxants use. The authors suggested individualizing the respiratory support, IV or NIV, based on patient characteristics[18]. On the contrary, Al-Tarbsheh *et al* believed that the timing of intubation was not associated with poor clinical outcomes. This was based on the results of their retrospective study involving 128 patients, out of which 66.4% required early intubation, and 33.6% required late intubation. The 28-day all-cause mortality and hospital and ICU length of stay were equal regardless of the timing of intubation[9]. Similarly, Matta *et al* concluded that the timing of intubation has no impact on clinical outcomes among patients with COVID-19 pneumonia. This was based on their observational study involving 111 patients and out of which 76 (68%) underwent early intubation based on a higher sequential organ failure assessment score. On analysis, it was revealed that the overall outcome was comparable between early and late intubation[19].

There are several limitations of this study. Firstly, it was an observational study that is retrospective. Secondly, the data gathered and analyzed was from a single institute only. Moreover, we did not do a sub-group analysis of NIV and HFNC because in many cases it was used alternatively (especially during feeding and at times in an awake prone position). Many parameters such as inflammatory markers, chest radiographs, computed tomography scans, ventilatory settings, secondary bacterial infections, fluid balance, delirium, and sedation scores were not compared. These factors could also have been responsible for the disease severity, LOS, morbidity, and mortality eventually.

When selecting the appropriate respiratory support, NIV can be safely and effectively used in patients with COVID-19 ARDS. Based on existing pieces of evidence, it is not clear if early intubation is superior to NIV in these patients. Respiratory co-morbidity is a significant adverse predictor of survival outcome. Particular attention should be pay to patients with respiratory con-morbidity, and the decision on the type of respiratory support should be made on a patient-to-patient basis. Further studies, systematic reviews, and meta-analyses are needed to define the optimal timing of initiating IV and the duration of NIV in such patients.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

All authors contributed to the concept development. AN, JP, and AY designed the study. AN and JP defined the intellectual content and edited the manuscript. AN and AY performed literature review. AN prepared for, and also reviewed the manuscript with AY and KAS.

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