ORIGINAL ARTICLE

Helmet NIV in Acute Hypoxemic Respiratory Failure due to COVID-19: Change in PaO_2/FiO_2 Ratio a Predictor of Success

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Abstract

In acute respiratory failure due to severe coronavirus disease 2019 (COVID-19) pneumonia, mechanical ventilation remains challenging and may result in high mortality. The use of noninvasive ventilation (NIV) may delay required invasive ventilation, increase adverse outcomes, and have a potential aerosol risk to caregivers. Data of 30 patients were collected from patient files and analyzed. Twenty-one (70%) patients were weaned successfully after helmet-NIV support (NIV success group), and invasive mechanical ventilation was required in 9 (30%) patients (NIV failure group) of which 8 (26.7%) patients died. In NIV success vs failure patients, the mean baseline PaO_2/FiO_2 ratio (PFR) (147.2 ± 57.9 vs 156.8 ± 59.0 mm Hg; $p = 0.683$) and PFR before initiation of helmet (132.3 ± 46.9 vs 121.6 ± 32.7 mm Hg; $p = 0.541$) were comparable. The NIV success group demonstrated a progressive improvement in PFR in comparison with the failure group at 2 hours (158.8 ± 56.1 vs 118.7 ± 40.7 mm Hg; $p = 0.063$) and 24 hours (PFR-24) (204.4 ± 94.3 vs 121.3 ± 32.6; $p = 0.016$). As predictor variables, PFR-24 and change (delta) in PFR at 24 hours from baseline or helmet initiation (dPFR-24) were significantly associated with NIV success in univariate analysis but similar significance could not be reflected in multivariate analysis perhaps due to a small sample size of the study. The PFR-24 cutoff of 161 mm Hg and dPFR-24 cutoff of −1.44 mm Hg discriminate NIV success and failure groups with the area under curve (confidence interval) of 0.78 (0.62–0.95); $p = 0.015$ and 0.74 (0.55–0.93); $p = 0.039$, respectively. Helmet interface NIV may be a safe and effective tool for the management of patients with severe COVID-19 pneumonia with acute respiratory failure. More studies are needed to further evaluate the role of helmet NIV especially in patients with initial PFR <150 mm Hg to define PFR/dPFR cutoff at the earliest time point for prediction of helmet-NIV success.

Keywords: Acute hypoxemic respiratory failure, Acute respiratory distress syndrome, COVID pneumonia, COVID-19, Helmet, Noninvasive mechanical ventilation, PaO_2/FiO_2 ratio.

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Introduction

Coronavirus disease 2019 (COVID-19) is a potentially fatal infection caused by novel severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). The virus is highly contagious in nature and has the potential for rapid progression to acute respiratory distress syndrome (ARDS), thus overwhelming the healthcare systems.

The initial approach to severe ARDS due to COVID-19 pneumonia remains invasive ventilation and standard lung-protective ventilation strategy.[1] This may still be associated with ventilator-induced lung injury (VILI) and associated systemic inflammation.[1,2] In patients with mild-to-moderate ARDS, with a PaO_2-to-inspired oxygen fraction ratio (PFR) >150, different modalities of noninvasive ventilation (NIV) have been attempted to avoid intubation.[3,4] However, NIV could potentially lead to intubation delay and cause a patient self-inflicted lung injury (P-SILI),[5] due to the high transpulmonary pressures.

Conventional method of delivering NIV in the intensive care unit (ICU) is through a face (or oronasal) mask. In ARDS, NIV may require high levels of positive end-expiratory pressure (PEEP) to improve oxygenation. However, at high PEEP, there may be air leak and face mask intolerance, impeding effective oxygenation.[6] Another method to deliver NIV is through helmet interface. A helmet consists of a transparent hood that covers the entire head of the patient with a soft collar neck seal. Its advantage includes improved tolerability and less air leak due to helmet's lack of contact with the face and improved sealing at the neck.[7] Therefore, its design may allow increased titration of PEEP without substantial air leak. NIV delivered by a helmet interface (helmet NIV) in ARDS has been associated with a lower rate of intubation and mortality, compared to face mask NIV in one study.[8]

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Helmet interface has been used in COVID-19 hypoxemic respiratory failure in few studies only. We present our clinical experience with helmet NIV on adult patients (aged ≥18 years) with acute hypoxemic respiratory failure (AHRF) due to severe COVID-19 pneumonia, who were treated with helmet NIV.

Materials and Methods

Study Design

This is a retrospective, observational study conducted at Fortis Hospital, Noida, by examining data from the case records of patients with COVID-19 pneumonia admitted between June 2020 and October 2020. Patients admitted to COVID ICU were screened for eligibility.

Study Population

Adult patients (age >18 years) with laboratory-confirmed COVID-19 pneumonia [detection of SARS-CoV-2 on real-time

polymerase chain reaction (COVID RT-PCR) on nasopharyngeal swab] and AHRF treated with helmet-NIV support were enrolled in the study. AHRF was defined as SpO_2 ≤92% despite oxygen therapy by face mask or nasal prongs with respiratory rate >30/minute, and/or respiratory distress. Patients were initially admitted to a COVID-suspect area where they were treated with oxygen using nasal prongs, Hudson mask, mask with reservoir bag, or NIV via face mask (as per existing hospital practice). After a positive COVID RT-PCR test, patients were shifted to a dedicated COVID ICU. Helmet NIV was initiated in COVID ICU setting. The decision to initiate helmet NIV was at the discretion of the treating clinical team based on stepwise escalation of oxygen therapy. Patients with signs of respiratory fatigue, confusion state, absent or poor airway protective reflexes, upper airway obstruction, pregnancy, or impending cardiopulmonary arrest were excluded from helmet NIV.

Procedure

Patients received helmet NIV via an ICU ventilator (Maquet Servo-i) using a two-limb circuit, in pressure support with continuous positive airway pressure (CPAP) mode. Helmet interface was made of transparent latex-free polyvinyl chloride. The helmet was supported by padded armpit braces attached to two hooks on the front and back of a plastic ring connecting the helmet to a latex-free neck seal (Fig. 1). The appropriate size of helmet mask was chosen based on patient's neck circumference. PEEP was set at 8 cm of H_2O or higher. Pressure support (above PEEP) was set at 10 cm H_2O. Inspiratory trigger was set at 2 L/minute. Expiratory trigger sensitivity was set at 50%.[8] FiO_2 was adjusted to keep SpO_2 more than or equal to 92%. PEEP was increased in increments of 2 to 3 cm H_2O to keep SpO_2 more than or equal to 92%. Pressure support was increased in increments of 2 to 3 cm H_2O to keep respiratory rate less than 30/minute and disappearance of accessory muscle activity. Initial settings were targeted for expiratory minute volume above 25 L/minute and tidal volume (TV) above 1 L, which was adjusted subsequently as per arterial blood gas (ABG) parameters.

The patient's medical history including presenting complaints, duration of symptoms, comorbidities, surgical history, blood pressure, heart rate, respiratory rate, baseline SpO_2, and temperature were noted. Baseline investigations (complete blood count, kidney function test, liver function test, chest X-ray) were noted. Inflammatory markers [C-reactive protein (CRP), D-dimer, serum ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6), procalcitonin (PCT)] were also noted at the time of admission. Helmet-NIV settings (pressure support, PEEP, FiO_2) at the time of initiation were recorded. ABG values (pH, PaO_2, $PaCO_2$, PFR) were recorded at baseline (at admission), before helmet application, at 2 and 24 hours after helmet application, and in between as needed. Heart rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR) score was calculated 2 hours after face mask NIV application.[9]

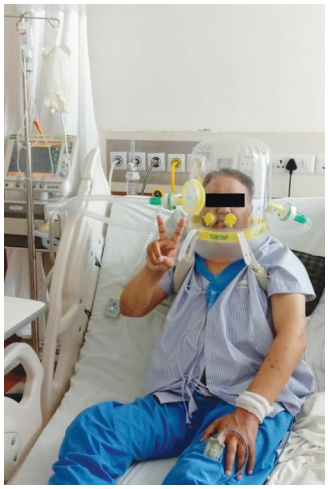


Fig. 1: Patient with severe COVID-19 on helmet-NIV support

Therapeutic interventions, like anticoagulation, steroids, convalescent plasma therapy, tocilizumab, and antiviral medications (remdesivir, favipiravir, hydroxychloroquine), were all physician directed. The decision of timing of intubation and invasive mechanical ventilation was determined by the treating clinical team and guided by a composite assessment of respiratory effort, patient exhaustion, persistent or worsening hypoxemia, rising arterial $PaCO_2$, altered mental status, intolerance to helmet NIV, or circulatory shock. The reason for intubation was recorded. Patients who were intubated had initial ventilator settings of assist-control (volume) mode with TV of 6ml/kg predicted body weight and titration of PEEP to achieve SpO_2 of 88 to 95%. Helmet-related complications like skin ulcers and eye irritation were recorded. Any ICU complications, like ventilator-associated pneumonia (VAP), barotrauma, gastrointestinal hemorrhage, pulmonary embolism, decubitus ulcer, delirium, ICU-acquired weakness, were recorded. All healthcare workers (HCW) involved in the COVID unit were screened for COVID-19 using RT-PCR on the fifth day after the end of a 2-week cycle of their duty during post-duty 1-week isolation and on any symptoms suggestive of COVID-19.

Statistical Analysis

Continuous variables were expressed as means with standard deviations. Categorical variables were expressed as frequencies with percentages. The Student's *t*-test was performed to compare means of continuous variables. The Chi-square test was performed to compare frequencies of nonparametric variables. Parametric correlation among continuous variables was tested using the Pearson's correlation test. Receiver-operating characteristics (ROC) curve was constructed, and Youden's index was calculated to get the best cutoff with maximized sensitivities and specificities for PFR at 24 hours after NIV, which can discriminate NIV success and successful outcome. A multivariate logistic regression analysis was also done to examine the association of helmet-NIV success with predictor variables chosen from the univariate regression analysis result. All descriptive and comparative parametric and nonparametric tests were performed using IBM-SPSS-Statistics-v.27 (2020) Software, and a p-value <0.05 was considered significant.

Outcomes

The primary outcome was the proportion of patients who were successfully weaned from helmet NIV, while failure comprised of patients who required intubation. We also looked at the hospital mortality in the two groups and the need for oxygen at discharge.

Results

During the study period, data of all the 30 COVID-19 positive patients [$n = 30$, age (mean ± SD) of 57.1 ± 11.9 years, 25 males (83.3%)] who were given helmet-NIV support were noted and analyzed. They presented to our hospital at a mean of 6.37 ± 2.82 days after initial symptoms. Demographic details, initial symptoms, vital signs, comorbidities, sequential organ failure assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) II, laboratory

and radiology parameters, and medical treatments are depicted in Table 1.

All patients were hypoxemic at presentation. The initial mode of oxygen support, initial NIV pressures, ABG parameters (baseline at initial hospital presentation, immediately before helmet-NIV initiation, 2 and 24 hours after helmet-NIV initiation), HACOR score at 2 hours after initiation of NIV, helmet-related complications, and reason of termination of helmet NIV are shown in Table 2.

Invasive mechanical ventilation was required in nine (30%) patients out of which eight (26.7% of all patients) died. The majority (89.9%) of NIV failure was because of respiratory cause. The mean length of stay in ICU and hospital was 14.5 ± 8.3 and 19.4 ± 8.0 days, respectively. ICU complications, like pneumothorax, subcutaneous emphysema, hospital-acquired pneumonia (HAP), and bedsore, were noted in three (10%), one (3.3%), two (6.7%), and two (6.7%) patients, respectively. Overall, 22 (73.3%) patients were discharged

Table 1: Baseline patient characteristics, investigations, treatment, and complications

Parameters	*All patients*	*Helmet-NIV success*	*Helmet-NIV failure*	*p value*
Demographic and clinical (mean ± SD)				
Age (years)	57.1 ± 11.9	55.1 ± 11.4	61.8 ± 12.6	0.170
Sex male, *n* (%)	25 (83.3)	17 (80.1)	8 (88.9)	0.593
Hospital LOS (days)	19.4 ± 8.0	18.4 ± 7.1	21.9 ± 9.9	0.282
ICU LOS (days)	14.5 ± 8.3	11.8 ± 6.04	21.0 ± 9.46	**0.003**
APACHE II	9.53 ± 3.3	9.43 ± 3.3	10.4 ± 3.6	0.494
SOFA	3.4 ± 0.89	3.5 ± 1.0	3.2 ± 0.44	0.486
First symptom duration (days)	6.37 ± 2.82	6.47 ± 2.75	6.11 ± 3.14	0.752
SBP (mm Hg)	130.4 ± 16.3	135.0 ± 16.3	119.8 ± 11.0	**0.017**
DBP (mm Hg)	73.6 ± 6.9	75.5 ± 6.0	69.3 ± 7.3	**0.023**
MAP (mm Hg)	92.6 ± 7.7	95.3 ± 6.8	86.1 ± 5.9	**0.002**
HR (/minute)	102.2 ± 18.8	104.1 ± 20.5	97.8 ± 14.1	0.407
RR (/minute)	27.4 ± 5.0	27.2 ± 5.5	26.8 ± 3.8	0.646
SpO_2 (%)	83.2 ± 8.5	85.2 ± 7.7	78.8 ± 9.18	0.073
Temp (°F)	98.5 ± 0.6	98.6 ± 0.5	98.4 ± 0.7	0.477
Symptoms *n* (%)				
Fever	28 (93.3)	20 (95.2)	8 (88.9)	0.523
Cough	29 (96.7)	21 (100)	8 (88.9)	0.120
Breathlessness	27 (90.0)	19 (90.5)	8 (88.9)	0.894
Headache	2 (6.7)	1 (4.8)	1 (11.1)	0.523
Myalgia	4 (13.3)	2 (9.5)	2 (22.2)	0.348
Chest pain	1 (3.3)	1 (4.8)	0 (0.0)	0.505
Pain abdomen	1 (3.3)	0 (0.0)	1 (11.1)	0.120
Urinary frequency	1 (3.3)	0 (0.0)	1 (11.1)	0.120
Comorbidities *n* (%)				
DM	18 (60.0)	13 (61.9)	5 (55.6)	0.745
HTN	14 (4.67)	8 (38.1)	6 (66.7)	0.151
Malignancy	3 (10.0)	2 (9.5)	1 (11.1)	0.894
Asthma	1 (3.3)	0 (0.0)	1 (11.1)	0.120
CAD	1 (3.3)	0 (0.0)	1 (11.1)	0.120
Dyslipidemia	1 (3.3)	1 (4.8)	0 (0.0)	0.505
Migraine	1 (3.3)	0 (0.0)	1 (11.1)	0.120
Pancreatitis	1 (3.3)	0 (0.0)	1 (11.1)	0.120
Laboratory parameters (mean ± SD)				
TLC (10^9/L)	8.9 ± 4.66	9.1 ± 4.2	8.3 ± 5.8	0.662
Platelets (10^9/L)	197.2 ± 53.5	199.9 ± 51.6	190.8 ± 60.4	0.676
Hemoglobin (g/dL)	12.3 ± 2.1	13.3 ± 2.5	12.4 ± 1.3	0.903
Bilirubin (mg/dL)	0.62 ± 0.25	0.65 ± 0.28	0.56 ± 0.17	0.384
Albumin (g/dL)	3.4 ± 0.53	3.5 ± 0.53	3.2 ± 0.50	0.117

(Contd...)

Table 1: *(Contd...)*

Parameters	*All patients*	*Helmet-NIV success*	*Helmet-NIV failure*	*p value*
SGOT (U/L)	56.5 ± 37.7	55.8 ± 40.0	58.0 ± 32.4	0.886
SGPT (U/L)	48.8 ± 27.4	52.0 ± 30.6	41.6 ± 16.9	0.350
BUN (mg/dL)	15.0 ± 6.9	15.3 ± 7.5	14.2 ± 5.7	0.695
Creatinine (mg/dL)	1.01 ± 0.40	1.1 ± 0.46	0.89 ± 0.20	0.282
Sodium (mEq/L)	135.9 ± 4.8	136.8 ± 5.0	133.8 ± 3.8	0.11
Potassium (mEq/L)	4.2 ± 0.58	4.1 ± 0.67	4.23 ± 0.31	0.693
Ferritin (ng/mL)	759.7 ± 489.5	725.4 ± 498.1	828.4 ± 493.5	0.616
IL-6 (pg/mL)	422 ± 1671.5	63.9 ± 61.7	1242.6 ± 3017.7	0.122
CRP (mg/L)	141.0 ± 87.88	140.9 ± 86.1	141.1 ± 99.4	0.996
PCT (ng/mL)	0.30 ± 0.24	0.28 ± 0.20	0.34 ± 0.32	0.645
D-dimer: *n* (%), (ng/mL)				
<0.5	15 (50.0)	12 (57.1)	3 (33.3)	0.089
>0.5 <1	2 (6.7)	0 (0.0)	2 (22.2)	
>1 <2	4 (13.3)	2 (9.5)	2 (22.2)	
>2 <4	4 (13.3)	4 (19.0)	0 (0.0)	
>4	3 (10.0)	2 (9.5)	1 (11.1)	
CXR number of quadrants involved: *n* (%)				
2	14 (46.7)	9 (42.9)	5 (55.6)	0.450
3	8 (26.7)	5 (23.8)	3 (33.3)	
4	8 (26.7)	7 (33.3)	1 (11.1)	
Treatment: *n* (%)				
HCQS	13 (43.3)	8 (38.1)	5 (55.6)	0.376
Azithromycin	4 (13.3)	2 (9.5)	2 (22.2)	0.348
Vitamin C	27 (90.0)	18 (85.7)	9 (100)	0.232
Steroid	29 (96.7)	20 (95.2)	9 (100)	0.506
Remdesivir	21 (70.0)	15 (71.4)	6 (66.7)	0.794
Plasma therapy	19 (63.3)	14 (66.7)	5 (55.6)	0.563
Tocilizumab	12 (40.0)	6 (28.6)	6 (66.7)	0.051
Cytosorb	1 (3.3)	0 (0.00)	1 (11.1)	0.120
Complications and outcomes: *n* (%)				
Helmet-NIV failure	9 (30)	0 (0.0)	9 (100)	NA
• Respiratory cause	8 (26.7)	0 (0.0)	8 (89.9)	
• Circulatory cause	1 (3.3)	0 (0.0)	1 (11.1)	
Pneumothorax	3 (10.0)	1 (4.8)	2 (22.2)	0.144
Subcutaneous emphysema	1 (3.3)	1 (4.8)	0 (0.0)	0.505
ACS	1 (3.3)	1 (4.8)	0 (0.0)	0.505
Bedsore	2 (6.7)	0 (0.0)	2 (22.2)	**0.025**
Hospital-acquired pneumonia	2 (6.7)	0 (0.0)	2 (22.2)	**0.025**
Death	8 (26.7)	0 (0.0)	8 (89.9)	**<0.001**
Patient discharged	22 (73.3)	21 (100)	1 (11.1)	**<0.001**
Discharged with O_2	3 (10.0)	2 (9.5)	1 (11.1)	0.894

ACS, acute coronary syndrome; APACHE, acute physiology and chronic health evaluation; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CAD, coronary artery disease; CXR, chest X-ray; DM, diabetes mellitus; HAP, hospital-acquired pneumonia; HTN, hypertension; ICU, intensive care unit; IL-6, interleukin-6; LOS, length of stay; NIV, noninvasive ventilation; PCT, procalcitonin; SOFA, sequential organ failure assessment; TLC, total leukocyte count

Table 2: Helmet-NIV ventilatory and blood gas parameters

Parameters	*All patients*	*Helmet-NIV success*	*Helmet-NIV failure*	*p value*	
O_2 therapy prior to helmet, *n* (%)					
Face mask NIV	23 (76.7)	14 (66.7)	9 (100)	**0.048**	0.271
Mask with reservoir bag	4 (13.3)	4 (19.0)	0 (0.0)	0.160	
Hudson mask	1 (3.3)	1 (4.8)	0 (0.0)	0.505	
Nasal prongs	2 (6.7)	2 (9.5)	0 (0.0)	0.338	
Reason for helmet termination, *n* (%)					
Weaning	19 (63.3)	19 (90.5)	0 (0.0)	**<0.001**	**<0.001**
Intubation	8 (26.7)	0 (0.0)	8 (88.9)	**<0.001**	
Noncompliance	2 (6.7)	1 (4.8)	1 (11.1)	0.523	
Barotrauma	1 (3.3)	1 (4.8)	0 (0.0)	0.505	
Helmet complication, *n* (%)					
Subcutaneous emphysema	1 (3.3)	1 (4.8)	0 (0.0)	0.505	
Parameters of NIV before helmet interface					
HACOR	3.8 ± 1.8	3.7 ± 2.3	4.2 ± 0.9	0.625	
≥5	11 (36.7)	7 (33.3)	4 (44.4)	0.795	
<5	12 (40.0)	7 (33.3)	5 (55.6)		
Duration of face mask NIV (hours)	48.9 ± 78.1	32.7 ± 18.0	74.1 ± 122.8	0.222	
Duration of helmet-NIV (hours)	135.7 ± 95.5	141.0 ± 102.7	123.4 ± 82.5	0.654	
Baseline arterial blood gas parameters					
pH	7.43 ± 0.05	7.42 ± 0.05	7.46 ± 0.03	0.057	
$PaCO_2$ (mm Hg)	32.6 ± 6.1	34.3 ± 6.0	28.8 ± 4.3	**0.020**	
PaO_2 (mm Hg)	75.0 ± 28.4	75.5 ± 27.9	73.6 ± 31.2	0.865	
PaO_2–FiO_2 ratio (PFR)	150.1 ± 57.4	147.2 ± 57.9	156.8 ± 59.0	0.683	
Arterial blood gas parameters before helmet interface initiation					
pH	7.42 ± 0.05	7.41 ± 0.06	7.42 ± 0.05	0.846	
$PaCO_2$ (mm Hg)	34.5 ± 5.2	34.4 ± 5.6	34.63 ± 4.4	0.899	
PaO_2 (mm Hg)	79.1 ± 25.1	81.0 ± 27.4	74.7 ± 19.5	0.544	
PaO_2–FiO_2 ratio (PFR)	129.1 ± 42.9	132.3 ± 46.9	121.6 ± 32.7	0.541	
Parameters of NIV with helmet interface					
PEEP (cm of H_2O)	9.0 ± 1.1	9.0 ± 1.2	9.1 ± 1.1	0.810	
Pressure support (cm of H_2O)	12.0 ± 2.4	11.6 ± 2.6	13.0 ± 1.6	0.147	
Initial FiO_2 (%)	61.8 ± 16.6	57.1 ± 14.7	72.8 ± 16.2	**0.015**	
Arterial blood gas parameters 2 hours after helmet interface initiation					
pH	7.43 ± 0.04	7.43 ± 0.05	7.43 ± 0.03	0.785	
$PaCO_2$ (mm Hg)	34.6 ± 4.9	35.2 ± 5.0	33.3 ± 4.8	0.336	
PaO_2 (mm Hg)	83.7 ± 25.0	82.5 ± 16.3	86.5 ± 39.9	0.696	
PaO_2–FiO_2 ratio (PFR)	146.8 ± 54.5	158.8 ± 56.1	118.7 ± 40.7	0.063	
Arterial blood gas parameters 24 hours after helmet interface initiation					
pH	7.46 ± 0.05	7.46 ± 0.06	7.44 ± 0.04	0.386	
$PaCO_2$ (mm Hg)	34.1 ± 4.8	33.5 ± 4.4	35.6 ± 5.7	0.281	
PaO_2 (mm Hg)	84.8 ± 25.7	88.1 ± 25.2	76.9 ± 26.6	0.281	
PaO_2–FiO_2 ratio (PFR)	179.5 ± 89.0	204.4 ± 94.3	121.3 ± 32.6	**0.016**	

BiPAP, bilevel positive airway pressure; MV, mechanical ventilator; NIV, noninvasive ventilation; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen

from ICU and hospital. Three (10.0%) patients were oxygen dependent at the time of discharge.

Data of the two groups, the helmet-NIV success group and helmet-NIV failure group, were compared for demography, parameters at presentation, interventions, responses to interventions, laboratory results, complications, and outcomes (Tables 1 and 2). Initial SpO_2 was lower in the NIV failure group (79 vs 85%, $p = 0.073$) but the difference was statistically not significant.

Demography, initial symptoms, duration of the first symptom at presentation, comorbidities, initial blood investigation reports, inflammatory markers (IL-6, CRP, D-dimer, and PCT), APACHE II and initial SOFA scores, radiology and medical therapies given to the patients were comparable in the two groups (Table 1).

Baseline ABG showed no significant difference in PaO_2 (75.5 ± 27.9 vs 73.6 ± 31.2 mm Hg; $p = 0.865$) and PFR (147.2 vs 156.8 mm Hg; $p = 0.683$). A significantly lower $PaCO_2$ (28.8 ± 4.3 vs 34.3 ± 6.1 mm Hg; $p = 0.020$) and a corresponding higher pH (7.46 ± 0.03 vs 7.42 ± 0.05; $p = 0.057$) were noted in baseline ABG of the NIV failure group in comparison to the NIV success group. Initially face mask NIV was given significantly more frequently in the NIV failure group (100 vs 66.7%; $p = 0.031$). Overall initial modality of oxygen therapy was not different in the two groups ($p = 0.271$). For patients who were given NIV support initially, the HACOR score at 2 hours after application of NIV was comparable in the two groups (3.7 ± 2.3 vs 4.2 ± 0.9; $p = 0.625$). The mean duration of NIV with face mask before application of helmet interface was not significantly different in the two groups (32.7 ± 18.0 vs 74.1 ± 122.8 hours; $p = 0.222$).

ABG done before helmet-NIV initiation showed no significant difference between the two groups. Initially applied pressures of NIV were not different for PEEP ($p = 0.810$) and pressure support ($p = 0.147$). A higher FiO_2 was given to the NIV failure group (72.8 ± 16.2 vs 57.1 ± 14.7 mm Hg; $p = 0.015$) after the initiation of helmet NIV. ABG 2 hours after initiation of helmet NIV showed lower PFR in the NIV failure group compared to the NIV success group (118.7 ± 40.7 vs 158.8 ± 56.1 mm Hg; $p = 0.063$) but the difference was not statistically significant. A repeat ABG at 24 hours after the initiation of NIV with helmet interface showed a significantly lower PFR in the NIV failure group (121.3 ± 32.6 vs 204.4 ± 94.3 mm Hg; $p = 0.016$) in comparison to the NIV success group. Difference between PFR at 24 and baseline (57.2 ± 102.2 vs −35.51 ± 72.6 mm Hg; $p = 0.020$) or initiation of helmet (72.1 ± 100.6 vs 0.30 ± 44.0 mm Hg; $p = 0.0488$) was significantly higher in the NIV success group on comparing with NIV failure group. In a multivariate logistic regression analysis, no significant relationship was seen between variables and helmet-NIV success, though a trend toward significance was seen for age ($p = 0.076$), initial SpO_2 ($p = 0.06$), PFR at 24 hours ($p = 0.069$), and change in PFR between before and 24 hours after helmet-NIV initiation ($p = 0.068$) (Table 3).

A graph in Figure 2 shows a comparison of the PFR in ABGs at different time points of the NIV success and failure groups. An initial faster decline in PFR in the NIV failure group in comparison to the NIV success group can be noted even before the application of helmet NIV. After initiation of Helmet NIV, a progressive improvement in PFR was noted in ABGs at 2 and 24 hours in the helmet success group. The mean duration of NIV with helmet interface application was not significantly different in NIV success and failure groups (141.0 ± 102.7 vs 123.4 ± 82.5 hours; $p = 0.654$).

Graphs in Figures 3A to D show ROC curves to find optimum cutoff PFR at 24 hours (PFR-24) and change (delta) in PFR at 24 hours from initiation of helmet interface (dPFR-24) to predict NIV success and successful patient outcomes. A PFR-24 cutoff point that maximized sensitivity and specificity (Youden's index) was at PFR 161 mm Hg with sensitivity and specificity of 71 and 89% for NIV success and 68 and 89% for predicting a good patient outcome, respectively. The area under curve (AUC) for PFR-24 for NIV success and successful patient outcome was 0.78 ($p = 0.015$) and 0.77 ($p = 0.024$), respectively. Similarly, for dPFR-24, the best discriminating point was −1.44 mm Hg with sensitivity and specificity for NIV success 86 and 67% and for successful patient outcome 86 and 75%, respectively. Here AUC for NIV success and successful patient outcome was 0.74 ($p = 0.039$) and 0.77 (0.024), respectively (Table 4).

Table 3: Multivariate logistic regression analysis for association of predictor variables to helmet-NIV success

Variable	*Adjusted odds ratio OR (95% CI)*	*p value*
Age	0.73 (0.52,1.03)	0.076
SpO_2 (%) ORA	1.52 (0.98,2.35)	0.060
2 hours PFR	0.94 (0.87,1.01)	0.103
24 hours PFR	1.14 (0.99,1.32)	0.069
dPFR-24	0.92 (0.84,1.01)	0.068
Tocilizumab	0.02 (0.00, 8.30)	0.205
Remdesivir	15.8 (0.35,719.6)	0.155

CI, 95% confidence interval; dPFR, change (delta) in PFR; ORA, on room air; PFR, PaO_2:FiO_2 ratio; SpO_2, oxygen saturation; dPFR-24, difference of PFR between after 24 hours and before helmet-NIV application

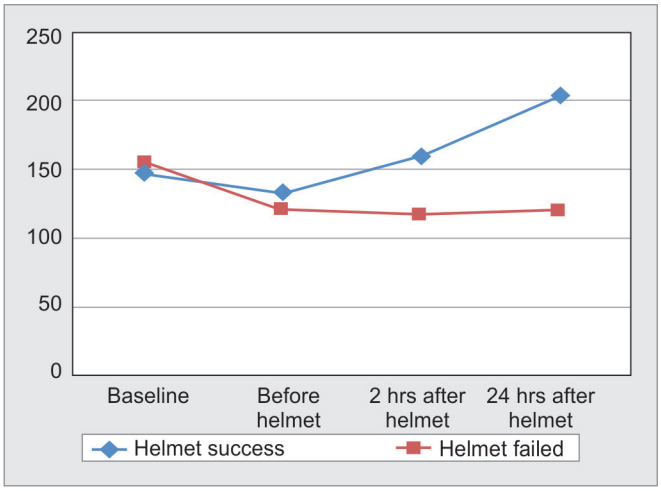
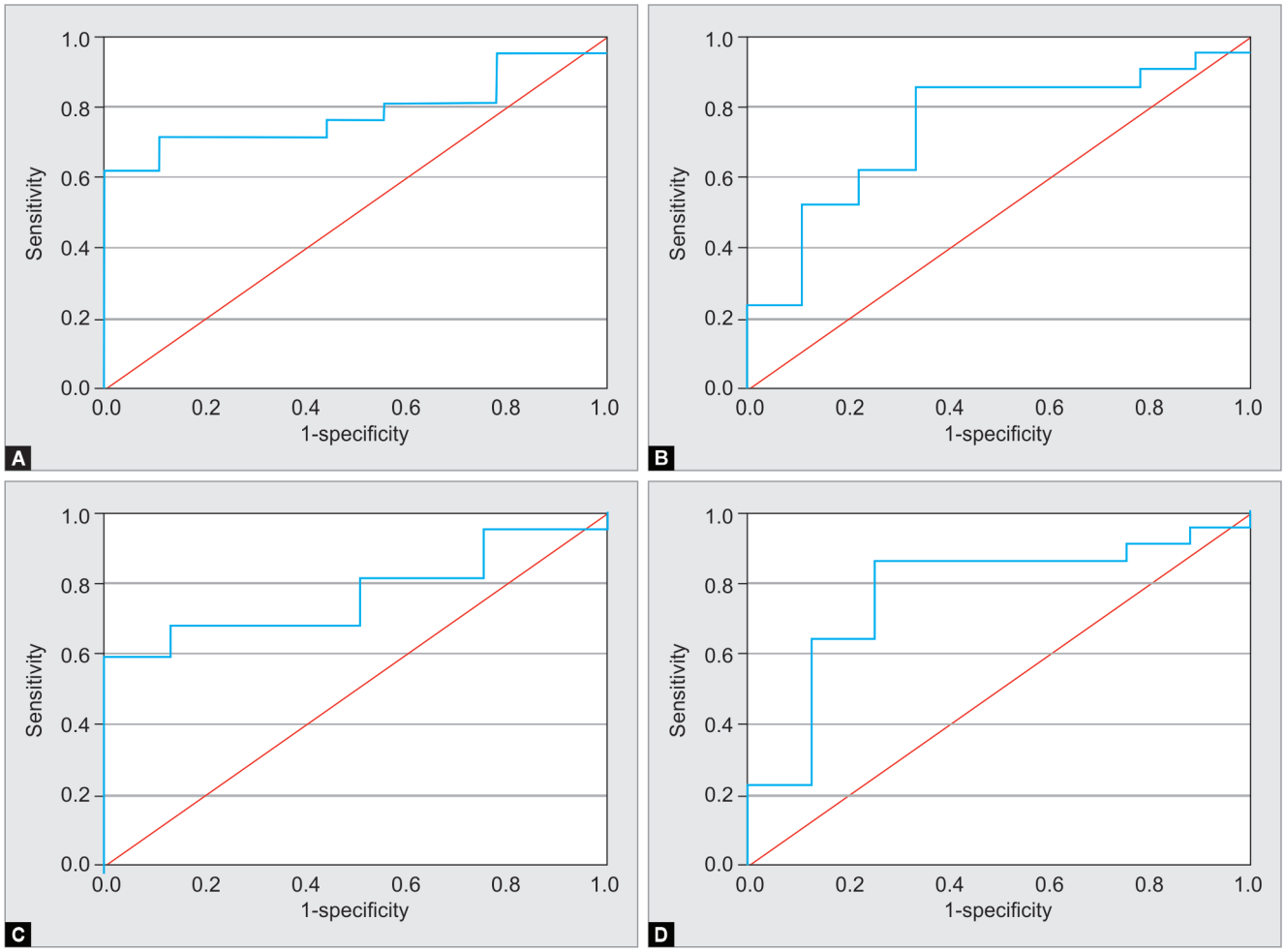


Fig. 2: Graph comparing PFR (on y-axis) of NIV success and NIV failure groups at different points of time (on x-axis)

The reason for termination of helmet NIV was primarily weaning (90.5%) in the NIV success group and intubation (88.9%) in the NIV failure group. On helmet-NIV support, only one patient had subcutaneous emphysema, which was in the NIV success group. Lower frequency of ICU complications was noted in the NIV success group for pneumothorax (4.8 vs 22.2%, $p = 0.114$), HAP (0.0 vs 22.2%; $p = 0.025$), and bedsore (0.0 vs 22.2%; $p = 0.025$). Significantly higher mortality was seen in the NIV failure group (89.9 vs 0.0%, $p < 0.001$). A significantly higher number of patients in the NIV success group were discharged from ICU and hospital in comparison to the NIV failure group (100 vs 11.1%, $p < 0.001$).

Discussion

Studies have shown the safe and effective use of NIV through various interfaces in mild-to-moderate ARDS.[10,11] Previously, pandemics, such as SARS,[12] Middle East respiratory syndrome (MERS),[13] and H1N1 influenza,[14] have all witnessed the successful use of NIV for the management of ARDS.



Figs 3A to D: ROC curves discriminating (A) NIV success with PFR at 24 hours; (B) NIV success with dPFR at 24 hours; (C) Patient outcome success with PFR at 24 hours; and (D) Patient outcome success with dPFR at 24 hours

Table 4: Accuracy of discriminating cutoffs and AUC with significance of ROC curves

	NIV success					*Patient outcome success*				
PFR24 cutoff	*Sn*	*Sp*	*AUC*	*CI*	*p value*	*Sn*	*Sp*	*AUC*	*CI*	*p value*
144	71	78	0.78	0.62–0.95	0.015	68	75	0.77	0.61–0.94	0.024
161	**71**	**89**				**68**	**89**			
183	62	100				59	100			
dPFR24 cutoff			0.74	0.55–0.93	0.039			0.77	0.57–0.97	0.024
−9.4	86	57				86	63			
−1.44	**86**	**67**				**86**	**75**			
33.4	62	78				64	88			

AUC, area under curve; CI, 95% confidence interval; dPFR, change (delta) in PFR; PFR, PaO_2:FiO_2 ratio; Sn, sensitivity; Sp, specificity

Australian and New Zealand Intensive Care Society (ANZICS) recommends against the use of NIV in patients with COVID-19 due to concern of high failure rate, delayed intubation, and possibly increased risk of aerosolization with poor mask fit.[15] However, COVID-19 has different pathophysiology characterized by injury to capillary endothelium rather than alveolar epithelium and a preserved lung compliance (L type ARDS).[16,17] Due to such pathophysiology along with the unprecedented demand for ventilators and the short numbers of skilled intensivists and ICU nurses (to manage invasive ventilation), NIV has assumed a significant role. It has been used for the management of AHRF in 3 to 83% of cases in various studies.[18] NIV can improve survival in COVID-19 patients when applied early for respiratory failure; however, the benefit is lost when it is used too late in respiratory deterioration.[19]

Despite improvements in the oronasal mask's characteristics, intolerance to the device represents a frequent cause of NIV

failure.[20] Helmet can be used to deliver airway pressure up to 40 cm H_2O without a leak. Studies have shown that helmet as interface is more comfortable for long-term ventilation and has low chances of viral transmission, and low intubation and low complication rates.[8,21] In our study, we also had one (3.3%) helmet-related complication in 30 patients, variable rates for which have been reported by other authors.[21] During the study period, no HCW involved in patient care in the COVID ICU (including helmet NIV) tested positive for COVID-19. One study showed 11.1% rate of HCW getting infected with SARS-CoV-2.[22]

Most previous studies had stringent cutoffs for NIV failure in ARDS, and many patients were intubated if no improvement was seen in the initial few hours.[11] As COVID ARDS has a different mechanism of hypoxemia at least in the initial stages,[16,17] and COVID patients on invasive mechanical ventilation have high mortality,[23] we gave longer NIV trials with close monitoring before switching to invasive ventilation. We found the helmet-NIV application time was not different in success and failure groups perhaps indicating that failure was not attributable to delayed intubation.

Patients in our study had moderate-to-severe ARDS (mean PFR before helmet initiation of 129.1 ± 42.9). Our clinical decision to use helmet NIV despite low PFR was based on preserved lung compliance in early COVID ARDS,[16,17] poor reported outcomes of invasively ventilated patients,[23] and lesser risk of infections to HCW as compared to NIV with oronasal mask interface.[24]

We found that out of 30 patients who were put on NIV helmet, only 9 patients (30%) had NIV failure and required intubation. NIV failure rate was similar to those reported by other COVID (ranging from 23 to 33%)[22,25] and non-COVID[11] ARDS studies.

Overall mortality in patients requiring NIV was 26.7%, which is similar to the reported mortality in COVID-19 ARDS patients.[23] However, patients who failed NIV had 89.9% mortality, which was again similar to high mortality shown by other studies.[23] Though there was no difference in APACHE or SOFA scores or comorbidities on comparing NIV failure group with NIV success group, more frequent initial need of NIV, lower oxygen saturation (though the difference is not significant), relatively faster decline in PFR before helmet application, need of higher FiO_2 on helmet application, and more frequent need of tocilizumab indicate possibly more aggressive disease in the NIV failure group. Although systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were significantly different in NIV success and failure groups, they remained in a normal range and none of the patients in either group was in shock.

We found a trend of improving mean PFR as early as 2 hours after helmet NIV application in the NIV success group. In this group, a progressive improvement in mean PFR was noted from PFR before helmet-NIV application to 2 and 24 hours after helmet-NIV application in the NIV success group, while the NIV failure group did not show such an improvement. Although the difference in PFR between success and failure groups at 2 hours was not statistically significant ($p = 0.063$), it achieved statistical significance ($p = 0.016$) at 24 hours. Constructing the ROC curve showed that both PFR-24 and dPFR-24 may be fair tools (AUC >0.7; $p < 0.05$) for discriminating patients with NIV success or successful outcomes. Using the ROC curve, we found the best PFR-24 cutoff (Youden's index) of 161 mm Hg which had a sensitivity and specificity of 71% and 89% for predicting NIV success and 68 and 89% for predicting good outcomes, respectively. The dPFR-24 with a cutoff 1.44 mm Hg also showed similar accuracy. Our result is similar to two other studies in non-COVID ARDS patients by Antonelli et al.[11] and Bellani et al.[10] Data show that VILI is more with NIV in stiffer lungs as tidal hyperinflation is more.[26,27] However, considering a different COVID-19 ARDS pathophysiology, we expected different results. As shown in a study of 507 COVID-19 ARDS patients, there was no difference in mortality among patients with baseline PFR of 201 to 250, 151 to 200, and 101 to 150 mm Hg (20.3, 25.2, and 24.2%, respectively); mortality was higher (45.5%) only at PFR below 50 mm Hg.[22] These studies encouraged us to use helmet NIV even at low PFR. In our study, PFR before initiation of helmet NIV was 129.1 ± 42.9 mm Hg (mean ± SD) and there was no difference between the two groups reflecting similar distribution of moderate and severe ARDS patients in both groups.

There was a significant improvement in PFR in the NIV success group but not in the failure group, and both groups were having an initial mean PFR of less than 150 mm Hg. These findings also suggest that change in PFR at 24 hours (dPFR-24) from baseline (57.2 ± 102.2 vs −35.51 ± 72.6; $p = 0.020$) or the initiation of helmet (72.1 ± 100.6 vs −0.30 ± 44.0; $p = 0.0488$) may be a better predictor for NIV success or outcome than baseline PFR *per se*. This difference was not significant at 2 hours. ABG sampling between 2 and 24 hours was done at varying time points based solely on clinical need, as this was not a prospective study with a predefined protocol. We thus do not have 6 or 12 hours ABGs in all patients to be able to comment on PFR changes at other timelines. In a multivariate logistic regression analysis, predictor variables have not shown significant association with helmet NIV outcomes but a trend toward significance has been seen with some variables (age, initial SpO_2, PFR-24, and dPFR-24). This could be due to a small sample size.

In our study, mean PEEP was 9.0 ± 1.1 cm H_2O, which was similar in both success and failure groups. Since PEEP levels required to adequately ventilate the failure group were not so high, our patients were probably L-phenotype or some were during transition to H-phenotype. PFR less than 161 mm Hg may not necessarily mean a stiff lung but high V/Q mismatch and more lung inflammation. The NIV failure in a subset of our patients may be attributable to the aggravation by P-SILI. Though there is a weak negative correlation between initial respiratory rate and pCO_2 in the NIV failure group, there was no difference in respiratory rate between the two groups. It is conceivable that a lower pCO_2 with similar respiratory rates in the NIV failure group may reflect higher TV resulting in higher P-SILI. Previous studies showed that stratified by severity of hypoxemia, TV greater than 9.0 mL/kg[28] predicts the failure of NIV support. Another study suggested lung-protective ventilation strategy may be helpful in patients with preserved compliance.[29]

High global strain on the lung may impact NIV success negatively and may increase mortality.[30,31] We did not strictly target a particular TV range, which could have aggravated P-SILI. Also, we did not prone patients with helmet NIV. Awake proning could attenuate p-SILI by reducing distending pressures and negative swings of intrathoracic pressure and increasing functional residual capacity.[32]

Our study suggests that helmet NIV may be a safe and effective tool for the management of COVID ARDS patients even when initial PFR is less than 150 mm Hg, only if PFR improves initially. An improvement in PFR in the first 24 hours may probably be a better marker than any cutoff PFR. We believe larger studies are needed to ascertain the limit for use of NIV in COVID patients especially in patients with PFR <150 mm Hg to

define a more suitable cutoff for PFR or change in PFR (possible better predictor of NIV success or outcome) and testing more frequent time points (like 2, 6, 12, and 24 hours) for early prediction. This study has multiple limitations, namely it is a retrospective and single-center study, with a small sample size. Further, criteria for intubation were not protocolized but were done based on clinician's bedside assessment alone.

Conclusion

Helmet NIV may be a safe and effective option in COVID-19 pneumonia–related AHRF. Larger studies are needed to ascertain the limit for use of NIV in COVID-19 patients especially in patients with PFR <150 mm Hg, to define a more suitable cutoff for PFR or change in PFR and testing more frequent time points for early prediction of success or failure.

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