Noninvasive Ventilation in the Management of Respiratory Failure Due to COVID-19 Infection: Experience From a Resource-Limited Setting

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Abstract

Objective: To study the role of noninvasive ventilation (NIV) in Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2) related acute respiratory failure (C-ARF).

Patients and Methods: Patients with C-ARF managed on NIV were categorized as NIV success or failure (death or intubation). Factors associated with failure were explored using regression analysis and expressed as odds ratio (OR) with 95% CI.

Results: Between April 1, 2020, and September 15, 2020, a total of 286 patients with a mean ± SD age of 53.1±11.6 years and Acute Physiology and Chronic Health Evaluation II score of 11.1±5.5 were initiated on NIV. Of the 182 patients (63.6%) successfully managed on NIV alone, 118 had moderate or severe acute respiratory distress syndrome. When compared with NIV success, NIV failure was associated with lower admission PaO_2 to fraction of inspired oxygen ratio ($P<.001$) and higher respiratory rate ($P<.001$). On penalized logistic regression analysis, NIV failure was associated with higher Acute Physiology and Chronic Health Evaluation II score (OR, 1.12; 95% CI, 1.01 to 1.24), severe acute respiratory distress syndrome (OR, 3.99; 95% CI, 1.24 to 12.9), D-dimer level of 1000 ng/mL DDU (to convert to mg/L, divide by 1000) or greater (OR, 2.60; 95% CI, 1.16 to 5.87), need for inotropes or dialysis (OR, 12.7; 95% CI, 4.3 to 37.7), and nosocomial infections (OR, 13.6; 95% CI, 4.06 to 45.9). Overall mortality was 30.1% (86/286). In patients requiring intubation, time to intubation was longer in nonsurvivors than survivors (median, 5; interquartile range, 3-8 vs 3; interquartile range, 2-3 days; $P<.001$).

Conclusion: Noninvasive ventilation can be used successfully in C-ARF. Illness severity and need for non—respiratory organ support predict NIV failure.

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N oninvasive ventilation (NIV) has an important role in the management of respiratory failure of diverse causes.[1] Noninvasive ventilation was not recommended for severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19])-related acute respiratory failure (C-ARF) during the initial phase of the pandemic given the aerosol-generating potential[2,3] and the inconsistent reports of benefit from previous pandemic experiences.[4-7] Reports indicate that patients with COVID-19 infection who required invasive mechanical ventilation fared poorly and had a fatality rate of more than 50%.[8]

In a large study of 1591 patients admitted to the intensive care unit (ICU) with COVID-19 infection,[9] 1287 of the

1300 patients (99%) analyzed required respiratory support; only 137 patients (11%) were managed with NIV. The ICU mortality was 26%. In this study, no exploratory analysis was provided on the subset of patients treated with NIV. In a recent cohort of 416 ICU patients[10] in whom the overall mortality was 38.2%, mortality was significantly higher ($P<.001$) with invasive ventilation (104/113; 92%) than with NIV (62/152; 40.8%). This study did not report failure rate with NIV or explore the characteristics that predicted NIV success in patients with COVID-19 infection. Recent publications have suggested a role for NIV in the non-ICU setting.[11-17]

There are several challenges to the provision of positive pressure ventilation in resource-limited settings given the lack of negative pressure rooms, the inability to scale up resources rapidly, and the cost involved in prolonged invasive ventilation. In this context, despite the initial concerns on the potential risk with NIV, a conscious decision was made in our institution to use NIV in an attempt to reduce the need for invasive ventilation. This study was undertaken to evaluate the success rate of NIV in patients admitted to the ICU with C-ARF and explore the factors associated with NIV failure.
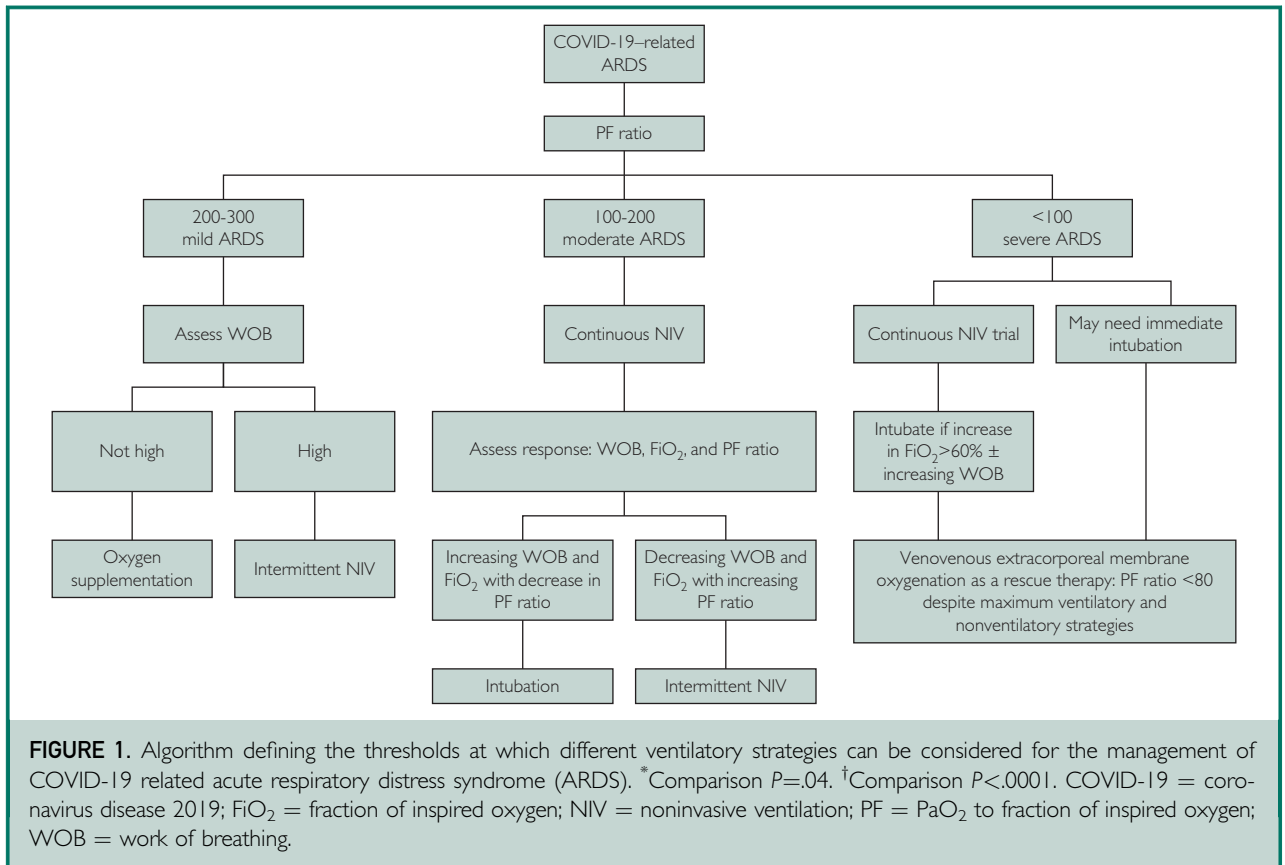
PATIENTS AND METHODS
This study was done in the medical ICU in a 2800-bed tertiary care university-affiliated teaching hospital in South India, which was rapidly upscaled from 2 to 4 ICU pods and from 24 to 50 beds during the pandemic. A total of 258 health care workers (HCWs) were involved in the care of critically ill patients with C-ARF. Patients requiring NIV at the time of ICU admission or during the course of the ICU stay were prospectively enrolled between April 1, 2020, and September 15, 2020, and followed up until death or discharge from the hospital. The study was approved by the Institutional Review Board and Ethics Committee of the hospital (Institutional Review Board no: 12743 dated 1/5/2020) and consent was obtained from the patient or next of kin.

Demographic data, comorbid conditions, treatment, and outcomes were recorded. Treatment included antiviral therapy (remdesivir) and anticoagulation therapy (either prophylactic or therapeutic). Therapeutic anticoagulation therapy was considered if D-dimer level was greater than 1000 ng/mL DDU (to convert to mg/L, divide by 1000) in the setting of worsening respiratory status with or without proven thrombotic events. Although corticosteroids were introduced to the standard protocol in July 2020 when the evidence for their use was published,[18] clinicians used corticosteroids based on some evidence of benefit in other clinical settings. Hydroxychloroquine was not used in our patients as per the treatment guidelines followed in our institution. Other adjunct therapies were recorded.

Patients were initiated on NIV if they had evidence of respiratory failure with increasing tachypnea (respiratory rate >24 breaths/min) and/or signs of increased work of breathing with accessory muscle use and were hemodynamically stable, conscious, and cooperative.[1] Noninvasive ventilation was provided in the ICU using mechanical ventilators designed for invasive ventilation through a facemask; dedicated NIV machines and portable devices were not used due to the problems of titrating the fraction of inspired oxygen (FiO_2) and the limitations in fine-tuning patient-ventilator synchrony. Continuous positive airway pressure mode was not considered as NIV. The pressure support was titrated to achieve a tidal volume of around 6 mL/kg; positive end-expiratory pressure and FiO_2 were adjusted to achieve a saturation greater than 92%. Awake proning was encouraged.

Patients in whom a trial of NIV failed (worsening work of breathing, worsening PaO_2:FiO_2 [PF] ratio, and/or increasing respiratory rate despite adequate ventilatory support) and patients with increasing hemodynamic instability, low Glasgow Coma Scale score (score <8), or impending respiratory or cardiac arrest were intubated unless there was a clear directive for nonescalation of care from either the patient or the next-of-kin. The decision to intubate

FIGURE 1. Algorithm defining the thresholds at which different ventilatory strategies can be considered for the management of COVID-19 related acute respiratory distress syndrome (ARDS). *Comparison *P*=.04. †Comparison *P*<.0001. COVID-19 = coronavirus disease 2019; FiO_2 = fraction of inspired oxygen; NIV = noninvasive ventilation; PF = PaO_2 to fraction of inspired oxygen; WOB = work of breathing.
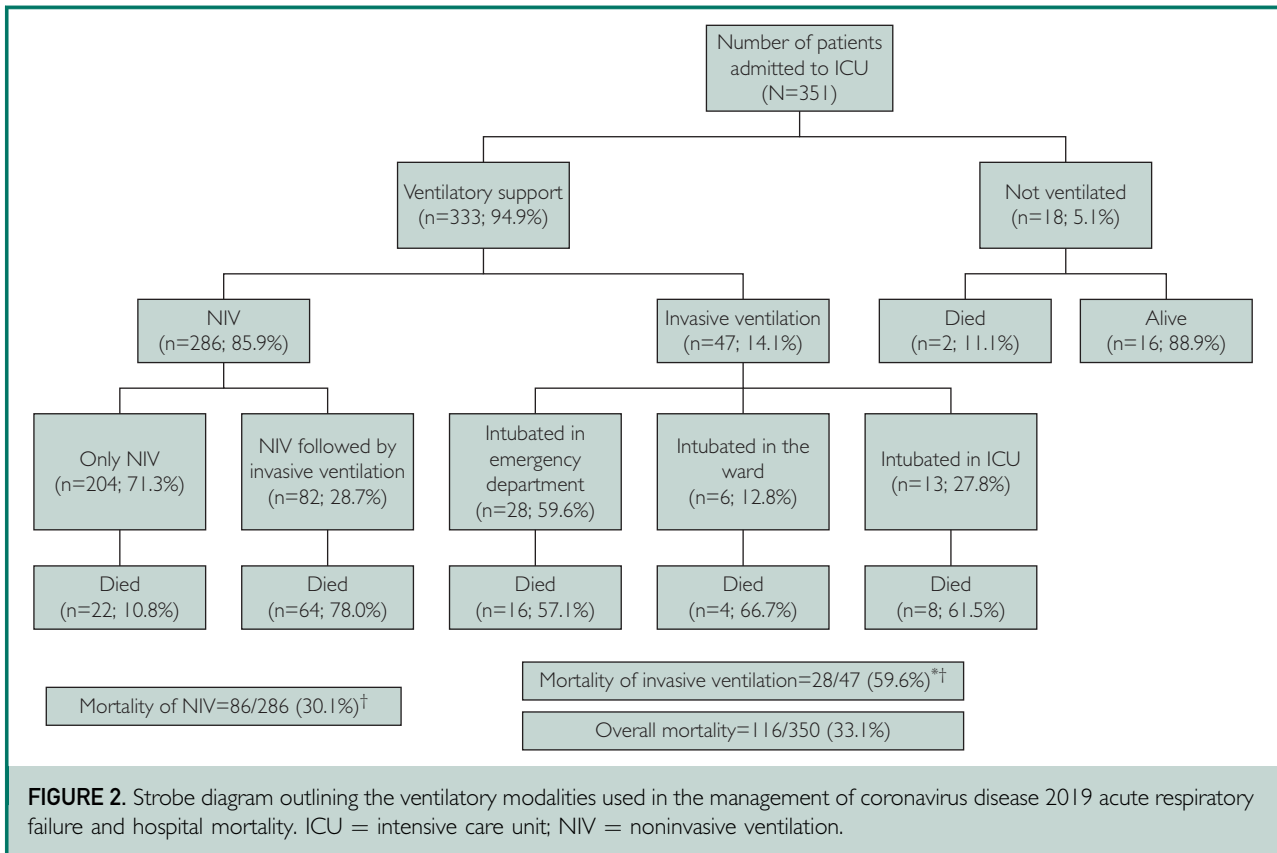
was not limited based on practical logistic considerations. Although broad guidelines for criteria for intubation were defined at the start of the pandemic and refined subsequently, based on our understanding of the role of NIV in COVID-19 (Figure 1), intensivists were allowed to use clinical discretion on the timing of intubation, as well as the thresholds. Patients who were intubated and ventilated received analgo-sedation and other organ support as required. Nosocomial infections and ventilator-related adverse events were diagnosed and managed as per guidelines.[19]

The COVID-19−related acute respiratory distress syndrome (C-ARDS) was diagnosed when a patient with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection fulfilled the 2012 Berlin ARDS diagnostic criteria[20] of acute hypoxemic respiratory failure. Patients who did not fulfil the definition of ARDS but had respiratory failure with increased work of breathing were labeled as C-ARF not meeting ARDS criteria (C-ARF no ARDS). The ARDS was further categorized based on the PF ratio as mild (PF ratio, 200-300), moderate (PF ratio, 100-200), and severe (PF ratio, <100) ARDS.

The primary outcome was NIV failure, defined as the need for invasive mechanical ventilation or death. Secondary outcomes included total duration of ventilation, nosocomial infections, other organ failure, complications, length of stay (ICU and hospital), and mortality (ICU and hospital).

Because the ICU areas did not have facilities for negative pressure and had limited isolation rooms (n=4), the remaining patients were cohorted in the common ICU areas. The units were modified to allow for 8 to 12 air exchanges every hour in an attempt to reduce the viral load within the unit. High efficiency particulate air filters were fitted to the exhaust system in the air-handling unit. In addition, viral filters were

FIGURE 2. Strobe diagram outlining the ventilatory modalities used in the management of coronavirus disease 2019 acute respiratory failure and hospital mortality. ICU = intensive care unit; NIV = noninvasive ventilation.

connected to the expiratory port of the ventilator. All HCWs in the ICU were provided hazardous materials suits, N95 masks, and eye protection (goggles or visors) and the duration of the shifts was restricted to a maximum of 8 to 10 hours. The proportion of HCWs in the ICU who became symptomatic and tested positive for SARS-CoV-2 during the study period was also recorded.

Statistical Methods

No sample size calculation was performed a priori because this was set out as a time frame study to record the initial observations on NIV in a resource-limited setting. The success rate with NIV was defined as the proportion of patients who were successfully weaned off NIV without the need for invasive mechanical ventilation and were discharged alive from the hospital. Summary data were presented as mean ± SD for normally distributed data and as median with interquartile range (IQR) if data were skewed. The characteristics of patients who failed or succeeded with NIV were compared using t test and Mann-Whitney U test for continuous data and categorical data were compared using χ^2/Fisher exact test as appropriate.

Factors associated with NIV failure ($P<.2$) on univariate analysis were considered for the multivariable regression analysis. Penalized logistic regression analysis was used[21,22] for multivariable analysis to get reliable odds ratios (ORs) and 95% CIs because some covariates, such as need for inotropes and dialysis, had few cell counts. Because many parameters were collinearly related (eg, length of ICU and hospital stay, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment scores, and ventilation data) and some variables were clinically insignificant (values in the normal range or just outside range) despite being statistically significant (eg, troponin and

TABLE 1. Association of Demographic, Laboratory, and Clinical Variables With NIV Success and Failure[a,b]

Variable	Overall (n=286)	NIV Success (n=182)	NIV Failure (n=104)	P
Age (y), mean ± SD	53.1±11.6	50.6±11.1	57.5±11.3	<.001
Sex ratio (male to female)	240:46	149:33	91:13	.21
Admission APACHE II score, mean ± SD	11.1±5.5	9.4±3.6	13.9±6.9	<.001
Admission SOFA score, mean ± SD	3.2±1.3	2.9±1.0	3.8±1.6	<.001
Comorbid conditions (≥2), no. (%)	164 (57.3)	107 (58.8)	57 (54.8)	.52
Main symptomatology, no. (%)				
Fever	235 (82.2)	156 (85.7)	79 (80.0)	.04
Cough	185 (64.7)	124 (68.1)	61 (58.7)	.11
Breathlessness	213 (74.5)	135 (74.2)	78 (75.0)	.88
Severity of respiratory failure, no. (%)				
C-ARF (not ARDS) or mild ARDS	77 (26.9)[c]	64 (35.2)	13 (12.5)	
Moderate ARDS	136 (47.6)	85 (46.7)	51 (49.0)	
Severe ARDS	73 (25.5)	33 (18.1)	40 (38.5)	<.001
Lag time illness to hospital (d), mean ± SD	4.7±2.6	4.9±2.6	4.4±2.8	.10
Lag time illness to ICU (d), mean ± SD	6.8±3.4	7.0±3.0	6.4±3.9	.17
Respiratory rate day 1 (breaths/min), mean ± SD	35.4±8.7	33.8±8.4	38.1±8.6	<.001
PaO$_2$ to fraction of inspired oxygen ratio day 1, mean ± SD	160.8±80	177.1±78.4	132.8±74.9	<.001
Laboratory variable				
Neutrophil to lymphocyte ratio, median (IQR)	9.2 (5.7-15.0)	8.4 (5.0-14.3)	11.0 (6.9-18.4)	.001
Creatinine kinase-MB fraction (IU/L), median (IQR)	1.3 (0.6-2.6)	1.10 (0.6-1.9)	1.8 (0.8-3.7)	<.001
Troponin (ng/mL), median (IQR)	9.6 (6.4-17.7)	8.60 (6.1-14.0)	13.0 (7.4-36.5)	.02
Peak D-dimer (ng/mL), no. (%)				
<1000	134 (47.5)	113 (62.4)	22 (21.4)	<.001
≥1000	149 (52.5)	68 (37.6)	81 (78.6)	
Ferritin (ng/mL), median (IQR)	588 (288-975)	551 (277-903)	595 (302-1122)	.38
Creatinine (mg/dL), median (IQR)	0.89 (0.75-1.14)	0.95 (0.71-1.07)	0.96 (0.81-1.31)	.002
Treatment and outcomes				
Remdesivir use, no. (%)	135 (47.2)	81 (44.5)	54 (51.9)	.18
Time to remdesivir use (d), median (IQR)	2 (1-4)	2 (1-3.3)	2 (1-4)	.89
Prophylactic anticoagulation, no. (%)	110 (39.6)	92 (50.6)	18 (17.3)	
Therapeutic anticoagulation, no. (%)	168 (60.4)	87 (47.8)	81 (77.9)	<.001
Duration of antibiotics, median (IQR)	7 (5-10)	6 (5-7)	12.5 (7-18.8)	<.001
Need for inotropes & dialysis, no. (%)	72 (25.2)	4 (2.2)	66 (63.5)	<.001
Time to inotropes initiation (d), median (IQR)	11 (6-15)	1 (1-10)	11.5 (6.8-15.3)	.04
NIV only, no. (%)	204 (71.3)	182 (100)	22 (21.2)	—
NIV followed by intubation, no. (%)	82 (28.7)	0 (0.0)	82 (78.8)	
Duration of ventilation (d), median (IQR)	8 (5-13)	6 (4-9)	15 (8-23)	<.001
Duration of NIV (d), median (IQR)	5 (3-8)	6 (4-9)	4 (2-6.8)	<.001
Duration of continuous NIV(d), median (IQR)	2 (1-3)	1 (1-3)	3 (1-5)	<.001
Duration of invasive ventilation(d), median (IQR)	11 (7-18)	0 (0-0)	11 (7-11)	
Time to intubation[d] (d), median (IQR)	4 (2-7)	0 (0-0)	4 (2-7)	—
Ventilator-free days, median (IQR)	19 (0-23)	22 (19-24)	0 (0-0)	—
Acute kidney injury, no. (%)	59 (20.6)	18 (9.9)	41 (39.4)	<.001
Need for dialysis, no. (%)	20 (7.0)	1 (0.6)	19 (18.3)	<.001
Nosocomial infections, no. (%)	66 (23.1)	9 (5.0)	57 (54.8)	<.001
Other complications, no. (%)				
Barotrauma	10 (3.6)	1 (0.6)	9 (8.7)	—
Major bleed	3 (1.0)	1 (0.6)	2 (1.9)	
Minor bleed	11 (3.8)	1 (0.6)	10 (9.6)	

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TABLE 1. Continued				
Variable	Overall (n=286)	NIV Success (n=182)	NIV Failure (n=104)	P
Treatment and outcomes, continued				
Thrombotic complications	11 (3.9)	4 (2.2)	7 (6.7)	
ICU length of stay (d), median (IQR)	9 (6-15)	7 (5.5-10)	15 (9-23)	<.001
Hospital length of stay (d), median (IQR)	16 (12-23)	15 (12-20.5)	19 (12-26)	.04

[a]APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; C-ARF = coronavirus disease 2019–related acute respiratory failure; ICU = intensive care unit; IQR = interquartile range; NIV = noninvasive ventilation; SOFA = Sequential Organ Failure Assessment.

[b]SI conversion factors: To convert troponin values to μg/L, multiply by 1.0; to convert D-dimer DDU values to mg/L, divide by 1000; to convert ferritin values to μmol/L, multiply by 88.4.

[c]Thirteen patients had C-ARF without ARDS.

[d]Time to intubation after ICU admission;

lactate dehydrogenase), 9 clinically relevant and statistically significant variables were considered for the penalized logistic regression. Given the clinical correlation of increasing D-dimer levels and worsening respiratory status, peak (rather than admission) D-dimer values were used in the regression analysis. Statistical significance was defined as $P<.05$. All analyses were performed using STATA (StateCorp LLC), version 15 and SPSS, version 22 (IBM SPSS Statistics Base 25.0).

RESULTS

Baseline Demographic Data
During the study period, 351 patients were admitted to the ICU; 333 patients had C-ARF (Figure 2). There were 286 of these patients with a mean ± SD age of 53.1±11.6 years who were initiated on NIV for respiratory failure and formed the study cohort. The mean ± SD APACHE II score was 11.1±5.5; 57.3% (164/286) had 2 or more comorbid conditions. The predominant symptomatology was fever (82.2%; n=235), breathlessness (74.5%; n=213), and cough (64.7%; n=185). The mean ± SD lag time to ICU admission from symptom onset was 6.8±3.4 days. The mean ± SD respiratory rate on day 1 of ICU admission was 35.4±8.7 breaths per minute and the PF ratio was 160.8±80. Of the 286 patients with C-ARF, ARDS was diagnosed in 273 patients, with the proportion of mild, moderate, and severe ARDS being 22.4% (n=64), 47.6% (n=136), and 25.5% (n=73), respectively

(Table 1). Thirteen patients (4.5%) with C-ARF did not fulfil the diagnostic criteria for ARDS.

Laboratory Variables at Admission and Treatment Data
The median neutrophil to lymphocyte ratio was 9.2 (IQR, 5.7-15) and the D-dimer level was 809 (IQR, 506-1432) ng/mL. There was no evidence of cardiac enzyme level elevation or increased creatinine level at admission (Table 1). A total of 47.2% (n=135) received Remdesivir (200 mg loading dose followed by 100 mg daily for 4 days) at a median of 2 (IQR, 1-4) days; 278 patients received anticoagulation therapy, of whom 60.4% (n=168) received therapeutic anticoagulation. Inotropes and dialysis were required in 24.1% (n=69) and 7% (n=20), respectively, during the course of the ICU stay. A total of 285 patients (99.7%) received corticosteroids at the dose of 6 mg per day of dexamethasone (n=236) or its equivalent as methylprednisolone (n=38) at a dose of 20 mg twice daily or hydrocortisone (n=11) at a dose of 100 mg thrice daily. The choice of corticosteroid was left to the treating clinician's preference. A total of 181 patients received a combination of β-lactams with macrolides at admission to the ICU to cover possible superadded bacterial infections. Antibiotic coverage was broadened in the setting of suspected or proven nosocomial infections in 93 patients, and 12 patients were not prescribed any antibiotics during

TABLE 2. Adjusted Analysis of Factors Associated With NIV Failure[a,b]

	Penalized Logistic Regression					
	Unadjusted			Adjusted		
Factor	OR	95% CI	P	OR	95% CI	P
Age	1.06	1.03-1.08	<.001			
APACHE II score	1.21	1.13-1.29	<.001	1.12	1.01-1.24	.02
SOFA, admission score	1.86	1.46-2.36	.001			
Creatine kinase-MB	1.22	1.09-1.38	.001			
Troponin	1.00	0.99-1.00	.12			
Lactate dehydrogenase	1.00	0.99-1.00	.006			
Creatinine	1.50	1.12-2.01	.01			
N-terminal pro B-type natriuretic peptide	1.00	1.00-1.12	.02			
Time to remdesivir	0.98	0.90-1.06	.57			
Duration of antibiotic therapy	1.28	1.20-1.37	<.001			
Ventilation-free days	0.73	0.69 -0.78	<.001			
Total duration of ventilation	1.18	1.12-1.23	<.001			
Duration of NIV	0.88	0.82-0.95	.001			
Duration of continuous NIV	1.24	1.12-1.37	<.001	1.18	1.03 - 1.36	.01
ICU length of stay	1.16	1.11-1.21	<.001			
Hospital length of stay	1.03	1.01-1.06	.020	0.91	0.86 - 0.96	<.001
Lag time to hospital	0.92	0.93-1.02	.11	0.94	0.82 - 1.08	.41
Lag time to ICU	0.95	0.88-1.02	.19			
Categorical variables:						
Fever	0.53	0.29-0.97	.04	0.90	0.35 - 2.30	.83
Inotropes and/or dialysis	58.1	23.7-148.4	<.001	12.7	4.3-37.7	<.001
ARDS						
No/mild ARDS	1.00					
Moderate ARDS	3.33	1.65-6.91	.001	2.61	0.89-7.70	.08
Severe ARDS	4.83	3.12-14.7	<.001	3.99	1.24-12.9	.02
Nosocomial infection	22.1	10.4-47.2	<.001	13.6	4.06-45.9	<.001
Peak D-dimer (ng/mL) (≥1000)	6.00	3.45-10.45	<.001	2.60	1.16-5.87	.02

[a]APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; NIV = noninvasive ventilation; OR = odds ratio; SOFA = Sequential Organ Failure Assessment.

[b]Factors identified on unadjusted regression analysis (P<.2) were considered for the adjusted penalized logistic regression. However, because many parameters were collinearly related (eg, length of ICU and hospital stay, APACHE II and SOFA scores, and several ventilation characteristics) and some of the statistically significant variables were not clinically significant in terms of actual values being in the normal range or just outside the range (eg, troponin and lactate dehydrogenase), 9 clinically relevant and statistically significant variables were considered for the penalized logistic regression.

the course of their ICU stay. Median duration of antibiotic therapy was 7 (IQR, 5-10) days.

Ventilation and Outcome Data

Of the 351 patients admitted to the ICU, 18 patients with incidental COVID-19 positivity did not receive ventilatory support and 2 patients (11.1%) died (Figure 2). Both patients had clear directives for limitation of treatment. Forty-seven patients were managed exclusively with invasive ventilation;

mortality was 59.6% (n=28) in this subset of patients (Figure 2).

The remaining 286 patients were initiated on NIV (study cohort); in 82 patients (28.7%), a trial of NIV failed, and they required intubation (Figure 2). In the 82 patients (28.7%) in whom the NIV trial failed and who needed invasive ventilation, mortality was 78.0% (n=64). The rest (n=204; 71.3%) were managed exclusively on NIV. In the subgroup exclusively managed on NIV, 22 patients died (10.8%; 95% CI,
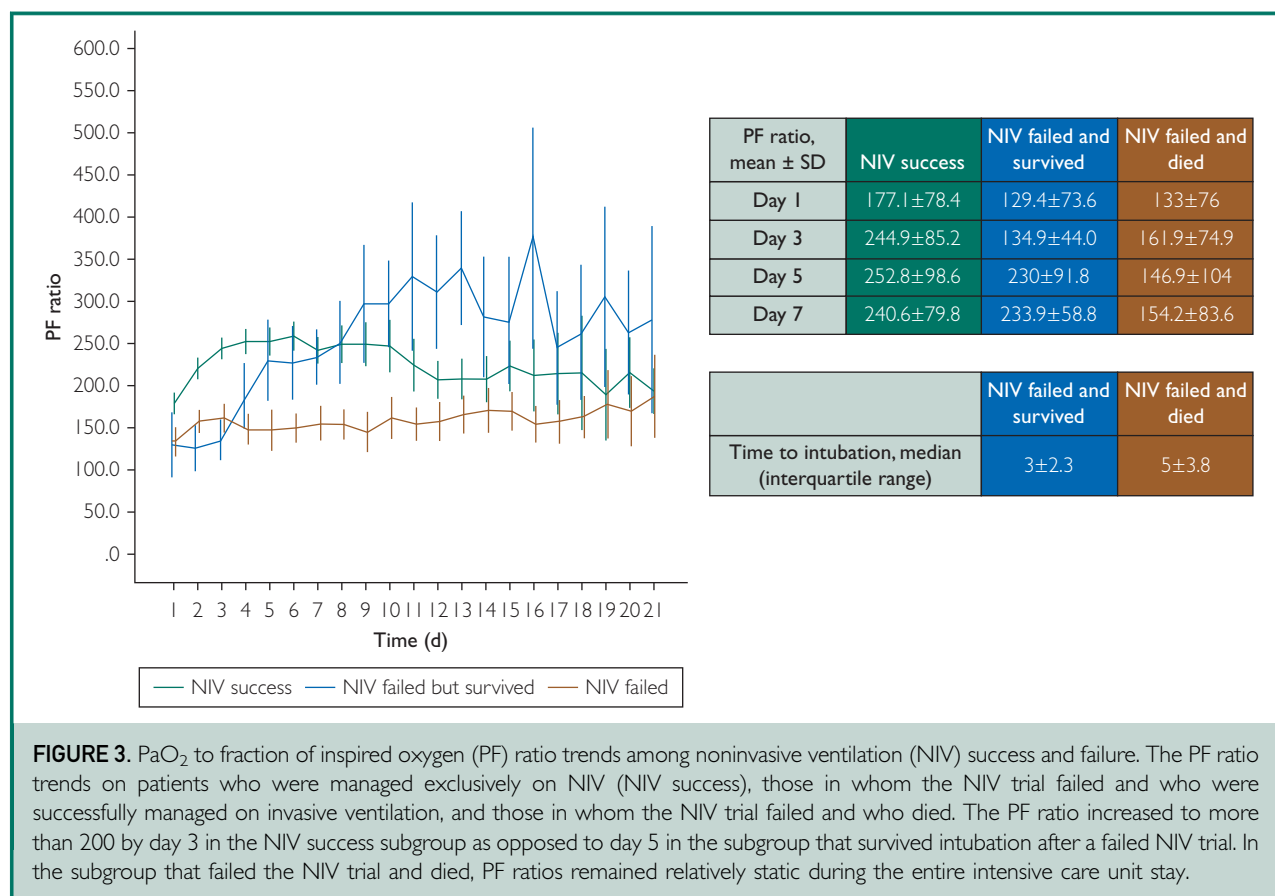
FIGURE 3. PaO$_2$ to fraction of inspired oxygen (PF) ratio trends among noninvasive ventilation (NIV) success and failure. The PF ratio trends on patients who were managed exclusively on NIV (NIV success), those in whom the NIV trial failed and who were successfully managed on invasive ventilation, and those in whom the NIV trial failed and who died. The PF ratio increased to more than 200 by day 3 in the NIV success subgroup as opposed to day 5 in the subgroup that survived intubation after a failed NIV trial. In the subgroup that failed the NIV trial and died, PF ratios remained relatively static during the entire intensive care unit stay.

6.5% to 15%); all these patients had directives for NIV as the limitation of care. Thus, the success rate with NIV was 63.6% (182/286; 95% CI, 58% to 69.2%).

The overall mortality in patients who were initiated on NIV was 30.1% (86/286; 95% CI, 24.9% to 35.8%). The median duration of ventilation of the cohort was 8 (IQR, 5-13) days, of which NIV was used for 5 (IQR, 3-8) days and invasive ventilation for 11 (IQR, 7-18) days. The median time to intubation after ICU admission in this cohort was 4 (IQR, 2-7) days.

Acute kidney injury developed in 20.6% (n=59) and 7% (n=20) required dialysis; 23.1% (n=66) developed nosocomial infections. Eleven patients (3.9%) had proven thrombotic complications while on anticoagulation therapy; 4% (n=11) of this cohort had minor bleeds and only 1% (n=3) had major bleeds that required transfusion. The median ICU length of stay was 9 (IQR,

6-15) days and the hospital length of stay was 16 (IQR, 12-23) days.

Factors Associated With NIV Failure

When compared with NIV success, NIV failure was significantly associated with (Table 1) older age, higher disease severity, lower admission PF ratio, higher respiratory rate, higher creatine kinase-MB level, need for organ support, longer duration of continuous NIV, and longer ICU and hospital lengths of stay.

On adjusted penalized logistic regression analysis (Table 2), higher admission APACHE II score (OR, 1.12; 95% CI, 1.01 to 1.24), severe ARDS (OR, 3.99; 95% CI, 1.24 to 12.9), peak D-dimer level of 1000 ng/mL or greater (OR, 2.60; 95% CI, 1.16 to 5.87), and the need for inotropes or dialysis (OR, 12.7; 95% CI, 4.3 to 37.7) were associated with a higher risk for NIV failure. Additionally, longer periods receiving continuous
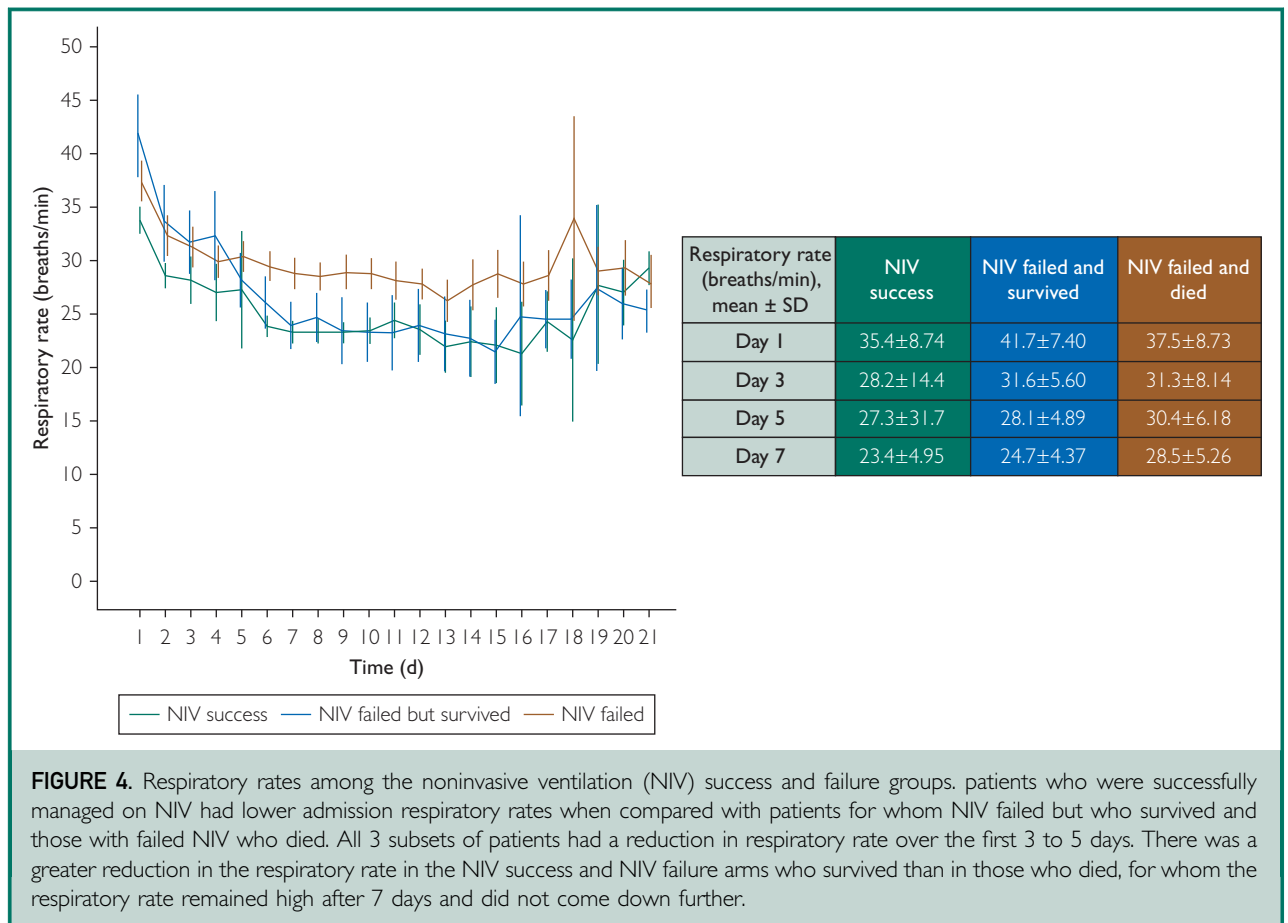
FIGURE 4. Respiratory rates among the noninvasive ventilation (NIV) success and failure groups. patients who were successfully managed on NIV had lower admission respiratory rates when compared with patients for whom NIV failed but who survived and those with failed NIV who died. All 3 subsets of patients had a reduction in respiratory rate over the first 3 to 5 days. There was a greater reduction in the respiratory rate in the NIV success and NIV failure arms who survived than in those who died, for whom the respiratory rate remained high after 7 days and did not come down further.

NIV (OR, 1.18; 95% CI, 1.03 to 1.36) were associated with NIV failure. The duration of hospital stay was shorter among the NIV failure group (OR, 0.91, 95% CI, 0.86 to 0.96).

PF Ratio and Respiratory Trends Among NIV Success and Failure Groups

The patients in this cohort had pure hypoxemic respiratory failure. In the group successfully managed with NIV, the PF ratio (Figure 3) steadily improved from day 1 onward. After day 5, there was a marginal decrease in PF ratio, probably reflecting weaning from NIV. In contrast, in the NIV failure group, the PF ratio remained almost static in the first 3 days. In the subset with NIV failure who survived, there was a dramatic increase in PF ratio from day 3 to day 5, whereas in those who died, PF ratio continued to remain low (Figure 3). With regard to trends in respiratory rate, all 3 subsets of patients had a reduction in respiratory rate over the first 3 to 5 days (Figure 4). There was a greater reduction in the respiratory rate in the NIV success and NIV failure arms who survived than in those who died, for whom the respiratory rate remained high even after 7 days. In patients requiring intubation, time to intubation was longer in non-survivors when compared with survivors (median, 5; IQR, 3-8 vs 3; IQR, 2-3 days; P=.001).

Factors Associated With Hospital Mortality

On unadjusted penalized logistic regression analysis, several factors were associated with hospital mortality (Table 3). On adjusted analysis (Table 3), mortality was associated with older age (OR, 1.08; 95% CI, 1.04 to 1.12), severe ARDS (OR, 4.04; 95% CI, 1.08 to 15.1), higher peak D-dimer level (OR, 2.75; 95% CI, 1.19 to 6.37),

TABLE 3. Adjusted Analysis of Factors Associated With Hospital Mortality[a,b,c]

| | Penalized Logistic Regression | | | | | |
| | Unadjusted | | | Adjusted | | |
Variable	OR	95% CI	P	OR	95% CI	P
Age	1.07	1.04-1.10	<.001	1.08	1.04-1.12	<.001
Male sex	2.20	1.00-4.85	.04	1.93	0.63-5.93	.25
Admission APACHE II score	1.15	1.09-1.22	<.001	0.94	0.87-1.02	.13
Admission SOFA score	1.78	1.40-2.25	<.001			
≥2 comorbid conditions	0.75	0.45-1.25	.28			
Creatine kinase-MB	1.24	1.10-1.39	<.001			
Troponin	1.00	0.99-1.00	.05			
Neutrophil to lymphocyte ratio	1.03	1.00-1.05	.01			
Duration of continuous NIV	1.29	1.16-1.43	<.001			
Time to intubation	1.51	1.08-2.14	.001	0.89	0.77-1.01	.07
Lag time to hospital	0.90	0.81-1.01	.05			
ICU length of stay	1.11	1.07-1.15	<.001			
Hospital length of stay	1.01	0.98-1.04	.65			
Categorical variables:						
Inotropes and/or dialysis	32.5	15.7-67.3	<.001	9.19	2.83-29.9	<.001
Severity of respiratory failure						
C-ARF (not ARDS)[d]/mild ARDS	1.00					
Moderate ARDS	4.59	1.99-10.6	<.001	3.45	1.03-11.5	.04
Severe ARDS	7.15	2.96-17.3	<.001	4.04	1.08-15.1	.03
Peak D-dimer						
≥1000 ng/mL	6.83	3.68-12.8	<.001	2.75	1.19-6.37	.02
Ventilation data						
NIV only	1.00					
NIV followed by intubation	29.9	15.1-59.4	<.001	9.36	3.38-25.9	<.001
Nosocomial infections	10.6	5.67-19.9	<.001	0.87	0.28-2.67	.81
Remdesivir use	1.26	0.76-2.10	.19			
Prophylactic anticoagulation	1.00					
Therapeutic anticoagulation	6.25	3.15-12.4	<.001			

[a]APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; C-ARF = coronavirus disease 2019—related acute respiratory failure; ICU = intensive care unit; IQR = interquartile range; NIV = noninvasive ventilation; OR = odds ratio; SOFA = Sequential Organ Failure Assessment.

[b]SI conversion factor: To convert D-b dimer DDU values to mg/L, divide by 1000.

[c]Factors identified on unadjusted regression analysis (P<.2) were considered for the adjusted penalized logistic regression. However, because many parameters were collinearly related (eg, APACHE II and SOFA scores and several ventilation characteristics) and some of the statistically significant variables were not clinically significant in terms of actual values being in the normal range or just outside the range (eg, troponin and lactate dehydrogenase), 9 clinically relevant and statistically significant variables were considered for the penalized logistic regression.

requirement for intubation (OR, 9.36; 95% CI, 3.38 to 25.94), and need for inotropes and/or dialysis (OR, 9.19; 95% CI, 2.83 to 29.9).

Proportion of Staff Who Developed SARS-CoV-2 Infection

Of 258 HCWs, 8 (3.1%) HCWs developed SARS-CoV-2 infection during the study period, all of whom had mild disease.

DISCUSSION

In this study spanning 6 months, 81.5% of patients (286/351) admitted to the ICU were initiated on NIV. Although the overall mortality in this NIV cohort was 30.1% (86/286), the mortality in those managed exclusively on NIV was 10.8% (22/204) as opposed to 78% (64/82) in those in whom NIV failed and who needed intubation. The NIV success rate was 63.6% (n=182), of whom two-thirds had moderate (n=85) or

TABLE 4. Summary Table of Studies Looking at NIV for C-ARF[a]

Reference, year (country)	Setting	Mode	NIV Failure Definition	PF Ratio[b]	Disease Severity[c]	No. Receiving NIV	NIV Duration	NIV Failure[d]	Mortality	Predictors of Failure
Sivaloganathan et al,[11] July 2020 (United Kingdom)	Ward or ICU	NIV	Requirement of intubation	17 kPa (14.3-20.4)[e]	APACHE II, 11 (8-12.5); SOFA, 3 (4-3)[e]	58	72 (41-132) h	27 (46.6%)	39.6%	Admission SOFA
Mukhtar et al,[12] July 2020 (Egypt)	ICU	NIV	Requirement of intubation	170 (112-224)[e]	APACHE II, 10±4.4	39	NA	9 (30.7%)	23.1%	NA
Faraone et al,[13] November 2020 (Italy)	Non ICU	Respironics-CPAP or BiPAP	Intubation or death during hospital stay	130.1 (63.5)	SOFA, 3.1±1.2	50	187 (181) h	31 (62%)	50%	Treatment limitation
Avdeev et al,[14] January 2021 (Russia)	Ward	CPAP or PSV Respironics	Intubation or death during hospital stay	198.8 (155.2-242.4)[e]	NA	61	NA	17 (27.9%)	24.6%	D-dimer
Daniel et al,[15] January 2021 (United States)	COVID only center	CPAP or BiPAP	No definition	NA	NA	131	NA	104 (79.3%)	74.0%	Age
Bertaina et al,[16] March 2021 (HOPE COVID-19 registry)	Ward and ICU	NIV	Composite end point; death or intubation	NA	NA	390 (86 in ICU)	NA	173 (44.4%)	37.7%	Age, hypertension, admission SpO$_2$ <92% RA, use of antibiotics, lymphocytopenia
Menzella et al,[17] March 2021 (Italy)	Ward	Respironics or Hamilton G5	Need for intubation; persistence of low PF ratio <100 on NIV	120.1 (41.6)	SOFA, 4.3±1.3	79	6.6 (4.5) d	41 (51.9%)	25.3%	SOFA score

Continued on next page

TABLE 4. Continued

Reference, year (country)	Setting	Mode	NIV Failure Definition	PF Ratio[b]	Disease Severity[c]	No. Receiving NIV	NIV Duration	NIV Failure[d]	Mortality	Predictors of Failure
Current study	ICU	NIV	Intubation or death during hospital stay	160.7 (80)	APACHE II, 11.1±5.5; SOFA, 3.2±1.3	286	5 (3-8)[e] d	104 (36.4%)	30.1%	APACHE II, duration of continuous NIV, need for inotropes or dialysis, severe ARDS, nosocomial infections

aAPACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; BiPAP = bilevel positive airway pressure; C-ARF = coronavirus disease 2019–related acute respiratory failure; COVID = coronavirus disease; CPAP = continuous positive airway pressure; ICU = intensive care unit; NA = data not available; NIV = noninvasive ventilation; NIV failure rate = NIV failure/total patients receiving NIV; PF ratio = PaO$_2$ to fraction of inspired oxygen ratio; PSV = pressure support ventilation; RA = room air; SOFA = Sequential Organ Failure Assessment; SpO$_2$ = oxygen saturation as measured by pulse oximetry.

bAdmission PF ratio (in mm Hg, unless specified otherwise).

cValues are expressed as mean ± SD or median (interquartile range) as quoted in the publication.

dNIV failure as defined in the study. In the study in which the definition was not provided, NIV failure was defined as the need for intubation after a failed NIV trial or death.

eMedian (interquartile range).

severe (n=33) ARDS. Noninvasive ventilation failure was associated with higher APACHE II scores, severe ARDS, longer duration of continuous NIV, peak D-dimer level of 1000 ng/mL or greater, need for non-pulmonary organ support, and nosocomial infections.

The role of NIV in the treatment of C-ARF is debated[15] because of the potential for aerosol generation,[23] the nature of respiratory failure (predominantly hypoxemic),[17,24] and the protracted course of illness. The concern also stems from evidence of NIV failure in ARDS of diverse cause ranging from 22%[25] to as high as 92.4%[4] and conflicting results on the role of NIV from studies during the H1N1 and SARS pandemics.[5-7]

Despite the controversies surrounding the safety and benefit of NIV in C-ARF, with the increasing burden of C-ARF that overwhelmed ICU capacity, NIV use increased from 11% in the early months of the pandemic[9,26] to 56%[27] as time progressed. Further, the hypothesis that NIV may play a role in reducing the progression from the L phenotype of C-ARDS to the H phenotype[28] could have also contributed to increased use.

In most of the studies published to date, NIV was delivered in a non-ICU setting (Table 4). However, data on the use of NIV in the ICU setting and its predictors of success are limited. To our knowledge, this is the largest ICU-based study that has explored the role of NIV in terms of effectiveness in consecutive patients with C-ARF. In this study, an overwhelming majority (85.9%; 286/333) of patients who presented with C-ARF were initiated on NIV treatment irrespective of the severity of ARDS. This contrasts with the subgroup analysis of the LUNG SAFE study in which the NIV subgroup had a high failure rate (defined as the need for intubation) and death among patients with moderate to severe ARDS.[25]

In this cohort, NIV failed in 104 (36.4%) patients (Table 1). The NIV failure rate in the various studies ranged from 30.7%[12] to 62%[13] (Table 4). Comparison of NIV failure rates in the various studies was challenging

because a variable definition of NIV failure was used; 3 studies defined NIV failure as the requirement of intubation,[11,12,17] whereas 3 other studies[13,14,16] defined NIV failure as need for intubation or death.

It was interesting to note that the PF ratios in the current study increased to more than 200 by day 3 in the NIV success subgroup as opposed to day 5 in the subgroup that survived intubation after a failed NIV trial. In contrast, the subgroup in which the NIV trial failed and who died, PF ratios remained relatively static during the entire first week following ICU admission (Figure 3). Our observations are consonant with that of Faraone et al,[13] who reported that increasing PF ratios 24 to 48 hours after NIV initiation may help in identifying potential NIV responders.

The mortality of the entire cohort was 30.1% (86/286); notably the mortality was low (10.8%; 22/204) among patients who received only NIV, all of whom had limitations on care (Figure 2). Mortality in the other NIV cohorts ranged from 23.1%[12] to 74%.[15] However, it is concerning that the NIV failure arm that required intubation had higher mortality (78%; 64/82) when compared with the group that required intubation (59.6%; 28/47) at or prior to ICU admission (Figure 2). On exploratory analysis, it was observed that the time to intubation was significantly longer in nonsurvivors when compared with survivors (median, 5; IQR, 3-8 vs 3; IQR, 2-3 days; $P<.001$), suggesting that delay in intubation in those receiving NIV may contribute to mortality. This contrasts with the study by Daniel et al[15] and the meta-analysis by the COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators[24] that suggested that timing of intubation had no effect on mortality.

In the early stages of the pandemic, it was observed that a combination of factors (increasing FiO_2, persistently high FiO_2 >70%, PF ratio <100, and increased work of breathing while receiving continuous NIV) seemed to affect the outcomes of patients who were intubated after a failed NIV trial. Based on these observations, the

guidelines for the thresholds for intubation in our ICU were dynamically re-defined over time. This finally resulted in the reduction of the FiO_2 threshold for intubation from 0.7 to 0.6 (in the context of PF ratio <100), and the increasing work of breathing was made an optional (+/−) rather than a mandatory criterion (Figure 1). However, as stated in the Patients and Methods section, these protocols were offered as guidelines and the decision on intubation was taken by the treating intensivist based on the clinical assessment. These modifications in the ventilatory protocol may have positively affected outcomes in our study. However, the optimal timing of intubation warrants further study. Although it may be challenging to plan a trial of early vs delayed intubation, it will be interesting to see whether there is greater clarity on the timing of intubation in COVID-19 ARDS from large data sets.

The delivery of NIV in our setting appeared safe in terms of HCWs developing clinical infections (3.1%; 8/258) despite the resource-limited setting without standard negative pressure rooms. A similar pattern was seen in other studies in which there was no added risk to HCWs with the use of NIV.[14,29] This contrasted with reports from China and Italy in which HCWs contributed up to 12% of reported COVID-19 cases.[13] In our cohort, NIV was delivered exclusively using oronasal facemasks; helmet interfaces were not used. Antimicrobial filters were applied to the exhalation port in the ventilators to limit SARS-CoV-2 spread.[30]

The study has the following limitations. This was an observational study from a single-center ICU. The lack of a control group precludes definite conclusions on the benefit of NIV on patient outcomes over early intubation. It would have been useful to collect expiratory tidal volume data and use the HACOR (heart rate, acidosis, consciousness level, oxygenation and respiratory rate) score to predict NIV failure[31]; these were not done. Nevertheless, this study shows that a significant proportion of patients who present with C-ARDS can be successfully managed using NIV.

CONCLUSION

This study adds to the body of evidence that NIV can be effective as a primary ventilatory support in patients with C-ARF in the ICU. Noninvasive ventilation was successful in nearly two-thirds of patients with C-ARF and can be used even in patients with moderate to severe ARDS. Illness severity, prolonged requirement of continuous NIV, need for nonrespiratory organ support, peak D-dimer level of 1000 ng/mL or greater, and development of nosocomial infections predict NIV failure. Further studies are required to clarify the optimal timing of intubation in those who do not improve with NIV.

Abbreviations and Acronyms: **APACHE II**, Acute Physiology and Chronic Health Evaluation II; **ARDS**, acute respiratory distress syndrome; **BiPAP**, bilevel positive airway pressure; **C-ARDS**, coronavirus disease 2019—related acute respiratory distress syndrome; **C-ARF**, coronavirus disease 2019—related acute respiratory failure; **COVID-19**, coronavirus disease 2019; **CPAP**, continuous positive airway pressure; **FiO2**, fraction of inspired oxygen; **HCW**, health care worker; **ICU**, intensive care unit; **IQR**, interquartile range; **NA**, not applicable; **NIV**, noninvasive ventilation; **OR**, odds ratio; **PF ratio**, PaO2 to fraction of inspired oxygen ratio; **PSV**, pressure support ventilation; **RA**, room air; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SOFA**, Sequential Organ Failure Assessment; **SpO2**, oxygen saturation as measured by pulse oximetry; **WOB**, work of breathing

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