Combined Noninvasive Respiratory Support Therapies to Treat COVID-19

Nicolas Colaianni-Alfonso, Guillermo Montiel, Mauro Castro-Sayat, Catalina Siroti, Maria Laura Vega, Ada Toledo, Santiago Haedo, Ignacio Previgliano, Guido Mazzinari, and José Miguel Alonso-Íñigo

BACKGROUND: The roles of high-flow nasal cannula (HFNC) and CPAP in coronavirus disease 2019 (COVID-19) are controversial. The objective of the study was to evaluate the impact of the application of a noninvasive respiratory support algorithm on clinical outcomes in subjects with COVID-19 and with acute respiratory failure. METHODS: We performed a single-center prospective observational study of subjects with respiratory failure from COVID-19 managed with HFNC and with CPAP plus HFNC (combined therapy). The main outcome was the intubation rate, which defined failure of therapy. We also analyzed the role of the ROX index ($[S_{pO_2}/F_{IO_2}]$/breathing frequency) to predict the need for intubation. RESULTS: From June to December 2020, 113 subjects with COVID-19 respiratory failure were admitted to our respiratory intermediate care unit. HFNC was applied in 65 subjects (57.52%) and combined therapy in 48 subjects (42.47%). A total of 83 subjects (73.45%) were successfully treated with noninvasive respiratory support. The intubation rate was 26.54%, and the overall mortality rate was 14.15%. The mortality rate in subjects who were intubated was 55.2%. An ROX index of 6.28 at 12 h predicted noninvasive respiratory support failure, with 97.6% sensitivity and 51.8% specificity. CONCLUSIONS: Data from our cohort managed in a respiratory intermediate care unit showed that combined noninvasive respiratory support was feasible, with favorable outcomes. Further prospective studies are required. *Key words: COVID-19; SARS-CoV-2; high-flow nasal cannula; continuous positive airway pressure; combined therapy; hypoxemic respiratory failure.*
[Respir Care 2021;66(12):1831–1839. © 2021 Daedalus Enterprises]

Introduction

On March 11, 2020, the World Health Organization declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic due to the constantly increasing number of cases outside China.[1] Patients with SARS-CoV-2 infection can develop coronavirus disease 2019 (COVID-19), which has resulted in high rates of hospitalization and ICU admission.[2] The clinical spectrum of SARS-CoV-2 infection seems to be wide, including asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure, and even death, with many patients being hospitalized with pneumonia.[3] In the COVID-19 population, 14% of the patients were categorized as severe cases and 5% as critical cases.[4] A systematic review and meta-analysis pooled 31 articles that involved 46,959 cases of patients with COVID-19 and reported that the incidence of ICU admission was 29.3%.[5] Some experts have

Mr Colainni-Alfonso, Dr Montiel, Mr Castro-Sayat, Ms Siroti, Ms Vega, Dr Toledo, Dr Haedo, and Dr Previgliano are affiliated with the Respiratory Intermediate Care Unit, Hospital Juan A. Fernández, Ciudad Autónoma de Buenos Aires, Argentina. Department of Pneumology. Drs Mazzinari and Alonso-Inigo are affiliated with the Hospital Universitario y Politécnico la Fe, Valencia, Spain. Research Group in Perioperative Medicine, Department of Anesthesiology.

Dr Alonso-Iñigo discloses a relationship with Vygon. The other authors have disclosed no conflicts of interest.

Correspondence: Nicolás Colaianni-Alfonso RRT, Hospital Juan A. Fernández, Unidad Soporte Ventilatorio No Invasivo, Av. Cerviño 3356, C1425 Ciudad Autónoma de Buenos Aires, Argentina. E-mail: nicolkf@gmail.com.

DOI: 10.4187/respcare.09162

argued that invasive ventilation should be used early to prevent patients with COVID-19 progressing from mild disease to more severe lung injury.[6] Patients with COVID-19 who require invasive ventilation are at high risk for poor outcomes and have a likelihood of mortality estimated at approximately 50%–97%.[7-9] Mortality may be related to the progressive course of the viral infection but could be perpetuated by the inherent complications of mechanical ventilation itself.

Other recommendations at the beginning of the pandemic were to avoid noninvasive respiratory support.[10] Two main concerns that deal with the use of noninvasive respiratory support are the risk of delaying intubation in case of failure and the fear of virus spreading among health-care workers during noninvasive respiratory treatment.[11] At the early stage, high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV) was used in 20%–62% of hospitalized patients.[12,13] When comparing different countries, the use of noninvasive respiratory support has been highly variable. Thus, in the Lombardy region of Italy, NIV was used in 11% of patients in the ICU; however, in the United States, in the Seattle region of Washington, HFNC was used in 42% of the patients who were critically ill.[14,15] Current recommendations state that patients with COVID-19-related acute respiratory failure (ARF) should be monitored and supported with HFNC or NIV when standard oxygen therapy fails.[16] In this regard, during the months of June to December of 2020, COVID-19 created a significant increase in the health-care burden across Argentina because 45–59% of admitted patients required critical care management.[17]

The ICU beds and invasive mechanical ventilators were assumed to have limits of availability during the pandemic, so the willingness to use and availability of noninvasive respiratory support was a valuable option to maintain respiratory conditions. Therefore, a proper health-care resource management is necessary to warrant adequate patient care. Respiratory intermediate care units can be a useful resource for the management of complex patients who do not require ICU admission, invasive ventilation, or invasive monitoring. Respiratory intermediate care units can function as a place for the management of treatment escalation and de-escalation between the general ward and the ICU, especially when closer patient monitoring is needed and/or when noninvasive respiratory support is required. Benefits of a respiratory intermediate care unit include reducing the ICU admission time, increasing ICU bed capacity, as well as lowering mortality and health-care costs.[10-12] The objective of our study was to evaluate the impact of the application of a noninvasive respiratory support algorithm on clinical outcomes in patients with COVID-19 and with ARF.

QUICK LOOK

Current knowledge

High-flow nasal cannula (HFNC) and CPAP are routinely used as part of the care of patients with COVID-19–related respiratory failure. There is significant debate about the effectiveness of these noninvasive therapies compared with invasive ventilation.

What this article adds to our knowledge

This article adds to our knowledge, the feasibility of being able to perform combined therapies of noninvasive respiratory support and the possibility of using the ROX index ($[S_{pO_2}/F_{IO_2}]$/breathing frequency) as a predictor of noninvasive respiratory support failure. Prolonged use of HFNC or combined therapy (CPAP plus HFNC) may be reasonable in the care of patients with COVID-19 as a measure to avoid intubation.

Methods

Study Design and Subjects

This was a prospective observational study conducted in Hospital General de Agudos Juan A. Fernández, Buenos Aires, Argentina. Institutional review boards reviewed the protocol and authorized prospective data collection. We collected data from patients admitted to the respiratory intermediate care unit from June 1, 2020, to December 31, 2020. A confirmed case of COVID-19 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction assay of nasal and pharyngeal swabs. Criteria for respiratory intermediate care unit admission were suspected COVID-19 pneumonia with at least $P_{aO_2}/F_{IO_2} \leq 200$ mm Hg, supplemental oxygen requirement > 10 L/min, and breathing frequency ≥ 30 breaths/min with or without the use of accessory muscles. Patients were transferred to the ICU in the case of rapid deterioration or the need for intubation to start invasive ventilation. Decisions on ceiling limits of care and escalation to the ICU were made within an agreed ethics framework and were based on the clinical need and appropriateness for escalation. There were no limitations on resources.

Noninvasive Respiratory Support Protocol

Respiratory support was provided throughout a decision-making algorithm (Fig. 1). All the subjects received respiratory support with the subject in the awake proneposition or decubitus position changes at least 18 h per day, avoiding the supine position as much as possible. The prone position

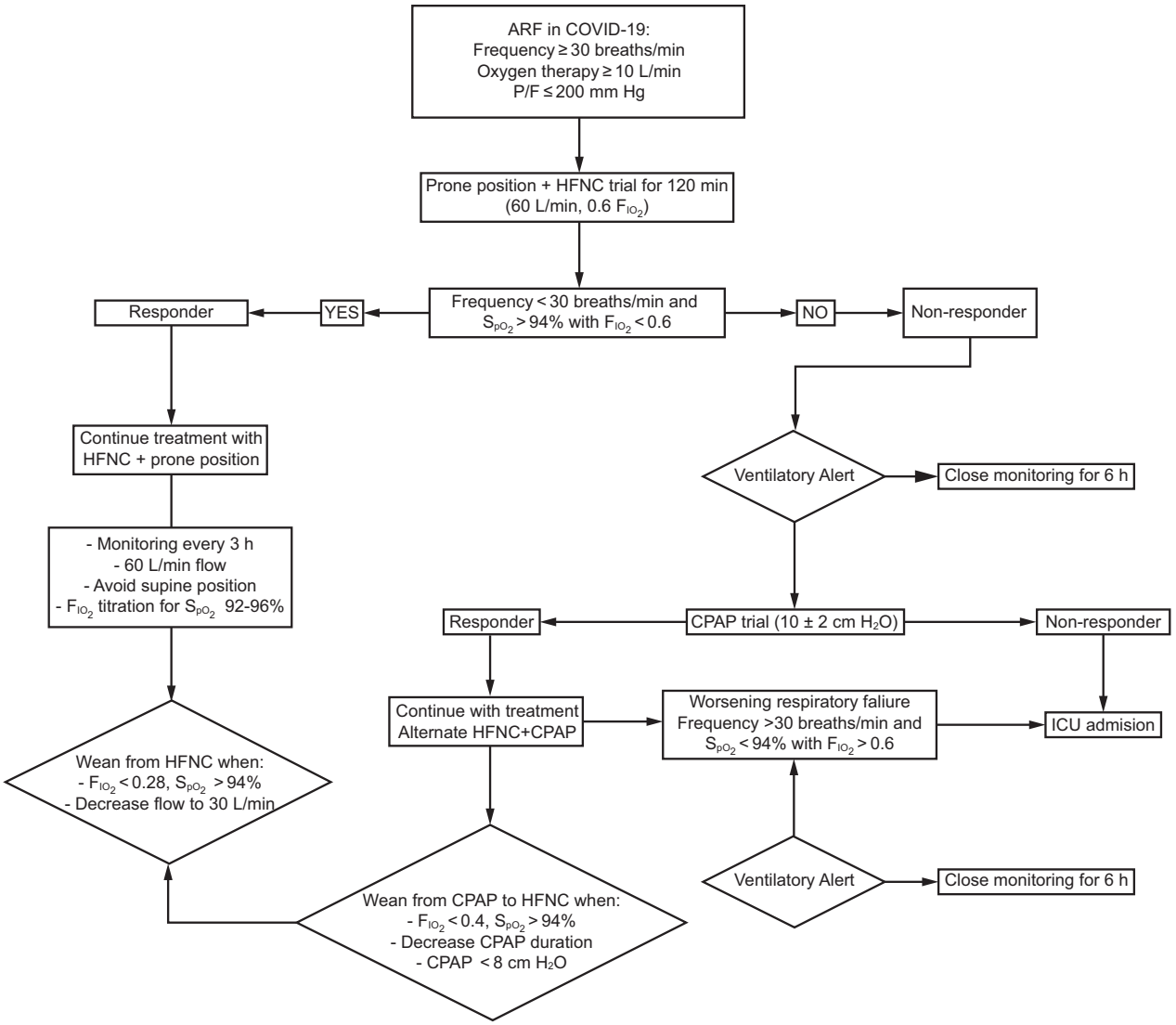

Fig. 1. Decision-making algorithm for noninvasive respiratory support. ARF = acute respiratory failure, P/F = P_{aO_2}/F_{IO_2}, HFNC = high-flow nasal cannula.

was not considered in the case of patient intolerance, morbid obesity, or patient refusal. In these cases, an alternating lateral decubitus position was performed. To check the initial response to treatment, all the subjects underwent a 2-h trial of HFNC at 60 L/min and F_{IO_2} of 0.6, and, as adjuvant therapy, the awake prone position or decubitus position changes were performed. Subjects were considered as responders when the frequency decreased $<$ 30 breaths/min and S_{pO_2} increased $>$ 94% with $F_{IO_2} < 0.6$.

The subjects who did not meet these criteria after the trial were considered as non-responders and were assigned an alert code (ventilatory alert), which escalated ventilatory support with CPAP, and initiated closer monitoring for 6 h. CPAP and HFNC were used alternatively and complementarity in accordance to the subject's ventilatory needs and clinical end points, within a strategy of therapy rotation to increase comfort and tolerance to treatment. The subjects who did not improve throughout the treatment were transferred to the ICU for close monitoring and invasive ventilation if necessary. Weaning from noninvasive respiratory support to standard oxygen therapy was performed by following a strict protocol (Fig. 1). Monitoring and clinical evaluation were performed every 3 h for responders and every hour for the first 6 h for non-responders.

The CPAP interface was chosen according to the patient's tolerance. CPAP was delivered by dedicated ventilator (Astral 150, Resmed, San Diego, California) provided with a low-pressure oxygen source via a nonvented oronasal mask with a blue elbow (FreeMotion RT041, Fisher and Paykel, Auckland, New Zealand) or a helmet (NIV Helmet, Ecleris, Buenos Aires, Argentina). In the case of the oronasal mask, a double-limb circuit with an

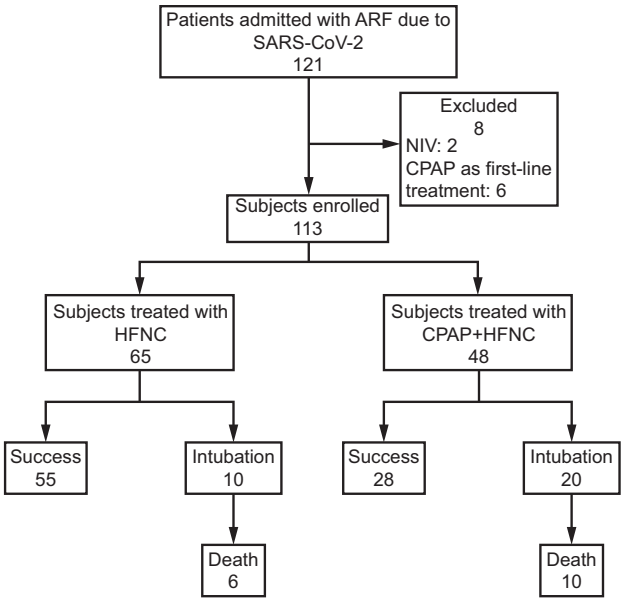

Fig. 2. Flow chart. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ARF= acute respiratory failure; NIV= noninvasive ventilation; HFNC = high-flow nasal cannula.

expiratory valve was used, whereas, in the case of a helmet, we used a single-limb circuit with an exhalation hole in one of the helmet ports. To limit the production of virus-laden aerosols, filters were placed between the interfaces and the circuit, and in the inlet and outlet ventilator ports. HFNC was delivered by using standard devices (Airvo 2, Fisher and Paykel). HFNC was set at 60 L/min. CPAP was initially set at 10 cm H_2O with an increase up to 14 cm H_2O if needed. CPAP levels were modified at the discretion of the attending physician according to the clinical situation of the subjects. In both treatments, F_{IO_2} was titrated to maintain S_{pO_2} between 94% and 96%.

Data Collection

On admission to the respiratory intermediate care unit, the following data were recorded: demographics (age, sex, body mass index), comorbidities (obesity, hypertension, diabetes, COPD, asthma, cardiovascular disease, no history for comorbidities), disease chronology (time from onset of symptoms, time from hospital admission to initiation of respiratory support, and time from COVID-19 diagnosis to noninvasive respiratory support onset), symptoms at respiratory intermediate care unit admission, vital signs (ie, breathing frequency, temperature, mean arterial pressure, heart rate), blood gas analysis, and laboratory tests. We calculated the following scores: National Early Warning Score, APACHE II, SOFA, and lung ultrasound score. P_{aO_2}/F_{IO_2} and arterial oxygen saturation (S_{pO_2})/F_{IO_2} were calculated before starting ventilatory support. We also recorded respiratory intermediate care unit length of stay (LOS) and hospital LOS. Endotracheal intubation rates, mortality of subjects who were intubated, and overall hospital mortality were also recorded. The ROX index ([S_{pO_2}/F_{IO_2}]/breathing frequency) was calculated at different times: after 30 min, and 2, 6, and 12 h after initiation of noninvasive respiratory support .

Personal Protective Equipment

The respiratory intermediate care unit consisted of 5 negative-pressure beds located in 2 shared rooms and 1 single room with 2 beds that contained a high efficiency particulate air filter. For staff safety, personal protective equipment protocols were readjusted in conjunction with the hospital's infectious disease service because most procedures related to the care of these patients are considered "super spreaders." Thus, the personal protective equipment level 3 model recommended by the World Health Organization, which designed a water-repellent and disposable hood that covers the whole head, neck, and leaves vision free, was modified. Personal protective equipment included a respirator mask (N95 respirators, FFP2, FFP3, or equivalent), a disposable long-sleeved gown or protective suit, double gloves, goggles (or alternatively, a face shield), and shoe covers.

Statistical Analysis

We used data of all available patients without a formal sample size calculation because the purpose of the analysis was to explore the effect of noninvasive respiratory support, we did not specify any a priori effect size. Continuous variables are reported as median (interquartile range), and categorical variables are reported as *n* (%). Normality of distributions was assessed by inspecting quantile–quantile plots. If the variables were normally distributed, then the 2-sample *t*-test was used; if not, then the Wilcoxon rank-sum test was used. We used the chi-square test or Fisher exact test for categorical variables. Statistical uncertainty was expressed by showing the 95% CI. We assessed the ability of the ROX index to classify the success of noninvasive respiratory support treatment by fitting receiver operating characteristic curves at all time points and by calculating the C index (area under the curve). The receiver operating characteristic curves for each time point were compared by using the DeLong U-test. Statistical significance was considered for 2-tailed $P < .05$. No imputation routine of missing values and no correction for multiple comparisons were prespecified; thus, all the findings should be viewed as exploratory. All analyses were performed with R 4.3 (R Foundation for Statistical Computing, Vienna, Austria). www.r-project.org).

Table 1. Baseline Characteristics of Subjects Treated with Noninvasive Respiratory Support

Characteristic	Total Cohort ($N = 113$)	Success ($n = 83$)	Failure ($n = 30$)	P
Age, y	55 (46–64)	53 (41–61)	64 (57–70)	<.001
Women	24 (21.2)	18 (21.7)	6 (20)	.98
Time from symptom onset to hospital admission, d	9 (6–10)	9 (6–10)	8 (6–11)	.76
Time from symptom onset to respiratory intermediate care unit admission, d	8 (6–10)	8 (7–10)	9 (6–11)	.77
APACHE II score	8 (7–10)	8 (6–9)	10 (8–11)	<.001
SOFA score	2 (2–3)	2 (2–2)	3 (2–3)	<.001
NEWS	10 (9–12)	10 (9–12)	11 (10–12)	.17
LUS	21(18–25)	20 (17–24)	23 (20–26)	.10
BMI, kg/m^2	28.4 (25.5–32.8)	28.6 (25.0–32.8)	27.6 (26.0–31.8)	.83
Comorbidities				
Obesity	49 (43.4)	38 (45.8)	11 (36.7)	.51
Hypertension	22 (19.5)	13 (15.7)	9 (30.0)	.15
Diabetes	10 (8.8)	8 (9.6)	2 (6.7)	.90
COPD	1 (0.9)	1 (1.2)	0 (0)	.95
Asthma	3 (2.7)	3 (3.6)	0 (0)	.69
Cardiovascular disease	1 (0.9)	0 (0)	1 (3.3)	.59
Chronic kidney disease	1 (0.9)	0 (0)	1 (3.3)	.59
No history of comorbidities	35 (31.0)	29 (34.9)	6 (20.0)	.19
Symptoms				
Dyspnea	85 (75.2)	63 (75.9)	22 (73.3)	.97
Cough	83 (73.5)	58 (69.9)	25 (83.3)	.23
Fever	101 (89.4)	73 (88.0)	28 (93.3)	.63
Myalgia	22 (19.5)	18 (21.7)	4 (13.3)	.47
Diarrhea	18 (15.9)	14 (16.9)	4 (13.3)	.87
Nausea	6 (5.3)	4 (4.8)	2 (6.7)	.97
Headache	38 (33.6)	29 (34.9)	9 (30.0)	.79
Anosmia and dysgeusia	29 (25.7)	24 (28.9)	5 (16.7)	.28
Odynophagia	22 (19.5)	16 (19.3)	6 (20.0)	.99
Chest pain	4 (3.5)	3 (3.6)	1 (3.3)	.98
Laboratory blood tests				
Leukocyte count, $\times 10^9$/L	8 (6–10)	8 (6–10)	8 (6–11)	.58
Lymphocyte count, $\times 10^9$/L	15 (10–22)	15 (10–23)	13 (6–19)	.09
D-dimer, μg/L	346 (274–533)	328 (258–501)	443 (313–619)	.12
Ferritin, μg/L	819 (438–1,363)	768 (441–1,108)	1253 (516–1,500)	.14
C-reactive protein, mg/L	11.0 (6.4–15.5)	10.8 (6.2–13.7)	12.3 (7.6–21.7)	.18

Data are presented as median (interquartile range) or n (%).
APACHE II = Acute Physiology and Chronic Health Evaluation II
SOFA = Sequential Organ Failure Assessment
NEWS = National Early Warning Score
LUS = Lung Ultrasound Score
BMI = body mass index

Results

A total of 121 patients were admitted to the respiratory intermediate care unit from June 1 to December 31, 2020, due to COVID-19 pneumonia. The flow chart of enrolled subjects is shown in Figure 2. Eight patients were excluded because CPAP or NIV was used as first-line treatment. A total of 113 subjects were included in the final analysis. Among them, HFNC was used as the only therapy in 65 subjects and combined therapy (HFNC plus CPAP) was used in 48 subjects (Fig. 1). Among the subjects who were treated with HFNC alone, 10 could not be treated with CPAP due to interface intolerance, which ultimately required intubation. The primary outcome was to assess the rate of endotracheal intubation. Eighty-three subjects (73.45%) were discharged from the respiratory intermediate care unit (success group), and 30 subjects (26.54%) required endotracheal intubation and ICU admission (failure group). The causes of treatment failure were septic refractory hypoxemia (57%), alterations of consciousness (10%), and interface intolerance (33%).

The clinical characteristics of the subjects according to success or failure are summarized in Table 1. The median (interquartile range) age was significantly higher in the

Table 2. Oxygenation Data

Parameter	Success Group ($n = 83$)	Failure Group ($n = 30$)	P
pH on admission	7.41 (7.40–7.43)	7.41 (7.40–7.43)	.43
P_{aCO_2} on admission, mm Hg	34 (32–38)	36 (33–40)	.15
P_{aO_2} on admission, mm Hg	85 (76–105)	82.00 (67–100)	.22
S_{pO_2}/F_{IO_2} on admission, %/%	118 (114–120)	117 (114–120)	.46
P_{aO_2}/F_{IO_2} on admission, mm Hg	106 (95–131)	103 (84–125)	.22
ROX index at			
30 min	7.52 (6.25–9.37)	6.88 (5.31–9.19)	.12
2 h	8.09 (7.04–10.19)	7.89 (5.64–8.78)	.004
6 h	8.44 (7.72–10.66)	7.47 (5.60–10.10)	.002
12 h	9.13 (7.92–11.88)	6.28 (5.45–8.71)	<.001

Data presented as median (interquartile range).
ROX index = (S_{pO_2}/F_{IO_2})/breathing frequency

Table 3. Subjects Treated With Noninvasive Respiratory Support

Parameter	Success Group ($n = 83$)	Failure Group ($n = 30$)	P
Respiratory intermediate care unit LOS, d	7 (5–10)	2 (1– 3)	<.001
Hospital LOS, d	12 (9–16)	26 (19–43)	<.001
Mortality	0 (0)	16 (55.2)	<.001

Data presented as median (interquartile range) or n (%).
LOS = length of stay

failure group than in the success group (53.00 [40.50–60.50] vs 63.50 [57.00–69.50]; $P < .001$). Disease severity scores, APACHE II and SOFA, were higher in the failure group (8 vs 10, $P < .001$ and 2 vs 2.5, $P < .001$ respectively). There were no differences in the proportion of comorbidity, symptoms, and laboratory tests between the groups. Oxygenation rates on admission were similar between those subjects in the failed group and subjects in the success group. We found a significant difference in ROX index values at 2, 6, and 12 h (Table 2), with the maximum difference between the groups at 12 h (success group, median (IQR), 9.13 [7.92–11.88] vs failure group, 6.28 [5.45, 8.71]; $P < .001$).

Secondary outcomes such as respiratory intermediate care unit LOS, hospital LOS, mortality in the failure group, hospital mortality, and the ROX index at different times were evaluated in both groups. The respiratory intermediate care unit LOS of the success group was 7 d versus 2 d in the failure group ($P < .001$). The hospital LOS was significantly longer in the failure group (26 vs 12 d; $P <. 001$). In the subjects in whom noninvasive respiratory support failed, 16 (55.2%) died (Table 3). The overall mortality was 14.15%. The ROX indexes at 2, 6, and 12 h have been shown to have good diagnostic performance in predicting the need for intubation. The area under the receiver operating characteristic curve for the ROX indexes at 30 min, 2 h, 6 h, and 12 h were 0.535 (95% CI 0.478–0.593), 0.588 (95% CI 0.533–0.643), and 0.627 (95% CI 0.567–0.687) and the area under the receiver operating characteristic curve of 0.772 (95% CI 0.719–0.824), respectively (Fig. 3). By using the ROX index of 6.28 at 12 h as the cutoff value to predict failure, the sensitivity was 97.6% and specificity was 51.8%. All the subjects received dexamethasone (100%), convalescent plasma (3%), interferon β (4%), remdesivir (2%), prophylactic/intermediate dose heparins (12%), and anticoagulation (4%).

Discussion

This was the first study, that evaluated the application of combined noninvasive respiratory support in subjects with ARF secondary to COVID-19 through a stepwise treatment algorithm. Our main findings were a low endotracheal intubation rate and mortality. Only 26.54% of our subjects were intubated, similar to previous studies that reported the use of noninvasive respiratory support outside the ICU.[18-20] With regard to the overall mortality, in previous studies that used HFNC and CPAP as first-line respiratory support in subjects with ARF secondary to COVID-19, the rates ranged from 24% to 50%.[18-20] One explanation for our results is that the use of combined noninvasive respiratory support, especially in the subjects with severe hypoxemic ARF, allowed a longer therapy time and better comfort, which increased adherence to treatment.

A relevant aspect of our protocol was the implementation of a strategy of interface rotation and use of different types of noninvasive respiratory support for avoiding periods without ventilatory support. Moreover, our algorithm was based on close monitoring and treatment escalation, trying not to delay intubation in case of failure. NIV/CPAP failure has been considered a risk factor for increased mortality in patients with hypoxemic ARF.[14] In this regard, Bhatraju et al[15] showed an extremely high mortality rate both with NIV and HFNC

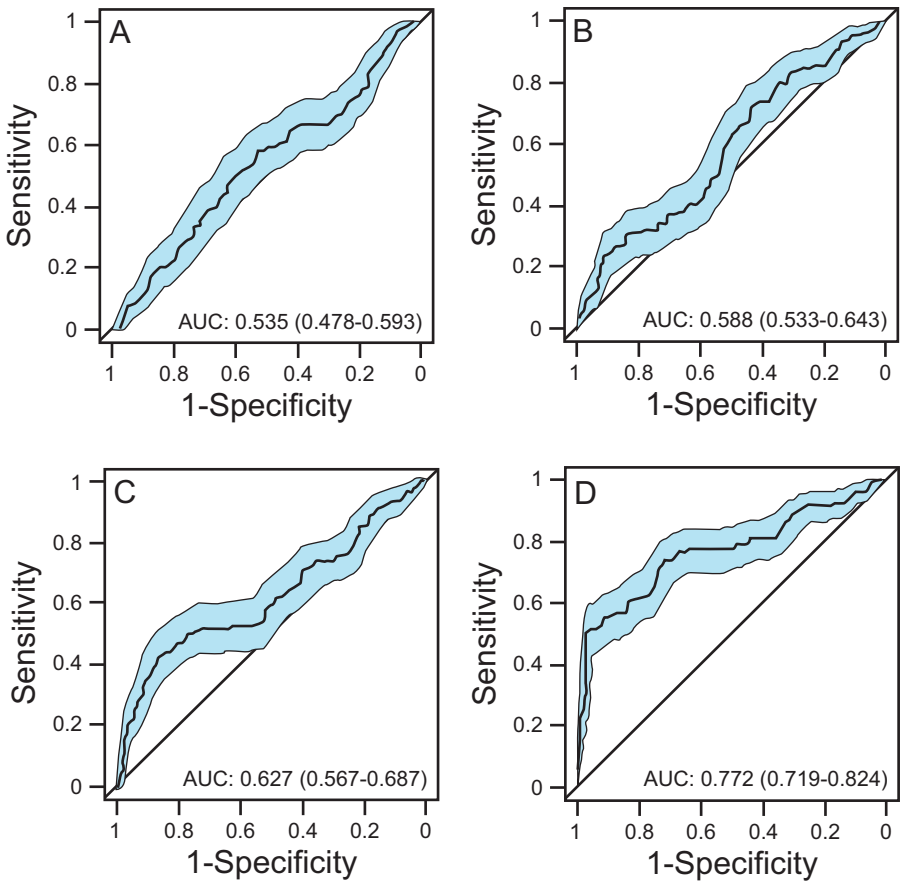

Fig. 3. Receiver operating characteristic curves for the ROX index ([S_{pO_2}/F_{IO_2}]/breathing frequency) at 30 min (A), 2 h (B), 6 h (C), and 12 h (D), after initiation of noninvasive respiratory support as a predictor of support failure. Shaded areas show 95% CI. AUC = area under the curve.

failure (80% and 52%, respectively) in patients with COVID-19 who were admitted to the ICU with SARS-CoV-2. In our study, mortality in the subjects who were intubated was 55.2%, like those in whom invasive ventilation was applied as first-line treatment, suggesting the usefulness of the algorithm.

Another point to highlight is that, during admission to our unit, we encourage patients to be in a prone position for at least 18 h per day. This therapy has strong evidence in patients undergoing invasive ventilation. Recent work published by Yoshida et al[21] showed that the prone position may reduce the risk of stress-dependent lung injury in ARDS. Compared with the supine position, the prone position during spontaneous breathing improves gas exchange, reduces the intensity of spontaneous inspiratory effort and dynamic lung stress, and attenuates systemic inflammation. Despite this, the benefits of the awake prone position in patients with noninvasive respiratory support remains controversial. In a recent study in subjects with COVID-19 ARF treated with HFNC, the use of the awake prone position did not reduce the need for intubation or affect mortality.[22] However, most studies observed that the use of the awake prone position in subjects with ARF treated with HFNC and CPAP was safe and feasible, improved physiologic measures of oxygenation and contributed to avoiding intubation.[23-26] There is no current evidence that supports the use of the awake prone position in COVID-19; however, some observational studies have tested this coadjuvant strategy with promising results.[27]

The ROX index was first described and validated in patients with hypoxemic respiratory failure treated with HFNC before the COVID-19 outbreak.[28] It may help to select patients who could benefit from HFNC by identifying those with low and those with a high risk for intubation. In a recent retrospective review, the ROX index was sensitive for the identification of subjects with COVID-19 who were successfully weaned from HFNC.[29] The investigators found that a ROX index > 3.0 at 2, 6, and 12 h after initiation of HFNC was 85.3% sensitive for identifying subsequent HFNC success.[29] Although the ROX index was validated in the subjects treated with HFNC, a recent study showed that the use of the awake prone position alongside CPAP significantly increased the ROX index, which demonstrated that the ROX index can be a good indicator to predict the success of CPAP or NIV in patients who are hypoxemic.[23]

In our study, we found that a 12-h ROX index < 6.28 showed a high sensitivity (97.6%) for predicting the need for intubation. Interestingly, the ROX index was significantly higher in subjects who were responders at 2 h after the onset of noninvasive respiratory support, with a maximum difference at 12 h. Analysis of these data suggests that the optimum time for application of noninvasive respiratory support would be at 12 h and that, by monitoring the ROX index at different time intervals after noninvasive respiratory support, clinicians can quickly detect treatment failure and not delay intubation. Given the similarity in clinical outcomes between subjects with early and those with late failure in our cohort, prediction of HFNC success may be of clinical utility. Further studies to validate the role of the ROX index in patients with SARS-CoV-2 who receive noninvasive respiratory support are required.

This study had several limitations as an uncontrolled non-randomized observational study, including being a single center. Our cohort included only critically ill subjects because we focused on the role of the respiratory intermediate care unit in patient management. This may limit the generalization of our results to patients with less-severe cases. However, the number of participants was higher than most previous studies, and our results agreed with observations from different cohorts.

Conclusions

The use of combined noninvasive respiratory support in patients with severe ARF secondary to COVID-19 can be a alternative to invasive ventilation in selected patients. Strict treatment protocols and algorithms can help clinicians in selecting the most appropriate ventilatory support. The ROX index remains a good indicator of failure at noninvasive respiratory support. Further randomized controlled trials are needed.

REFERENCES

1. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Published February, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. *Accessed March 25, 2020.*
2. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response: early experience and forecast during an emergency response. JAMA 2020;323(16):1545-1546.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-1242.
5. Cao Y, Liu X, Xiong L, Cai K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis. J Med Virol 2020;92(9):1449-1459.
6. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323(22):2329-2330.
7. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al; The Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323(20):2052-2059.
8. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934-943.
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-1062.
10. Ñamendys-Silva SA. Respiratory support for patients with COVID-19 infection. Lancet Respir Med 2020;8(4):e18.
11. Remy KE, Lin JC, Verhoef PA. High-flow nasal cannula may be no safer than non-invasive positive pressure ventilation for COVID-19 patients. Crit Care 2020;24(1):169.
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061-1069.
13. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708-1720.
14. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323(16):1574-1581.
15. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med 2020;382(21):2012-2022.
16. Cinesi Gómez C, Peñuelas Rodríguez Ó, Luján Torné M, Egea Santaolalla C, Masa Jiménez JF, García Fernández J, et al. Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to SARS-CoV-2 infection. Arch Bronconeumol 2020;56(Suppl 2):11-18.
17. Analysis of the evolution of the COVID-19 pandemic in Argentina. [Internet]. Gob.ar. Available at: https://www.argentina.gob.ar/noticias/analisis-de-la-evolucion-de-la-pandemia-de-covid-19-en-argentina. *Accessed March 31, 2020.*
18. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J 2020;56(5):2002130.
19. Burns GP, Lane ND, Tedd HM, Deutsch E, Douglas F, West SD, et al. Improved survival following ward-based non-invasive pressure support for severe hypoxia in a cohort of frail patients with COVID-19: retrospective analysis from a UK teaching hospital. BMJ Open Respir Res 2020;7(1)e000621.
20. Di Domenico SL, Coen D, Bergamaschi M, Albertini V, Ghezzi L, Cazzaniga MM, et al. Clinical characteristics and respiratory support of 310 COVID-19 patients, diagnosed at the emergency room: a single-center retrospective study. Intern Emerg Med. 2021;16(4):1051-1060.
21. Yoshida T, Tanaka A, Roldan R, Quispe R, Taenaka H, Uchiyama A, Fujino Y. Prone position reduces spontaneous inspiratory effort in patients with acute respiratory distress syndrome: a bicenter study. Am J Respir Crit Care Med 2021;203(11):1437-1440.
22. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, et al; COVID-19 Spanish ICU Network. Awake prone positioning

does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Crit Care 2020;24(1):597.
23. Winearls S, Swingwood EL, Hardaker CL, Smith AM, Easton FM, Millington KJ, et al. Early conscious prone positioning in patients with COVID-19 receiving continuous positive airway pressure: a retrospective analysis. BMJ Open Resp Res 2020;7(1):e000711.
24. Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med 2020;8(8):765-774.
25. Xu Q, Wang T, Qin X, Jie Y, Zha L, Lu W. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19: a case series. Crit Care 2020;24(1):250.
26. Tu G-W, Liao Y-X, Li Q-Y, Dong H, Yang L-Y, Zhang X-Y, et al. Prone positioning in high-flow nasal cannula for COVID-19 patients with severe hypoxemia: a pilot study. Ann Transl Med 2020;8 (9):598.
27. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care 2020;24(1):28.
28. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med 2019;199(11):1368-1376.
29. Chandel A, Patolia S, Brown AW, Collins AC, Sahjwani D, Khangoora V, et al. High-flow nasal cannula therapy in COVID-19: using the ROX index to predict success. Respir Care 2021;66(6):909-919.