Noninvasive Respiratory Assist Devices in the Management of COVID-19-related Hypoxic Respiratory Failure: Pune ISCCM COVID-19 ARDS Study Consortium (PICASo)

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Abstract

Objective: To determine whether high-flow nasal oxygen (HFNO) or noninvasive ventilator (NIV) can avoid invasive mechanical ventilation (IMV) in COVID-19-related acute respiratory distress syndrome (ADRS), and the outcome predictors of these modalities.

Design: Multicenter retrospective study conducted in 12 ICUs in Pune, India.

Patients: Patients with COVID-19 pneumonia who had PaO_2/FiO_2 ratio <150 and were treated with HFNO and/or NIV.

Intervention: HFNO and/or NIV.

Measurements: The primary outcome was to assess the need of IMV. Secondary outcomes were death at Day 28 and mortality rates in different treatment groups.

Main results: Among 1,201 patients who met the inclusion criteria, 35.9% (431/1,201) were treated successfully with HFNO and/or NIV and did not require IMV. About 59.5% (714/1,201) patients needed IMV for the failure of HFNO and/or NIV. About 48.3, 61.6, and 63.6% of patients who were treated with HFNO, NIV, or both, respectively, needed IMV. The need of IMV was significantly lower in the HFNO group (p <0.001). The 28-day mortality was 44.9, 59.9, and 59.6% in the patients treated with HFNO, NIV, or both, respectively (p <0.001). On multivariate regression analysis, presence of any comorbidity, SpO_2 <90%, and presence of nonrespiratory organ dysfunction were independent and significant determinants of mortality (p <0.05).

Conclusions: During COVID-19 pandemic surge, HFNO and/or NIV could successfully avoid IMV in 35.5% individuals with PO_2/FiO_2 ratio <150. Those who needed IMV due to failure of HFNO or NIV had high (87.5%) mortality.

Keywords: High-flow nasal oxygen, Mechanical ventilation, Moderate-to-severe acute respiratory distress syndrome, Noninvasive ventilation.

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Highlight

In resource-limited setting, of the 1,201 severe ARDS patients treated with HFNO and/or NIV during COVID-19 pandemic surge due to unavailability of invasive mechanical ventilators, 35.9% successfully avoided IMV and survived. Those who needed invasive mechanical ventilation due to failure of HFNO or NIV had high (87.5%) mortality.

Introduction

Coronavirus disease-2019 (COVID-19) has severely impacted health care systems all over the world. Patients infected with COVID-19 present in various stages of hypoxia due to rapidly progressive respiratory failure. At times, they develop bilateral pneumonia leading to ARDS which is associated with higher mortality rates (30–90%)[1] compared to non-COVID-19 ARDS (23–47%).[2]

Noninvasive respiratory assist devices (NIRADs) are commonly used in the management of respiratory failure of varied etiologies. Particularly, NIVs, such as BiPAP and CPAP, are useful in cases of acute respiratory failure due to chronic obstructive pulmonary disease and cardiogenic pulmonary edema.[3–5] On the contrary, HFNO has been shown to reduce the need for invasive mechanical ventilation (IMV) in hypoxic patients.[6]

During the pre-COVID era, the standard practice involved giving a trial of NIRAD to patients with PaO_2/FiO_2 greater than

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150, whereas those with PaO_2/FiO_2 less than 150 were intubated and mechanically ventilated while implementing lung protection strategies as per the ARDSnet protocols. However, there were no definitive data about the role of NIRAD in the management of severely hypoxic patients.[7–9] The COVID-19 pandemic presented a unique opportunity, owing to severe resource constraints, to evaluate NIRAD use in severe hypoxic respiratory failure (HRF) associated with COVID-19.

In this study named as Pune ISCCM COVID-19 ARDS Study Consortium (PICASo), our primary objective was to study the effectiveness of NIRAD in avoiding IMV in COVID-19-associated severe HRF. The secondary outcomes studied were the mortality rates in different treatment groups and their outcome predictors.

MATERIALS AND METHODS

Study Overview

It is a multicentre retrospective cohort study involving 12 tertiary care hospitals in Pune, India. The study cohort included COVID-19 patients with HRF who were treated with NIRAD (HFNO or NIV or both) during April 1, 2020–December 31, 2020. During this study period, all the ICUs were facing serious scarcity of trained workforce and ventilators. Thus, the patients who were otherwise candidates for invasive mechanical ventilation were managed with HFNO and/or NIV as per the discretion of the treating intensivist. Only those adult patients presenting with the first episode of HRF were considered (see eligibility criteria). The study was approved by all the Institutional Ethics Committees of the participating hospitals. Written informed consent was waived by the all the Institutional Ethics Committees in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care. The demographic, clinical, laboratory, treatment, and outcome data of patients were extracted from the electronic medical records of the participating hospitals using a standardized data collection form by ICU registrars and were analyzed by the respective intensivists. Data of all the patients who fulfilled inclusion criteria and did not have any exclusion criteria during this study period were collected to avoid any selection bias. We did not use the term "acute respiratory distress syndrome" for defining COVID-19 disease-related hypoxia as many of our patients did not receive any form of positive pressure ventilation and were managed by HFNO alone, and thus, current Berlin definition of ARDS was not applicable to them.

Eligibility for the Study

Inclusion Criteria
- COVID-19 patients admitted to ICU, disease status confirmed by RT-PCR or antigen test
- Age greater than 18 years
- First episode of COVID-19-related acute hypoxic respiratory failure with P/F ratio < 150 treated with HFNO and or NIV

Exclusion Criteria
- Application of NIRAD for less than 6 consecutive hours
- Postextubation respiratory failure
- Post-COVID-19 respiratory failure (respiratory failure developed at least 21 days after COVID-19 infection)
- Patients with advance directive of "do not intubate" in whom NIRAD application was intended to provide comfort care

Outcomes

The primary outcome was the proportion of patients on NIRAD who eventually required IMV. The secondary outcomes studied were the mortality rates in different treatment groups and their outcome predictors.

Statistical Analysis

The data involving categorical variables are summarized here as proportions (% of cases) and those involving numerical variables as mean (+standard variables). Sample proportions were compared using Chi-square test or Fisher's exact probability test (if more than 20% cells had expected frequency less than 5). On the contrary, sample means were compared using independent sample *t*-test for two groups and by ANOVA for more than two groups. The underlying normality assumption was tested before subjecting the study variables to these tests. Appropriate variance stabilizing transformations were applied if any data were found to be non-normally distributed.[10,11]

In the entire study, 95% confidence level (p <0.05) was considered for statistical significance. The data were statistically analyzed using Statistical Package for Social Sciences (SPSS version 22.0, IBM Corporation, USA) for MS Windows.

Variability was expressed as SD for normally distributed variables and as median [interquartile range (IQR)] for non-normally distributed. Since this was a retrospective study involving standard of care, there were no missing data.

RESULTS

During the study period of 9 months, a total of 1,217 COVID-19-positive patients were admitted in the participating ICUs. Of these, 16 patients did not meet the inclusion criteria [decision to withdraw life sustaining therapy ($n = 3$), discharged against medical advice ($n = 13$)]. Thus, we analyzed data of 1,201 patients and there were no missing data for the analysis. Among 1,201 patients, 236 (19.7%) were treated with HFNO, 690 (56.9%) with NIV/CPAP, and 275 (22.9%) with both (HFNO and NIV) (Flowchart 1).

Baseline Characteristics

The baseline characteristics of the patients across different outcome groups are presented in Table 1. Majority of the enrolled patients were male. There was a statistically significant association between subsequent requirement of IMV or death on NIRAD and older age, presence of certain comorbidities like hypertension and ischemic heart disease, higher heart rate and respiratory rate, lowest oxygen saturation (SpO_2) before initiation of NIRAD, higher pCO_2 ratio, and lower PaO_2/FiO_2 ratio.

Primary Outcome

Out of all the subjects, 236/1,201 (19.6%) received HFNO alone, 690/1,201 (57.4%) received NIV alone, and 275/1,201 (22.9%) were

Flowchart 1: Flowchart showing patient enrolment process, the primary outcome, and one of the secondary outcomes (discharge vs death)
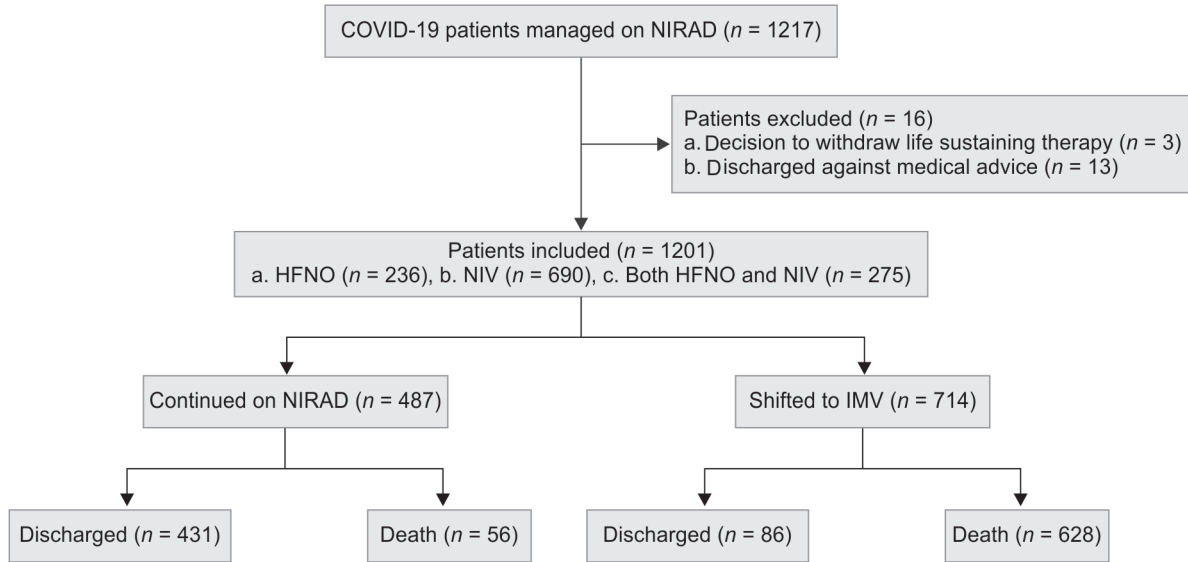

Table 1: Baseline characteristics across different outcome groups

Parameter	Discharged and not required IMV on NIRAD (n = 431)	Required IMV on NIRAD (n = 714)	Death on NIRAD (n = 56)	p-value
Demography				
Age (years) Mean ± SD	56.3 ± 13.4	61.3 ± 12.6	68.8 ± 11.2	0.001***
Sex n (% Male)	310 (71.9%)	506 (70.9%)	36 (64.3%)	0.495NS
Comorbidities				
Diabetes n (%)	178 (41.3%)	281 (39.4%)	30 (53.6%)	0.108NS
Hypertension n (%)	174 (40.4%)	362 (50.7%)	27 (48.2%)	0.003**
Ischemic heart disease n (%)	40 (9.3%)	91 (12.7%)	13 (23.2%)	0.007**
Obesity n (%)	39 (9.0%)	51 (7.1%)	5 (8.9%)	0.491NS
Other n (%)	51 (11.8%)	128 (17.9%)	13 (23.2%)	0.008**
Duration of illness before NIRAD (days) Mean ± SD	5.9 ± 3.4	5.8 ± 3.5	6.5 ± 4.2	0.305NS
Vital parameters				
HR (beats/minute) Mean ± SD	92.0 ± 17.2	95.2 ± 17.8	93.3 ± 17.7	0.011*
MAP (mm Hg) Mean ± SD	86.6 ± 23.4	86.6 ± 22.9	88.1 ± 16.2	0.891NS
RR (breaths/minute) Mean ± SD	28.3 ± 8.7	29.5 ± 7.2	30.2 ± 7.8	0.028*
SpO_2 Mean ± SD	84.8 ± 7.9	82.4 ± 9.7	86.2 ± 6.9	0.001***
ABG				
pH Median (IQR)	7.4 [7.36–7.44]	7.4 [7.35–7.44]	7.4 [7.33–7.43]	0.109NS
PO_2 Median (IQR)	62.4 [49.0–78.4]	57.0 [47.0–70.0]	56.0 [47.0–68.0]	0.113NS
pCO_2 Median (IQR)	35.0 [30.0–40.5]	32.3 [28.0–39.0]	36.0 [30.6–41.0]	0.009**
P/F ratio Median (IQR)	92.6 [70.0–139.0]	81.0 [62.0–127.5]	88.5 [59.0–111.0]	0.015*

*p <0.05, **p <0.01, ***p <0.001; NS, statistically nonsignificant

treated with both, HFNO and NIV. Out of all the subjects, 40.5% were managed only with NIRAD (487/1,201), while 59.5% (714/1,201) subsequently needed IMV (Table 2). About 48.3% (114/236), 61.6% (425/690), and 63.6% (175/275) of patients who were initially on HFNO, NIV, or both, respectively, eventually needed IMV (Table 2). The need for intubation and mechanical ventilation was significantly lower in the HFNO group compared to other two groups (p <0.001) (Fig. 1).

Table 2: Endpoints of patients treated with NIRAD

Parameter	No. (%)	HFNO (n = 236)	NIV (n = 690)	Both (n = 275)	p-value
Final outcome on NIRAD n = 1,201					
Discharged	n (%)	130 (55.1%)	277 (40.1%)	111 (40.4%)	0.001[**]
Death	n (%)	106 (44.9%)	413 (59.9%)	164 (59.6%)	
Length of hospital stay Days	Median (IQR)	14.0 [10.0–19.0]	13.0 [9.0–19.0]	15.0 (11.0) [10.0–21.0]	0.001[**]
Outcome on IMV group n = 714		**HFNO (n = 114)**	**NIV (n = 425)**	**Both (n = 175)**	
Discharged	n (%)	15 (13.2%)	49 (11.5%)	N22 (12.6%)	0.867[NS]
Death	n (%)	99 (86.8%)	376 (88.5%)	153 (87.4%)	
Length of hospital stay Days	Median (IQR)	12.0 [9.0–18.0]	12.0 [8.0–18.0]	13.0 [10.0–20.0]	0.008[*]

p values for categorical variables by Chi-square test, p values for continuous variables by ANOVA on normalized data. $p < 0.05$ is considered to be statistically significant. [*]$p < 0.01$, [**]$p < 0.001$; NS, statistically nonsignificant
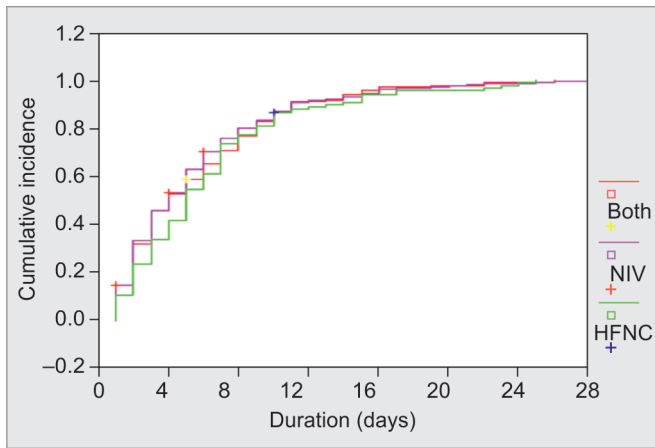

Fig. 1: Kaplan–Meier (KM) plot comparing NIV, HFNO, and both for intubation

Secondary Outcomes

The mortality rate in patients treated with NIRAD was 11.5% (56/487) against 87.9% (628/714) in those who progressed to IMV (Table 2). Among those receiving NIRAD only, HFNO treatment was associated with the least mortality (44.9%) compared to the other two (59.9 and 59.6%) (Table 2).

Distribution of Outcomes of NIRAD

On multivariate logistic regression analysis (Table 3), higher age-group (>50 years), presence of any medical comorbidity, baseline SpO_2 <90%, and presence of nonrespiratory organ dysfunction are the independent and significant determinants of incidence of mortality after correcting for sex, duration of illness before NIRAD, RV dysfunction, duration on NIRAD, and the level of worst P/F ratio on NIRAD ($p < 0.05$ for all).

Discussion

In resource-limited settings, during COVID-19 pandemic surge, NIRADs like HFNO and/or NIV could successfully avoid intubation and invasive mechanical ventilation in 35.5% individuals with acute severe hypoxic failure. Invasive mechanical ventilation applied after failure of NIRAD was associated with very high (87.9%) mortality in these patients. Our study also showed that higher age-group (>50 years), presence of any medical comorbidity, baseline SpO_2 <90%, and presence of nonrespiratory

Table 3: Multivariate logistic regression analysis to obtain the independent determinants of incidence of mortality

Risk factors (variables included in the model)	Odds ratio (OR)	95% CI for odds ratio	p-value
Age-group			
<50 years	1.00	—	—
>50 years	3.98	2.65–6.77	0.001[***]
Sex			
Female	1.00	—	—
Male	1.49	0.89–3.83	0.127[NS]
Medical comorbidity			
Absent	1.00	—	—
Present	4.53	2.41–8.37	0.001[***]
Duration of illness			
<5 days	1.00	—	—
>5 days	2.13	0.90–4.53	0.104[NS]
Baseline SpO_2			
>90%	1.00	—	—
<90%	3.59	1.92–6.63	0.001[***]
Nonrespiratory organ dysfunction			
Absent	1.00	—	—
Present	4.05	2.15–8.06	0.001[***]
RV dysfunction			
Absent	1.00	—	—
Present	2.22	0.94–4.82	0.089[NS]
Duration on NIRAD			
>96 hours	1.00	—	—
<96 hours	1.77	0.86–4.93	0.196[NS]
Worst P/F ratio on NIRAD			
>81 (median)	1.00	—	—
<81 (median)	1.88	0.83–3.05	0.113[NS]

(Odds ratio = 1.00: Reference Category). Dependent variable: mortality (death). [*]$p < 0.05$, [***]$p < 0.001$; NS, statistically nonsignificant

organ dysfunction are independent and significant determinants of mortality on NIRAD.

NIRADs were used commonly in the pre-COVID-19 era for providing respiratory support in patients with PaO_2/FiO_2 ratio above 150. However, very limited data existed regarding their definitive role in patients with P/F ratio <150 and more importantly below 100.[12–14] During the pandemic, various factors like severe resource

constraints (including ICU beds, ventilators, trained staff, and drugs including oxygen), a huge deluge of patients, and high mortality rates in patients treated with IMV compelled use of NIRAD even in the latter cases. Moreover, the use of NIRAD was not restricted to the intensive care setting and hospitals started offering this modality even in the wards to patients who were refractory to conventional oxygen therapy.

Numerous studies describing the effectiveness of NIRAD in the management of COVID-19-associated severe HRF have been published.[14–29] Majority of these studies are retrospective observational studies, and very few of them have included all the modes of NIRAD, either alone or together. The published data show high failure rates ranging from 30 to 60% in patients managed with HFNO[14,16–19] and similar rates (39–50%) for NIV[20–29] with no definitive survival benefits.

Ours is the first study that evaluates different NIRAD modes (alone and in combination) in the management of COVID-19-related severe HRF. It is also one of the largest studies in this regard. It collated data from 14 different ICUs that showed that NIRAD could be used to provide respiratory support even in patients with severe hypoxemia with P/F ratio below 150. IMV could be avoided altogether in 40.5% of such patients. Patients managed with HFNO had better survival compared to NIV or their combination. It also showed some survival benefit of NIRAD in the study cohort especially when it was not required to transfer NIRAD patients to IMV.

As was the inevitability, the participant hospitals were working with variable and depleted resources during the study period. As a result, clinicians had to employ unconventional strategies to avoid intubation that included initiation of NIRAD in patients with severe hypoxia and continuation of respiratory support till the definitive outcome; which was either discharge, initiation of IMV on freeing of ventilators, or death on NIRAD itself. NIV was especially used liberally in many centers in the initial management of COVID-19 patients even though its role in patients with severe HRF is debated.[4,21–27,30] Similarly, HFNO was employed in many patients, either standalone or in combination with NIV in an attempt to delay IMV. As a matter of fact, there is very little literature supporting the utility of using both these modalities in unison for the purpose[8,29,31,32] and the data on their exact sequence or on subsequent escalation do not exist.

Despite the above limitations, our mortality rates were comparable with the data published in many studies during the pandemic. Although the discharge rate in our study in patients managed on HFNO alone was comparable to other studies, mortality among HFNO failures was higher 87.9% compared to Calligaro et al. (75%)[19] and was similar to that published by Rorat et al. (92%).[20] The latter was conducted in a resource-limited setting like ours. A similar trend was observed when NIV alone was used as the respiratory support method. These high mortality rates could be partly explained by the severity of hypoxemia compared to other studies[22] and partly by the absence of a helmet-based interface for providing NIV that has been shown to be well-tolerated and to improve clinical outcomes in one study.[23] When both these modalities were implemented in tandem, around one-third of patients were discharged, while the mortality on failure was still high at around 60%. These data are similar to the findings by Liu et al.[32] in terms of success rates, even though an exact comparison is not possible owing to differences in demographics and available resources. We could also identify a few potential prognostic indicators for COVID-19 patients undergoing NIRAD therapy, such as age of the patient, preexisting comorbidities, oxygenation indices, and development of organ dysfunction during the course of treatment.

Undue prolongation of treatment with NIRAD could worsen the already hypoxic and damaged lungs leading to increase in mortality once IMV is initiated in COVID-19 patients. Also, there is need to triage patients for fair allocation of resources in resource-limited settings. Some scoring systems like the ROX index[33] and the HACOR score[34,35] have been developed to identify population at risk for NIRAD failure who could benefit from early initiation of IMV in patients with acute HRF due to non-COVID etiologies. Similar scoring system needs to be developed for COVID-19 patients with the help of a prospective studies in the future. Older age, medical comorbidities, prolonged duration of NIRAD therapy, and worsening or nonimproving oxygenation on NIRAD are well-known poor prognostic indicators for survival in these patients. Our study additionally showed that development of RV dysfunction and development of new nonrespiratory organ dysfunction on NIRAD are also poor prognostic indicators.

Limitations of Study

The main limitation of our study is its retrospective nature. Secondly, the clinical data were collected during the peak period of the pandemic when the participating ICUs were not in a position to deliver standard ICU care due to lack of trained workforce, appropriate machines and devices, and drugs including oxygen. Thirdly, application of the type of NIRAD was not protocolized and was applied as per the availability of the devices and the choice of the treating intensivist. Fourthly, the decision of intubation and application of mechanical ventilation were largely based on individual physician's discretion and the availability of resources for invasive mechanical ventilation.

CONCLUSION

In resource-limited settings, during COVID-19 pandemic surge, NIRADs like HFNO and/or NIV can successfully avoid IMV in 35.5% individuals with acute severe hypoxic failure. Invasive mechanical ventilation applied after failure of NIRAD is associated with very high (87.9%) mortality in these patients.

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