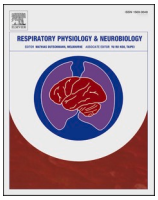
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Physiology & Neurobiology 298 (2022) 103842

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol



Noninvasive ventilation and high-flow nasal cannula in patients with acute hypoxemic respiratory failure by covid-19: A retrospective study of the feasibility, safety and outcomes

Wesla Neves da Silva Costa, Juliana Padovezi Miguel, Fabiana dos Santos Prado, Liz Helena Santos de Mello Lula, Gustavo Adolpho Junqueira Amarante, Renato Fraga Righetti, Wellington Pereira Yamaguti *

Hospital Sírio-Libanês, São Paulo, Brazil

ARTICLE INFO

Edited by M Dutsmann

Keywords:
SARS-CoV-2
COVID-19
Noninvasive ventilation
High-flow nasal cannula
Acute respiratory failure

ABSTRACT

Background: Noninvasive ventilation (NIV) and High-flow nasal cannula (HFNC) are the main forms of treatment for acute respiratory failure. This study aimed to evaluate the effect, safety, and applicability of the NIV and HFNC in patients with acute hypoxemic respiratory failure (AHRF) caused by COVID-19.

Methods: In this retrospective study, we monitored the effect of NIV and HFNC on the SpO_2 and respiratory rate before, during, and after treatment, length of stay, rates of endotracheal intubation, and mortality in patients with AHRF caused by COVID-19. Additionally, data regarding RT-PCR from physiotherapists who were directly involved in assisting COVID-19 patients and non−COVID-19.

Results: 62.2 % of patients were treated with HFNC. ROX index increased during and after NIV and HFNC treatment ($P < 0.05$). SpO_2 increased during NIV treatment ($P < 0.05$), but was not maintained after treatment ($P = 0.17$). In addition, there was no difference in the respiratory rate during or after the NIV ($P = 0.95$) or HFNC ($P = 0.60$) treatment. The mortality rate was 35.7 % for NIV vs 21.4 % for HFNC ($P = 0.45$), while the total endotracheal intubation rate was 57.1 % for NIV vs 69.6 % for HFNC ($P = 0.49$). Two adverse events occurred during treatment with NIV and eight occurred during treatment with HFNC. There was no difference in the physiotherapists who tested positive for SARS−COV-2 directly involved in assisting COVID-19 patients and non−COVID-19 ones ($P = 0.81$).

Conclusion: The application of NIV and HFNC in the critical care unit is feasible and associated with favorable outcomes. In addition, there was no increase in the infection of physiotherapists with SARS-CoV-2.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging viral infection that is rapidly spreading across the globe and three months after the emergence, the World Health Organization declared it a pandemic (World Health Organization, 2020). Several hospitals needed to prepare and create guidelines for the healthcare team for coping and managing these patients (Lazzeri et al., 2020; Righetti et al., 2020).

Patients with COVID-19 present several symptoms, such as fever, cough, fatigue, sputum production, and shortness of breath (Huang et al., 2020). Approximately 14 % of patients develop a severe form of COVID-19, requiring hospitalization, and the percentage of patients who required ICU care has varied from 5% to 32 % (Huang et al., 2020; Guan et al., 2020; Grasselli et al., 2020a). Older patients and those with chronic underlying conditions can develop severe illness and present complications such as acute hypoxemic respiratory failure (AHRF), acute respiratory disease syndrome (ARDS), sepsis, septic shock, and kidney and cardiac failure, which require treatment in an intensive care unit (ICU) and supportive respiratory therapy (Yang et al., 2020).

Noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) are the main forms of treatment for acute respiratory failure (Spoletini

* Corresponding author at: Hospital Sírio-Libanês, Centro de Reabilitação, Rua Dona Adma Jafet, 91 - Bela Vista, São Paulo, SP, 01308-050, Brazil.
E-mail addresses: wesla.nsilva@hsl.org.br (W.N.S. Costa), juliana.pmiguel@hsl.org.br (J.P. Miguel), fabiana.sprado@hsl.org.br (F.S. Prado), liz.hsmlula@hsl.org.br (L.H.S.M. Lula), gustavo.amarante@hsl.org.br (G.A.J. Amarante), refragar@gmail.com (R.F. Righetti), wellington.psyamaguti@hsl.org.br, wellpsy@yahoo.com.br (W.P. Yamaguti).

https://doi.org/10.1016/j.resp.2022.103842
Received 1 August 2021; Received in revised form 2 December 2021; Accepted 8 January 2022
Available online 10 January 2022

and Hill, 2016). Recent guidelines for the respiratory management of SARS-CoV-2 infection suggest the use of the NIV and HFNC also for the treatment of AHRF caused by SARS-CoV-2 unresponsive to conventional oxygen therapy (Lazzeri et al., 2020; Righetti et al., 2020; Alhazzani et al., 2020). However, data on the safety and applicability of NIV and HFNC in these patients are scarce and there are major concerns on the possibility of spreading infection among healthcare personnel caring for patients in SARS-CoV-2 dedicated areas. The present study aims to evaluate the effect, safety, and applicability of the NIV and HFNC in patients with acute hypoxemic respiratory failure (AHRF) caused by COVID-19.

2. Materials and methods

This research was approved by the Human Research Ethics Committee of Hospital Sírio-Libanês (number 3,994,535).

2.1. Institutional context

The present study was conducted at a private tertiary hospital (Hospital Sírio-Libanês), located in São Paulo, Brazil. In March 2020, the hospital had the first admissions of patients with COVID-19 and in this period there were 479 beds, of which 327 were in the non-critical units and 152 were in critical care units. Patients with AHRF caused by COVID-19 and candidates for NIV or HFNC were admitted in the critical care units with negative-pressure rooms or in SARS-CoV-2 dedicated areas.

NIV was performed in devices with a heat moisture exchange filter (HMEF) between the face mask or total face mask and the NIV device. Additional high-efficiency particulate arrestance (HEPA) filter on the exhalation output of the mechanical ventilator was also used (Righetti et al., 2020; Kaur et al., 2020). The patients were ventilated with positive end-expiratory pressure (PEEP) $\geq$8 cmH_2O, support pressure for a tidal volume (TV) $\leq$8 mL/kg of the predicted weight, and the fraction of inspired oxygen (FiO_2) to maintain peripheral oxygen saturation (SpO_2) >92 %. A face mask or total face mask should be used during the application of NIV, but for applications longer than 2 h the use of total face mask was recommended in order to reduce the risk of skin breakdown (Yamaguti et al., 2014). Patients wearing a face mask used a protective pad on the nasal area. For HFNC, a flow rate of 40–50 L/min should be maintained, and FiO_2 to maintain SpO_2 >92 % should be started (Righetti et al., 2020). NIV or HFNC was applied to subjects admitted to the critical care unit who presented SpO_2 < 93 % despite oxygen delivered through a nasal cannula (oxygen flow >6 L/min), venturi mask (FiO_2~30 %), or oxygen bag (FiO_2~100 %) and signs of respiratory distress (Righetti et al., 2020). The criteria for orotracheal intubation and invasive mechanical ventilation are FiO2 > 60 % in noninvasive ventilation or TV $\geq$ 9 mL/kg or inability to tolerate <2 h without non-invasive ventilation or presence of other organic dysfunctions. For high-flow nasal cannula, the criteria for orotracheal intubation are FiO_2 >60 % or signs of respiratory distress, or other organic dysfunctions. It is important to reassess the patient after 30−60 min; if there is no improvement or if there is worsening of ventilatory parameters, endotracheal intubation and invasive mechanical ventilation should be considered (Rochwerg et al., 2017; Righetti et al., 2020).

In our institution, physiotherapists together with the physicians are responsible for respiratory assessment, indication, and management of the application of NIV and HFNC. Due to the risk of aerosol formation, all professionals involved in the application of NIV and HFNC were instructed to wear surgical caps, safety goggles, face shield, N95 masks or equivalent, gowns, and gloves (World Health Organization, 2020; Righetti et al., 2020).

2.2. Study design

A retrospective study of adult patients (older than 18 years) with COVID-19 in spontaneous breathing hospitalized between March 2020 and April 2020 in critical care units of the Hospital Sírio-Libanês in use of NIV or HFNC was conducted. Laboratory-confirmed SARS-CoV-2 was defined by the presence of positive real-time transcription-polymerase chain reaction (RT-PCR) in upper or lower respiratory specimens. The exclusion criteria were medical records that did not present complete information.

2.3. Data collection

The data collected from the medical records were: age, gender, critical care units and hospital length of stay, time between symptom onset and hospitalization, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, body mass index (BMI), ethnicity, smoking history, computed tomography (CT) scan of the chest and lung involvement at hospital admission, therapeutic strategies (medications, oxygen therapy and ventilatory support), comorbidities, clinical signs during hospitalization [peripheral oxygen saturation (SpO_2), systolic and diastolic blood pressures, heart rate, and body temperature] at admission and severity of COVID-19. The severity of COVID-19 was defined according to the guidelines for COVID-19 issued by the National Institutes of Health (National Institutes of Health, 2020).

Laboratory assessments included blood cell counts, C-reactive protein (CRP), D-dimer level, glutamate-pyruvate transaminase (GPT), glutamate-oxalacetate transaminase (GOT), total bilirubin (TB), plasma potassium and sodium levels.

Data collected from the NIV and HFNC were modality and ventilatory settings for NIV and flow rate for HFNC. To assess the effects of NIV and HFNC on AHRF induced by COVID-19, respiratory rate, SpO_2, and ROX index were collected before, during, and up to 1 h after treatment. ROX index was calculated using the formula (SpO_2/FiO_2)/respiratory rate. Also, adverse events from the application of NIV and HFNC, and outcomes of mortality and hospital discharge were collected.

The physiotherapists directly involved in assisting COVID-19 patients and non−COVID-19 ones were monitored. Physiotherapists with fever or respiratory symptoms underwent nasal and pharyngeal swab specimens collection and performed the real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) against SARS−COV-2.

2.4. Statistical analysis

Data were assessed for normality using the Shapiro-Wilk test. Parametric variables are presented as mean ± standard deviation and nonparametric variables as median and interquartile range. Categorical data are presented as the absolute (n) and relative frequency (%), using $\chi 2$ or Fisher's exact probability tests. Comparison between patients who received NIV and HFNC treatment were analyzed using the t-test, Mann-Whitney test, and the Wilcoxon signed-rank test as appropriate. For comparison before, during, and after NIV or HFNC treatment we used the One-way Repeated Measure ANOVA test. Statistical significance was indicated by a P value of less than 0.05.

3. Results

Between March 2020 and April 2020, 138 spontaneous breathing patients with COVID-19 and hospitalized in the critical care unit were considered. We excluded 101 patients that received only oxygen therapy and 37 patients were included and their data analyzed. From the included patients 10 patients died. Fig. 1 illustrates the patients' allocation to ventilatory support and clinical outcome.

3.1. Patients' characteristics

Table 1 shows the patients' characteristics. Most of the study patients were male, white people, and non-smokers. However, the group that

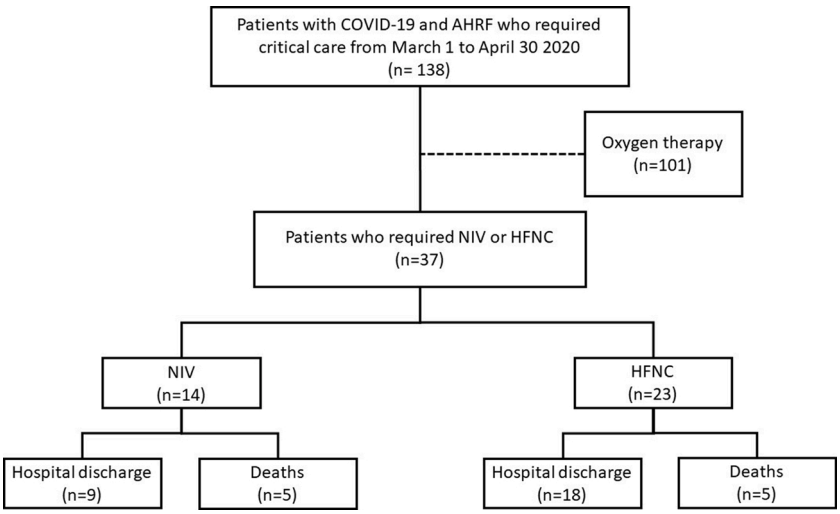


Fig. 1. Patient's allocation to ventilatory support and clinical outcome. COVID-19: coronavirus disease 2019; NIV: non-invasive ventilation; HFNC: high-flow nasal cannula.

received treatment with NIV was predominantly of women. There was no difference between patients who received treatment with NIV or HFNC in the time between symptom onset and hospitalization and the length of stay in the critical care unit or hospital stay. In the admission to the critical care unit, there was a difference in the APACHE II score in the NIV group compared to the HFNC group. There were no differences between the NIV and HFNC groups regarding the SOFA score. Most patients had critical and several forms of COVID-19. In addition, all patients had pulmonary involvement and the majority had bilateral pulmonary involvement, confirmed by chest computed tomography. Antibiotics, hydrocortisone, and anticoagulants were the most used drugs for treatment.

Hypertension, diabetes mellitus, chronic obstructive pulmonary disease, dyslipidemia, cardiovascular disorders, and cancer were the most represented comorbidities, evenly distributed between the groups. Most patients had three or more comorbidities and there was no difference between the NIV and HFNC groups. Patients who received HFNC had higher values of hemoglobin, leukocytes, neutrophils, lymphocytes, and platelets compared to NIV ($P < 0.05$) (Table 1).

3.2. Modality and ventilatory characteristics settings

HFNC was used on the majority of patients. For the NIV application, the most used interface was the face mask. The mean of the pressure support used in the NIV was 8.2 ± 4.8 cmH_2O, positive end-expiratory pressure (PEEP) was 9.3 ± 3.0 cmH_2O with a fraction of inspired oxygen (FiO_2) of 38.2 ± 20.8 %. The mean of the flow used in the HFNC was 45.2 ± 6.5 L/min with FiO_2 of 52.0 ± 17.2 % (Table 2).

3.3. Effects of the NIV and HFNC on the saturation of peripheral oxygen, respiratory rate, ROX index, and outcomes

The time of application with the device was longer in the group that was treated with HFNC compared to the group that received treatment with NIV ($P < 0.05$) (Fig. 2A). SpO_2 increased during NIV treatment. However, this increase of SpO_2 was not maintained after treatment interruption ($P < 0.05$). There was no difference in SpO_2 during and after HFNC treatment ($P = 0.17$) (Fig. 2C). In addition, there was no difference in the respiratory rate (Fig. 2B) during or after the NIV ($P = 0.79$) or HFNC ($P = 0.63$) treatment and endotracheal intubation ($P = 0.49$) (Table 1). ROX index increased during and after NIV and HFNC treatment ($P < 0.05$) (Fig. 2D). There was no difference in the ROX index between NIV or HFNC treatment. The main outcome found was hospital discharge. However, 5 (35.7 %) patients in the NIV group and 5 (21.4 %) in the HFNC group died. There was no difference between groups ($P = 0.45$) (Table 1). A total of 240 sessions of treatments with NIV and 374 sessions of treatments with HFNC were performed.

3.4. Safety of the use of NIV and HFNC for patients

The adverse events that occurred during treatment with NIV were 1 (7.14 %) bronchoaspiration and 1 (7.14 %) pressure ulcer outside the face region. In the treatment with HFNC, 3 (13 %) respiratory instabilities were registered, but none required urgent endotracheal intubation and 5 (21.7 %) pressure ulcers outside the face region. All adverse events occurred in different patients.

3.5. Professional healthcare workers and percentage of infection

A team of 93 physiotherapists were responsible for taking care of patients receiving ventilatory support in the critical care unit dedicated to patients with COVID-19 and a team of 67 in the critical care unit non-dedicated for COVID-19. In the first team, 10.7 % of the physiotherapists dedicated to COVID-19 patients tested positive for SARS-CoV-2 infection. The rate of physiotherapists not involved in the care of COVID-19 patients with positive test RT-PCR in our hospital was 11.9 % (Table 3). All showed mild symptoms of the disease and none required hospitalization. All infected physiotherapists recovered well.

4. Discussion

The present study showed that the majority of patients were treated with HFNC. SpO_2 increased during NIV treatment. However, this increase of SpO_2 was not maintained after treatment interruption. There was no difference in SpO_2 and respiratory rate after NIV and HFNC treatment compared to baseline. Critical care unit and hospital length of stay were not different between the groups. There was no difference in the mortality rate and endotracheal intubation for NIV and HFNC treatment. Two adverse events occurred during treatment with NIV and eight occurred during treatment with HFNC. There were no differences in the rates of physiotherapists who tested positive for SARS-CoV-2 in the critical care unit dedicated to the assistance of patients with COVID-19 compared to the critical care unit non-dedicated to COVID-19.

The population consisted mostly of men (70.3 %) and older individuals.. A previous study showed that male gender and older age are associated with severe COVID-19 (Rapp et al., 2020). However, Grasselli et al. (2020b) showed that the median age of the patients admitted to the intensive care unit is the same as the median age of all the positive

Table 1
Demographic and clinical characteristics of the patients.

Characteristics of the patients	**All Patients (N = 37)**	**NIV (N = 14)**	**HFNC (N = 23)**	***P*-value**
Age, mean (±SD), years	68.8 ± 18.5	74.5 ± 19.0	65.3 ± 17.7	N.S.
Male sex. No. (%)	26 (70.3)	5 (35.7)	21 (91.3)	< .05
Time between symptom onset and hospitalization, median (range), days	7 [4–9]	5 [3–8]	7 [4–9]	N.S.
Critical care unit length of stay, median (range), days	10 [6–10]	14 [10–25]	17 [10–28]	N.S.
Hospital length of stay, median (range), days	23 [13–33.2]	20.5 [12–35]	23 [14.7–32.5]	N.S.
APACHE II score, median (range)	12.5 [9–24]	23 [12–27]*	11 [6–16.7]	< .05
SOFA score, median (range)	4.5 [1–8]	5 [2.2–1]	4 [0–7.2]	N.S.
BMI (kg/m^2),	30.5 ± 5.3	32.4 ± 4.7	29.4 ± 5.5	N.S.
Ethnicity, n (%)				
White	34 (91.9)	13 (92.9)	21 (91.3)	N.S.
Black	2 (5.4)	1 (7.4)	1 (4.4)	N.S.
Other races	1(2.9)	0 (0)	1(4.4)	N.S.
Smoker, n (%)				
No	30 (81)	10 (71.4)	20 (87)	N.S.
Yes	1(2.7)	0 (0)	1 (4.4)	N.S.
Former smoker	6 (16.2)	4 (28.6)	2 (8.7)	N.S.
Vital signs on admission, median [IQR]				
Heart rate (bpm)	83 [71–97]	83 [73–94]	83 [69–97]	N.S.
Systolic blood pressure (mmHg)	120 [109–137]	123 [110–138]	120 [106.5–136.5]	N.S.
Diastolic blood pressure (mmHg)	65 [59–75]	64 [58–76]	66 [59–73]	N.S.
Temperature (°C)	36.4 [36.0–36.8]	36.5 [36.0–39.9]	36.4 [36.0–36.7]	N.S.
SpO_2 (%) at hospital admission	90 [88–94]	91 [88–95]	90 [88–93]	N.S.
Severity of COVID-19, n (%)				
Severe illness	12 (32.4)	6 (42.9)	6 (26)	N.S.
Critical illness	25 (67.6)	8 (57.1)	17 (73.9)	N.S.
Chest computerized tomography (CT) scans, n (%)				
Abnormalities n (%)	37 (100)	14 (100)	23 (100)	N.S.
Bilateral involvement, n (%)	35 (94.6)	12 (85.7)	23 (100)	N.S.
Unilateral involvement, n (%)	2 (5.4)	2 (14.3)	0 (0)	N.S.
Therapeutic strategies				
Antibiotics, n (%)	37 (100)	14 (100)	23 (100)	N.S.
Anticoagulants, n (%)	34 (91.9)	12 (85.7)	22 (95.7)	N.S.
Hydrocortisone, n (%)	26 (70.3)	6 (42.9)	20 (87)	N.S.
Vasoactive drugs, n (%)	22 (59.5)	8 (57.1)	14 (60.9)	N.S.
Sedation, n (%)	25 (67.6)	9 (64.3)	16 (69.6)	N.S.
Oxygen therapy, n (%)	37 (100)	14 (100)	23 (100)	N.S.
Laboratory findings, media [IQR]				
Hemoglobin/mm3	11 [9.7–12.8]	10.3 [9.2–12.1]*	11.3 [10.1–13.1]	< .05
Leukocytes/mm^3	8160 [5930–11220]	6890 [4800–8840]*	9440 [6785–12340]	< .05
Neutrophils/mm^3	6050 [4220–8960]	5220 [3387–7057]*	6940 [5187.5–9702.5]	< .05
Lymphocytes/mm^3	1005 [630–1600]	850 [580–1430]*	1115 [660–1775]	< .05
Platelets/mm^3	241,500 [163000–340000]	197,000 [134250–286000]*	277,000 [194000–368250]	< .05
C-reactive protein (mg/dL)	3.9 [1.0–10.3]	3.8 [1.0–9.1]	3.9 [1.1–11.0]	N.S.
D-dimer level (ng/mL)	1224.5 [777.5–2042]	1376 [7965.5–2200.7]	1171 [758.5–2018.2]	N.S.
GPT (U/L)	35.0 [21.5–56.0]	32.5 [20.0–56.0]	36.5 [22.0–56.0]	N.S.
GOT (U/L)	32 [25–45]	34 [26–46]	32 [24–45.5]	N.S.
TB (mg/dL)	0.33 [0.25–0.55]	0.31 [0.25–0.58]	0.37 [0.26–0.52]	N.S.
K^+ (mEq/L)	4.1 [3.8–4.4]	4.1 [3.8–4.4]	4.1 [3.7–4.4]	N.S.
Na^+ (mEq/L)	141 [138–144]	141 [139–145]*	140 [138–143]	< .05
Comorbidities, No. (%)				
Hypertension	24 (64.8)	10 (71.4)	14 (60.8)	N.S.
Diabetes Mellitus	14 (37.8)	5 (35.7)	9 (39.1)	N.S.
Chronic Obstructive Pulmonary Disease	9 (24.3)	5 (35.7)	4 (17.4)	N.S
Dyslipidemia	12 (32.4)	10 (71.4)	2 (8.7)	N.S.
Cardiovascular disease	10 (27)	5 (35.7)	5 (21.4)	N.S.
Cancer	8 (21.6)	3 (21.4)	5 (21.4)	N.S.
Number of comorbidities, No. (%)				
Without comorbidities	5 (13.5)	2 (14.3)	3 (13)	N.S.
One comorbidity	4 (10.1)	1 (7.1)	3 (13)	N.S.
Two comorbidities	5 (13.5)	2 (14.3)	3 (13)	N.S.
Three or more comorbidities	23 (62.1)	9 (64.3)	14 (60.9)	N.S.
Outcomes, No. (%)				
Endotracheal intubation	24 (64.9)	8 (57.1)	16 (69.6)	N.S.
Hospital discharge	27 (73)	9 (64.3)	18 (78.3)	N.S.
30-day mortality rate	6 (16.2)	3 (21.4)	3 (8.7)	N.S.
Death	10 (27)	5 (35.7)	5 (21.4)	N.S.

APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; SpO_2 = peripheral oxygen saturation; BMI = body mass index; GPT = glutamate-pyruvate transaminase; GOT = glutamate-oxalacetate transaminase; TB = total bilirubin; K^+ = potassium; Na^+ = sodium; AHRF = acute hypoxemic respiratory failure. *$P < .05$ vs HFNC group.

Table 2
Characteristics of ventilatory support mode and setting parameters according to support.

SETTING (n = 37)	
NIV, n (%)	14 (37.8)
PEEP (cmH_2O), mean ± SD ± SD	9.3 ± 3.0
Pressure support (cmH_2O), mean ± SD	8.2 ± 4.8
FiO_2 (%), mean ± SD	38.2 ± 20.8
Interface	
Face mask, n (%)	9 (69.2)
Total Face, n (%)	4 (30.8)
HFNC, n (%)	23 (62.2)
Flow (L/min), mean ± SD	45.2 ± 6.5
FiO_2 (%), mean ± SD	52.0 ± 17.2

NIV = Non-Invasive Mechanical Ventilation; HFNC = High-flow Nasal Cannula; PEEP = Positive end-expiratory pressure; FiO_2 = Fraction of inspired oxygen.

Italian cases with COVID-19, suggesting that the older age alone is not a risk factor for admission to the critical care unit. In the present study, 86 % of patients had at least one comorbidity and 62.1 % had three or more comorbidities, much higher than in others (Huang et al., 2020; Guan et al., 2020; Wang et al., 2020). Similar to other previous reports, hypertension was the most common comorbidity, followed by dyslipidemia, cardiovascular disorders, and diabetes (Guan et al., 2020; Wang et al., 2020). These data show that we studied a population with risk factors for developing severe disease, such as age and comorbidities, similar to other hospital centers.

The success and time of therapy of non-invasive strategies also depend on tolerance and patient compliance. The present study showed a longer therapy time in the HFNC group compared to the NIV group. HFNC can provide both adequate heating and humidification, which helps to increase the humidity of the airway, maintain mucosal function, promote secretion clearance, avoid epithelial injury, and improve patient comfort and tolerance (Nishimura, 2016). Intolerance to NIV can affect 20–25 % of patients treated for hypoxemic ARF (Demoule et al., 2006). In healthy subjects, low levels of humidification or the absence of any additional humidification system under NIV were associated with less comfort (Lellouche et al., 2009). Therefore, the possibility of maintaining heating and humidification and the low claustrophobic interface of HFNC appear to be the factors that better patient tolerance for a longer duration of device application compared to NIV (Lee et al., 2016; Sun et al., 2019).

There was no difference in SpO_2 and respiratory rate after NIV and HFNC treatment compared to baseline. Nair et al., 2021 evaluated patients with severe COVID-19 pneumonia with acute hypoxemic respiratory failure and treated with NIV and HFNC and did not show a significant improvement of oxygenation parameters. In addition, Duan et al. (2021) did not show variability in respiratory rate using NIV at 1–2 h, 12 h, and 24 h of NIV intervention. In the same study, HFNC reduced

Table 3
The fraction of active physiotherapists in COVID-19 and non−COVID-19 critical care units and percentage of infection.

	Critical Care Unit (COVID-19)		Critical Care Unit (non-COVID-19)		
	At work	Infected	At work	Infected	P-value
Physiotherapist, n (%)	93	10 (10.7)	67	8 (11.9)	N.S.

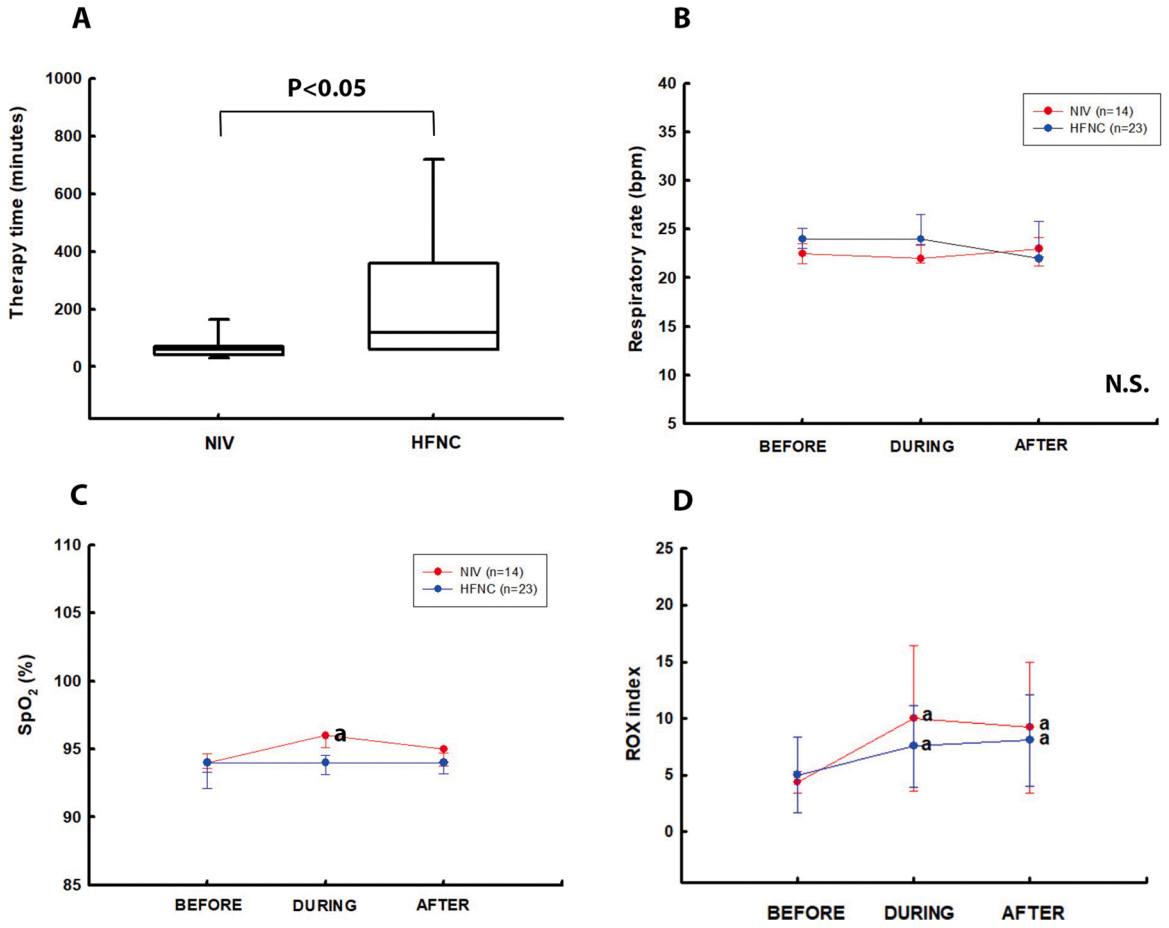


Fig. 2. Therapy time (A) and effects of NIV and HFNC on the respiratory rate (B), SpO_2 (C), and ROX index (D) before, during, and after treatment. aP < 0.05 compared to the before period. SpO_2: peripheral oxygen saturation; bpm: breaths per minute.

respiratory rate by 1–2 h, 12 h, and 24 h of intervention compared to NIV. ROX index is an index of the effect of respiratory rate added to SpO_2/FiO_2 and predicts the success of NIV and HFNC in patients with COVID-19 (Roca et al., 2019; Mukhtar et al., 2021). ROX at 4 h of starting HFNC $\geq$ 5.37 was significantly associated with a lower risk for intubation in COVID-19 hypoxemic respiratory failure in intensive care admitted patients from a retrospective single-center study (Zucman et al., 2020). In the present study, ROX index increased in NIV and HFNC treatment increased during and after treatment, showing benefits from the NIV and HFNC treatment.

COVID-19 is a new disease and its pathophysiology is uncertain. Polak et al. (2020) reviewed 129 cases of published lung samples (either full/partial autopsy or lung resection) and identified three main histological patterns: epithelial (85 %), with reactive epithelial changes and diffuse alveolar damage (DAD); vascular (59 %) with microvascular damage, microthrombi, and acute fibrinous and organizing pneumonia; and fibrotic (22 %) with interstitial fibrosis. The low response in SpO_2 and respiratory rate can be explained by the structural pulmonary changes that occur in this disease (Gattinoni et al., 2020; Grieco et al., 2020). In the present study, the low response in SpO_2 and the respiratory rate does not mean that HFNC and NIV cannot benefit these patients. Grieco et al. (2021) did not show differences in respiratory frequency in the HFNC intervention and the NIV in patients with COVID-19, but they did show a reduction in dyspnea symptoms.

The numbers of adverse events in the NIV and HFNC treatment were similar. Nasal and facial skin breakdown caused by long-time NIV therapy is relatively common and can also increase NIV intolerance (Navalesi et al., 2000, 2007). Sun et al. (2019) showed that the skin breakdown was significantly more common in the NIV group compared to the HFNC treatment (20.9 % vs 5.1 %). However, the present study did not present any skin lesion records. These findings are the result of institutional guidelines for monitoring skin health and the interface for the NIV treatment (Yamaguti et al., 2014). The most common adverse event reported was a pressure ulcer outside the face region. Li (2016) showed that patients with pressure ulcers had a longer length of stay than patients without pressure ulcer stay, especially those with periods of ICU stay above 7 days.

The need for invasive mechanical ventilation in these patients with COVID-19 was higher than that recently reported for other ICU units. Previous studies show different results of intubation needs: 88 % in Italy (Grasselli et al., 2020b), 71 % in Washington State (USA) (Arentz et al., 2020), and 47 % in Wuhan (China) (Wang et al., 2020). The need for invasive mechanical ventilation in these patients with severe COVID-19 was also higher compared with data reported by the Chinese study and lower compared with data reported by other studies. In the present study, the use of noninvasive ventilatory support prevented the need for intubation in 35.1 % of the patients.

Corroborating with our study, Franco et al. (2020) showed that three modes of ventilatory support (NIV, CPAP, and HFNC) had a similar impact and mortality outcome, both on intubation rate and length of stay. On the other hand, our mortality results are lower than those presented by Bhatraju et al. (2020), which showed a very high mortality rate both with NIV and HFNC (80 % and 52 %, respectively). However, it has to be noted that HFNC was usually applied in less severe patients compared with NIV. This may reflect the decision of the clinicians and physiotherapists to start NIV in cases in which they judged that applying a relatively high level of PEEP was more appropriate.

The use of NIV and HFNC is described in the literature as a potential aerosol generator and with the risk of infection of healthcare professionals (Agarwal et al., 2020; Ferioli et al., 2020). However, the World Health Organization (2020) and other guidelines developed by experts from different countries have used NIV and HFNC in the treatment of AHRF that occurred in COVID-19 (Lazzeri et al., 2020; Righetti et al., 2020; Alhazzani et al., 2020). For the application of these devices to be safer, several protective actions were implemented, mainly the placement of a filter in the ventilation circuit of the patients (Lucchini et al., 2020). Conventional heat and moisture exchange filter (HME) may allow up to 60 % of medical aerosol to pass through (Ari et al., 2016) so only the use of HME with an electrostatic bacterial filter (HMEF) should be considered to reduce exhaled pathogens from intubated patients during mechanical ventilation. Therefore, in our hospital, the HMEF was adopted to be used in NIV devices, but not for HFNC.

Franco et al. (2020) showed that the use of ventilatory support devices, including NIV and HFNC, outside ICUs, had an infection rate of 11.1 % for health workers. However, it is important to note that in the present study there was no difference in the infection rates of physiotherapists between the team in the critical care units dedicated for assisting patients with COVID-19 and that of the critical care units not dedicated for COVID-19 patients, which may indicate causes of community infection and not related to the use of NIV and HFNC. Corroborating these findings, Westafer et al. (2020) showed that the proportion of positive tests in clinical staff (41.5 %) was not higher than that in non-clinical staff (43.8 %). All physiotherapists followed the standards of the use of personal protective equipment (PPE) recommended by the World Health Organization (2020) for the application of treatment for devices that potentially generate aerosols.

The present retrospective analysis indicated that NIV and HFNC may help to treat severely affected COVID-19 patients in critical care units. This study has some limitations. First, in most real-life studies dealing with the COVID-19 pandemic period, missing data may be quite relevant. Second, most patients had not collected arterial blood gases, so we were unable to assess the effect of NIV and HFNC on the PaO_2/FiO_2 ratio of these patients, and the level of patient discomfort was not assessed, and this factor could limit the efficacy of these techniques. Third, we do not monitor the access to different environments by each professional outside the hospital. Finally, another physiological study with a longer duration of the treatment and also a larger randomized controlled study of NIV and HFNC in COVID-19 patients with acute hypoxemic respiratory failure are needed to confirm our results and to further elucidate the efficacy of NIV and HFNC in this patient population.

5. Conclusion

The application of NIV and HFNC in the critical care unit is feasible and associated with favorable outcomes. In addition, there was no increase in the infection rate of physiotherapists with SARS-CoV-2.

Data availability

Raw data and other supplementary material are available at the following repository: osf.io/7zpcj

No data was used for the research described in the article.

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Data will be made available on request.

Funding

We thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, number 18/16832−9) and Hospital Sírio-Libanês.

Data statement

The data used to support the findings of this study are included within the article

Authors' contributions

WNSC, JPM, FSP and LHSM, were responsible for the acquisition data, analysis, or interpretation. RFR and WPY were responsible for the conception of the idea, manuscript design and drafting manuscript. WNSC, RFR, JPM, FSP, LHSM, GAJA, and WPY helped in the manuscript design and drafting of the manuscript. RFR and WPY are the senior

authors who were responsible for the supervision and revising the final manuscript. All authors approved the final manuscript.

Declaration of Competing Interest

The authors report no conflict of interest in this research.

Acknowledgements

We thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, number 18/16832−9) and Hospital Sírio-Libanês.

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