Effectiveness and safety of non-invasive positive pressure ventilation in the treatment of COVID-19-associated acute hypoxemic respiratory failure: a single center, non-ICU setting experience.

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Abstract

Background

The role of non-invasive positive pressure ventilation (NIPPV) in COVID-19 patients with acute hypoxemic respiratory failure (AHRF) is uncertain. This study was aimed to assess the effectiveness and safety of NIPPV in patients with COVID-19-associated AHRF admitted to non-ICU wards.

Methods

We retrospectively evaluated all COVID-19 patients consecutively admitted to the COVID-19 general wards of a medium-size Italian hospital, from March 6 to May 7, 2020. Healthcare workers (HCWs) caring for COVID-19 patients were monitored, undergoing naso-pharyngeal swab for SARS-CoV-2 in case of onset of COVID-19 symptoms, and periodic SARS-CoV-2 screening serology.

Results

Overall, 50 of 143 patients (mean age 74.6 years) were treated with NIPPV, and 22 (44%) were successfully weaned. Due to limited life expectancy, 25 (50%) of 50 NIPPV-treated patients received a “do not intubate” order. Among these, only 6 (24%) were weaned from NIPPV. Of the remaining 25 NIPPV-treated patients, 16 (64%) were successfully weaned, 9 (36%) underwent delayed endotracheal intubation and, among these, 3 (33.3%) died. NIPPV success was predicted by the use of corticosteroids (OR 15.4, p 0.013), the PaO2/FiO2 ratio measured 24-48 hours after NIPPV initiation (OR 1.02, p 0.015), and the presence of a “do not intubate” order (OR 0.03, p 0.020). During the study period, 2 of 124 (1.6%) HCWs caring for COVID-19 patients were diagnosed with mild SARS-CoV-2 infection.

Conclusions

Apart from patients with limited life expectancy, NIPPV was effective in a substantially high percentage of patients with COVID-19-associated AHRF. The risk of SARS-CoV-2 infection among HCWs was low.

Introduction

Within a span of months, the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has seen a surge of patients with respiratory distress admitted to hospitals across the globe [1]. Patients presenting with COVID-19-associated acute hypoxemic respiratory failure (AHRF) despite conventional oxygen therapy commonly meet the criteria for the acute respiratory distress syndrome (ARDS), and require a ventilatory support. Across the globe, 7-26% of patients hospitalized with COVID-19 presented a critical disease with AHRF and were managed in intensive care unit (ICU) setting, in

most cases by means of invasive mechanical ventilation (MV) [2]. The role of non-invasive positive pressure ventilation (NIPPV) in patients with COVID-19-related AHRF is uncertain, as there is no direct evidence to support NIPPV in such patients [3, 4]. Studies on the use of NIPPV in AHRF with an etiology other than cardiogenic pulmonary edema have shown high rates of failure, with intubation rates up to 50% and high mortality [5-7]. Furthermore, there is concern that NIPPV use might increase the risk of nosocomial transmission of SARS-CoV-2 to healthcare workers (HCWs), by generating aerosols of infectious particles [4, 8-11].

Reflecting the current knowledge gap regarding risks and benefits associated with NIPPV use, international guidelines on clinical management of COVID-19 make only weak, conditional recommendations in favor of NIPPV, advocating the use of non-invasive ventilation in selected patients with mild ARDS, under close monitoring for worsening of respiratory failure, provided that appropriate airborne precautions are implemented [3, 4, 12].

The purpose of this study was to assess the effectiveness of NIPPV in treating AHRF in COVID-19 patients admitted to non-ICU wards, and to explore predictors of NIPPV success. Our secondary objective was to evaluate the risk of SARS-CoV-2 transmission among HCWs caring for NIPPV-treated COVID-19 patients.

Methods

Study design and participants

We conducted a single-center retrospective analysis on a cohort of patients with COVID-19-associated AHRF, consecutively admitted to the COVID-19 general wards of our institution between March 6 and May 7, 2020. The diagnosis of SARS-CoV-2 infection was confirmed using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasopharyngeal swab specimens. All the patients with COVID-19-associated AHRF who underwent NIPPV for at least a 2-hour trial were recruited. In addition, we evaluated all the HCWs who were in charge of the COVID-19 wards during the study period, exploring the risk of nosocomial SARS-CoV-2. The institutional review board approved the study. Informed consent from patients was not required due to the observational nature of the study; a verbal informed consent was acquired from HCWs.

Clinical setting

The study was performed in the 3 COVID-19 general wards of the San Giovanni di Dio Hospital, a medium-size acute care hospital (296 beds) in Florence, Italy. The COVID-19 general wards were equipped with 11 single, 8 double and 8 quadruple rooms, for a total of 59 beds. Patients were assigned to single rooms, or cohorted in multiple-bed rooms, depending on availability. The wards had a closed ventilation system with air recirculation; no negative pressure rooms, nor high-efficiency particulate air (HEPA) filtering systems were available. Transition zones for donning and doffing of protective personal

equipment (PPE) were created at the entry and exit of each ward, respectively. The wards were equipped with NIPPV ventilators and vital signs monitors for the assistance of severely to critically ill patients.

COVID-19 wards staff

The COVID-19 wards were managed by an exclusively dedicated internal medicine staff, with the collaboration of some specialist doctors and surgeons. Overall, the staff was composed by a total of 124 HCWs, including 22 physicians, 61 nurses, 28 health assistants, and 13 ward assistants (HCWs in charge of cleaning the wards). All the involved healthcare personnel were trained to correctly use PPE. The medical staff was trained on therapeutic management of COVID-19 patients, and strictly collaborated with the intensive care consultants for the management of patients with respiratory failure.

During the period of activity, HCWs were closely monitored for the appearance of symptoms of SARS-CoV-2 infection; in addition, they underwent voluntary testing for SARS-CoV-2 serology twice, after the first month of activity and 2 weeks after the termination of activity in the COVID-19 wards. A two-tiered serologic testing algorithm was adopted, including an initial chromatographic rapid immunoassay, followed – in case of positive result – by a chemiluminescence quantitative immunoassay (iFlash1800 CLIA analyzer for anti-SARS-CoV-2 antibodies IgM and IgG).

HCWs with COVID-19 symptoms or a positive serology test were subsequently evaluated by means of RT-PCR for SARS-CoV-2 on naso-pharyngeal swab.

Protective personal equipment

HCWs attending the COVID-19 general wards were recommended to adopt airborne, droplet and contact precautions. PPE included a respirator mask (N95 respirators, FFP2, FFP3, or equivalent), a disposable long-sleeved gown or protective suit, double gloves, goggles or, in alternative, a face shield, shoe covers. Donning and doffing procedures were supervised by physician and nurse leaders.

NIPPV delivery

NIPPV was delivered using a single-limb non-invasive ventilator (Philips Respironics V60), via a full-face or oro-nasal mask. In order to limit the production of virus-laden aerosols, non-vented masks were used, and a viral-bacterial filter was placed before the exhalation port of the NIPPV circuit.

Criteria for initiating NIPPV were: a) a Spo2 < 92%; b) respiratory fatigue, c) hypercapnia and respiratory acidosis.

Continuous positive airway pressure (CPAP) was the preferred mode of ventilation; positive end-expiratory pressure (PEEP) levels were adjusted to achieve target oxygenation, according to patient tolerance (pressure range 5 - 12 cmH_2O). A bilevel positive airway pressure (BiPAP) ventilation was applied to patients with COPD, hypercapnia, or persistent respiratory fatigue despite a brief trial of CPAP NIPPV.

During NIPPV, respiratory rate, oxygen saturation, and arterial blood gas results were closely monitored. Intensivist consultation and assessment for intubation were acquired for patients showing persistent or worsening respiratory distress after a 1-hour NIPPV trial.

Study outcomes

The primary outcome was the proportion of NIPPV-treated patients who were successfully weaned. Successful weaning was defined as the ability to be weaned from NIPPV for ³ 24 hours. The need to switch to invasive MV and AHRF-related death were considered as NIPPV treatment failure.

Predictors of NIPPV success were explored among patients' demographic, clinical and treatment characteristics.

The secondary outcome was the percentage of SARS-CoV-2 infection acquisition among HCWs caring for COVID-19 patients. SARS-CoV-2 infection among HCWs was directly attributed to healthcare-associated transmission if 1) the infection was diagnosed within 14 days of termination of activity in the COVID-19 ward, 2) the HCW had no other known exposure to SARS-CoV-2 infected individuals outside the COVID-19 ward.

Data collection

For each patient treated with NIPPV, the following demographic, clinical and treatment data were retrieved from electronic clinical records: sex, age, comorbidities, SOFA score, pre- and post- NIPPV arterial oxygen tension/inspiratory oxygen fraction (PaO2/FiO2) ratio, NIPPV duration, modality of non-invasive ventilatory support (CPAP vs BiPAP), drug treatments, length of hospital stay. Patient outcomes (successful weaning from NIPPV, ETI for invasive ventilation, and in-hospital death) were also retrieved.

Statistical analysis

Continuous and categorical variables were presented as mean (SD) and n (%), respectively. Statistical analysis was performed using the Student's t test for continuous variables and the Chi-square test or exact Fisher test for categorical variables, as appropriate. To explore the predictive factors associated with NIPPV success, univariable and multivariable logistic regression models were used. All data were analyzed using Med-Calc® version 12.3.0 (MedCalc Software; Mariakerke, Belgium). Statistical significance was set at $p < 0.05$.

Results

During the study period a total of 143 patients were admitted to the 3 COVID-19 general wards of our institution. Fifty patients (33 males) were enrolled in the study, as they presented AHRF and underwent NIPPV. The mean age of NIPPV-treated patients was 74.6 ± 11.0 years, the mean number of comorbidities was 2.4 ± 1.5, the mean SOFA score was 3.1 ± 1.2, and the mean PaO2/FiO2 ratio before starting NIPPV was 130.1 ± 63.5 mmHg. Due to advanced age, comorbidities and poor performance status, 25 (50%) of

the 50 NIPPV-treated patients had a limited life expectancy and received a treatment limitation decision, i.e. a “do not intubate” order. Demographics, clinical characteristics, treatments, and outcomes of the study population are shown in table 1. Overall, 22 patients (44%) were successfully weaned from NIPPV. Success rate of NIPPV in patients with a treatment limitation decision was 24% (6/25) (table 2). Among the 25 patients without treatment limitations, 16 (64%) were weaned from NIPPV and subsequently discharged, 9 (36%) underwent delayed ETI and were transferred to ICU due to worsening of respiratory distress (table 2). For these patients, the mean time between NIPPV initiation and ETI was 55.3 hours ± 81.4 (median 24 hours). Three (33.3%) of the intubated patients died during ICU stay; the remaining 6 were successfully weaned from MV and subsequently discharged from the hospital.

The overall in-hospital mortality among NIPPV-treated patients was 50% (25/50) (table 1). Mortality was significantly higher among patients with a treatment limitation decision than among patients with no preclusion to ETI (88% vs 12%, p <0.0001, table 2).

In the multivariable analysis, the presence of a treatment limitation decision (OR 0.03, CI 0.001 – 0.57, p 0.020), the use of corticosteroids (OR 15.4, CI 1.79 – 132.57, p 0.013), and the increase of the PaO2/FiO2 ratio measured 24-48 hours after initiation of NIPPV (OR 1.02, CI 1 – 1.03, p 0.015) were independently associated with NIPPV success (table 3).

During the study period, 1 of 124 HCWs (a health assistant) in charge of the 3 COVID-19 general wards developed mild symptoms (fatigue, myalgia, smell and taste loss, fever) and was diagnosed with SARS-CoV-2 infection by means of naso-pharyngeal swab. All healthcare personnel underwent the 2 scheduled screening serology tests for SARS-CoV-2. The second test for SARS-CoV-2 antibodies was positive (IgG and IgM) in 1 asymptomatic nurse, whose subsequent naso-pharyngeal swab tested negative. Globally, based on the results of molecular and serologic assays, 1.6% (2/124) of HCWs experienced a healthcare-associated SARS-CoV-2 infection.

Table 1. Demographics, clinical characteristics, treatments, and outcomes among patients who were or were not weaned from NIPPV.

Variables	Total	Patients weaned from NIPPV	Patients not weaned from NIPPV	P value
No.	50 (100%)	22 (44%)	28 (56%)	
Age, years, mean (SD)	74.6 (11)	71 (11.4)	77.5 (9.9)	0.0361
Female, n°	17 (34%)	6 (27.3%)	11 (39.3%)	0.5556
Comorbidities				
Atrial fibrillation, n°	14 (28%)	5 (22.7%)	9 (32.1%)	0.6754
Cardiovascular disease, n°	22 (44%)	8 (36.4%)	14 (50%)	0.4982
Chronic kidney disease, n°	10 (20%)	2 (9.1%)	8 (28.6%)	0.1535
Cognitive impairment, n°	7 (14%)	2 (9.1%)	5 (17.9%)	0.4444
COPD, n°	10 (20%)	4 (18.2%)	6 (21.4%)	1
Diabetes mellitus, n°	12 (24%)	5 (22.7%)	7 (25%)	0.8518
Hypertension, n°	28 (56%)	12 (54.5%)	16 (57.1%)	0.8543
Immunodeficiency, n°	3 (6%)	2 (9.1%)	1 (3.6%)	0.5757
Malignancy, n°	6 (12%)	1 (4.5%)	5 (17.9%)	0.2109
Stroke, n°	8 (16%)	2 (9.1%)	6 (21.4%)	0.4391
Number of comorbidities, mean (SD)	2.4 (1.5)	2 (1.6)	2.8 (1.3)	0.0569
SOFA score, mean (SD)	3.1 (1.2)	2.9 (1)	3.3 (1.4)	0.2635
PaO2/FiO2 before NIPPV, mm Hg, mean (SD)	130.1 (63.5)	136.8 (57.9)	124.9 (68.2)	0.5164
PaO2/FiO2 24-48h after NIPPV, mm Hg, mean (SD)	148.3 (63.5)	183.2 (64.7)	120.8 (70.2)	0.0022
NIPPV modality				
NIPPV BiPAP, n°	25 (50%)	8 (36.4%)	17 (60.7%)	0.1543
NIPPV CPAP, n°	25 (50%)	14 (63.6%)	11 (39.3%)	0.1543
NIPPV duration, hours, mean (SD)	187 (181)	264 (223.3)	126.4 (109.8)	0.0063
Treatments				
Treatment with corticosteroids, n°	35 (70%)	19 (86.4%)	16 (57.1%)	0.0325
Treatment with tocilizumab, n°	17 (34%)	12 (54.5%)	5 (17.9%)	0.0156
Treatment with antibiotics, n°	46 (92%)	20 (90.9%)	26 (92.9%)	1
Treatment limitation decision, n°	25 (50%)	6 (27.3%)	19 (67.9%)	0.0103
Outcomes				
Duration of hospital stay, days, mean (SD)	19.6 (14.5)	23 (11)	15.3 (13.1)	0.0319
In-hospital death, n°	25 (50%)	3 (13.6%)	22 (78.6%)	< 0.0001

Table 2. Clinical features and outcomes of NIPPV-treated patients with or without a treatment limitation decision.

Variables	Patients with treatment limitation (n=25)	Patients with no treatment limitation (n=25)	P value
Age, years, mean (SD)	82.1 (7.6)	67.1 (8.4)	0.0001
Number of comorbidities, mean (SD)	3 (1.3)	1.84 (1.4)	0.0039
SOFA score, mean (SD)	3.6 (1.4)	2.6 (0.8)	0.0032
PaO2/FiO2 pre-NIPPV (SD)	127.4 (67.9)	132.9 (60.2)	0.7632
PaO2/FiO2 post-NIPPV (SD)	127 (80.8)	169.6 (61.2)	0.0409
NIPPV success, n°	6 (24%)	16 (64%)	0.0103
Delayed ETI, n°	-	9 (36%)	-
In-hospital death, n°	22 (88%)	3 (12%)	<0.0001

Table 3. Predictors of NIPPV success, univariate and multivariate analysis

Variables	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age, years*	0.94 (0.89 - 1)	0.041	1.11 (0.95 – 1.28)	0.183
Female sex (vs male)	0.58 (0.17 – 1.94)	0.375	-	-
Atrial fibrillation	0.62 (0.17 – 2.22)	0.463		
Cardiovascular disease	0.57 (0.18 – 1.79)	0.337	-	-
Chronic kidney disease	0.25 (0.05 – 1.33)	0.103	-	-
Cognitive impairment	0.46 (0.08 – 2.64)	0.383	-	-
COPD	0.81 (0.2 – 3.34)	0.776	-	-
Diabetes mellitus	0.88 (0.24 – 3.28)	0.852	-	-
Hypertension	0.9 (0.29 – 2.77)	0.854	-	-
Immunodeficiency	2.7 (0.23 – 31.89)	0.430	-	-
Malignancy	0.22 (0.02 – 2.03)	0.181	-	-
Stroke	0.37 (0.7 – 2.03)	0.250	-	-
Total number of comorbidities*	0.73 (0.49 – 1.09)	0.122	-	-
SOFA score*	0.76 (0.47 – 1.26)	0.290	-	-
PaO2/FiO2 before NIPPV, mm Hg*	1 (0.99 – 1.01)	0.511	-	-
PaO2/FiO2 24-48h after NIPPV initiation, mm Hg*	1.01 (1 – 1.03)	0.008	1.02 (1 – 1.03)	0.015
NIPPV CPAP (vs BiPAP)	2.7 (0.85 – 8.57)	0.091	-	-
Antibiotics	0.77 (0.1 – 5.94)	0.801	-	-
Corticosteroids	4.75 (1.14 – 19.83)	0.033	15.4 (1.79 – 132.57)	0.013
Tocilizumab	5.52 (1.53 -19.86)	0.009	6.35 (0.88 – 45.86)	0.067
Treatment limitation decision	0.18 (0.05 – 0.61)	0.006	0.03 (0.001 – 0.57)	0.020

*** Per 1 unit increase**

Discussion

We explored the effectiveness of NIPPV in a cohort of patients with COVID-19-associated AHRF admitted to non-ICU wards, characterized by a mean age of 74.6 years, and a mean PaO2/FiO2 ratio before starting NIPPV of 130.1 mmHg. Overall, 44% (22/50) of patients were successfully weaned from NIPPV, avoiding ETI and transfer to ICU. The rate of success was substantially higher (64%) in the subgroup of patients without treatment limitations, whose in-hospital death rate was very low (12%). On the contrary, a high percentage (76%) of NIPPV failure and subsequent AHRF-related death was registered among older patients with a “do not intubate” order, whose in-hospital mortality reached 88%, due to the non-AHRF-related death of 3 patients who had been successfully weaned from NIPPV.

Delivery of NIPPV to COVID-19 patients in our study appeared safe for HCWs, as only 2 out of 124 individuals (1.6%) experienced a SARS-CoV-2 infection while on activity in the COVID-19 wards, in the absence of serious symptoms.

In general, the use of NIPPV in patients with AHRF is expected to improve oxygenation, decrease the work of breathing, and avoid intubation, reducing the complications associated with invasive MV, such as pneumonia, excessive sedation, delirium, and ICU–acquired weakness [7]. Risks of NIPPV include large tidal volumes and injurious transpulmonary pressures, and delayed initiation of invasive MV in a rapidly

decompensating patient, which can increase the risk of death and nosocomial spread of the infection [4, 13]. Previous studies on the use of NIPPV in patients with AHRF due to pandemic viral illnesses have yielded conflicting results, with failure rates ranging from 10 to 70% in patients with influenza, H1N1 and Severe Acute Respiratory Syndrome (SARS), and up to 92.4% in patients with Middle East Respiratory Syndrome (MERS) [4, 7, 14]. Furthermore, NIPPV is an aerosol generating procedure (AGP) with the potential to increase the risk of SARS-CoV-2 infection transmission to HCWs, as shown in previous studies on SARS epidemic [4, 11, 15, 16].

Despite controversies over the benefits and risks of NIPPV, reports from several countries have shown that 11 to 62% of patients hospitalized with severe to critical COVID-19 received NIPPV [17-21]. In Italy, NIPPV has been widely used, especially in non-ICU setting, since the huge number of patients with COVID-19-related AHRF outweighed the provision of ICU beds and ventilators [22, 23].

The results of our series seem to indicate that NIPPV, delivered via face mask, in a non-ICU setting, is considerably effective in the treatment of COVID-19-associated AHRF in patients without limited life expectancy. In addition, it is worth noting that the death rate of patients undergoing delayed ETI after an initial unsuccessful trial of NIPPV (33.3%) did not exceed the mortality reported for ARDS (35-45%) and death rates registered in series of mechanically ventilated COVID-19 patients [24]. Our findings are corroborated by the recent metanalysis from Ferreyro et al., which found that NIPPV, delivered via face mask or helmet, reduces mortality and intubation rate compared to standard oxygen therapy in patients with AHRF from any cause [25].

The high mortality rate (88%) registered in our series among patients with limited life expectancy, seems to indicate a scarce utility of NIPPV in this subset of COVID-19 individuals. However, if intubation and MV appear as an inappropriate choice, NIPPV could still play a role in the therapeutic management of such frail patients, since it allows, with a limited resource investment, to cure a small but not negligible proportion of patients (12%) and deliver palliative care to dying subjects with COVID-19-related respiratory failure [7].

Regarding predictors of NIPPV success, the multivariable logistic regression model identified several factors independently associated with NIPPV outcome (table 3). The analysis showed that an increase of the PO_2/FiO_2 ratio 24-48 hours after NIPPV initiation was predictive of successful weaning: as a consequence, the results of blood gas analysis acquired the day after the start of NIPPV might be used to early identify patients needing a treatment escalation toward ETI and ICU transfer.

Among the explored medical treatments, use of corticosteroids was associated with a higher probability of NIPPV success; this result appears in line with recent evidence demonstrating a survival benefit, and a lower rate of progression towards invasive MV in hypoxemic COVID-19 patients receiving steroids [26].

Finally, the presence of a treatment limitation decision (“do not intubate” order), determined by a limited life expectancy, appeared as a strong predictor of NIPPV failure. As a consequence, a careful clinical

assessment of patient's life expectancy, based on age, comorbidities and performance status, might be used to precociously identify patients with poor prognosis whose primary goal is palliative care.

HCWs represent a category at high risk of COVID-19 infection: up to 3.8% (1.716 of 44.674 confirmed cases) of the reported cases in China, and up to 12% (30.225 of 250.973) of all cases of COVID-19 in Italy have been among healthcare personnel [27, 28]. These data point out the crucial need to protect healthcare professionals, by adopting effective infection prevention and control measures.

SARS-CoV-2 is transmitted from person to person directly through respiratory droplets, or indirectly, via contaminated fomites. Another potential mode of transmission is the airborne route, i.e. the inhalation of respiratory particles smaller than droplets, generated by procedures such as non-invasive ventilation, tracheal intubation, tracheotomy, manual ventilation before intubation (AGP) [8, 9]. Based on these assumptions, airborne precautions (wearing of a respirator mask), in addition to droplet and contact precautions, are universally recommended when AGP are performed on COVID-19 patients [4, 9-11]. Moreover, international guidelines suggest to perform AGP in negative pressure isolation rooms [4, 10, 11]. Previous studies have shown that the adoption of adequate airborne precautions, and the use of negative pressure systems can minimize the risk of infection among HCWs caring for SARS patients treated with NIPPV [15, 29]. In our institution, HCWs caring for COVID-19 patients treated with NIPPV were equipped with respirators, and full contact and droplet precautions, according to national and international guidelines [4, 9-11, 30]. The low rate of SARS-CoV-2 infection registered among HCWs (1.6%), confirms that the adopted PPE is highly effective in preventing coronavirus transmission during NIPPV delivering, even in the absence of negative pressure rooms or HEPA air filtering systems.

Some authors have recently advocated the use of helmet interface for NIPPV delivery in COVID-19 patients, in spite of face masks, as a better fitting and tolerable interface, which might minimize widespread dispersion of exhaled air and reduce the risk of airborne SARS-CoV-2 transmission to HCWs [22, 23, 31, 32]. Furthermore, evidence exists that NIPPV delivered by helmet in patients with AHRF presents an advantage in terms of decreased intubation and improved mortality with respect to face mask [25, 33]. To date, however, no direct evidence of benefit of helmet over face mask in the treatment of COVID-19-associated AHRF exists [4]. At our institution, no helmet interfaces were available during the study period, and NIPPV was delivered exclusively via full-face or oro-nasal face masks. We attempted to limit SARS-CoV-2 spread into the ambient air by selecting non-vented masks and applying an antimicrobial filter to the exhalation port of the NIPPV circuits [34].

Our study presents several limitations. The limited number of enrolled patients and the retrospective design reduce generalizability of our results. Due to the retrospective nature of the study, we were unable to retrieve detailed settings of NIPPV (e.g., PEEP, driving pressure, FiO_2), respiratory rate and blood gas analysis parameters in the first hours after NIPPV initiation, and data on patient tolerance. The absence of a control group does not allow direct comparison of the cure rate between patients treated with NIPPV and patients undergoing early intubation.

Regarding the safety assessment of the use of NIPPV in COVID-19 patients, we did not compare the rate of SARS-CoV-2 infection between HCWs caring for NIPPV-treated patients and HCWs caring for non-ventilated patients, since the entire healthcare staff cared for both patient subgroups. As a consequence, we do not know which is the specific contribution of NIPPV to nosocomial transmission of SARS-CoV-2.

Conclusions

Apart from elderly patients with limited life expectancy, NIPPV was effective in a substantially high percentage of patients with COVID-19-associated AHRF in this study. Moreover, the rate of SARS-CoV-2 infection among HCWs caring for COVID-19 patients receiving NIPPV was quite low, suggesting that NIPPV is a safe practice, provided that strict adherence to appropriate infection prevention and control measures is ensured.

NIPPV could serve as an affordable and widely available supportive strategy for the treatment of patients with COVID-19-related AHRF in non-ICU setting. Further research is needed to confirm our encouraging results.

Declarations

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflicts of interest.

Statement of human and animal rights

The authors declare that all procedures performed in this study are in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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