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Noninvasive ventilation for acute hypoxemic respiratory failure in patients with COVID-19

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ABSTRACT

Aim: Noninvasive ventilation (NIV) is known to reduce intubation in patients with acute hypoxemic respiratory failure (AHRF). We aimed to assess the outcomes of NIV application in COVID-19 patients with AHRF.
Materials & methods: In this retrospective cohort study, patients with confirmed diagnosis of COVID-19 and AHRF receiving NIV in general wards were recruited from two university-affiliated hospitals. Demographic, clinical, and laboratory data were recorded at admission. The failure of NIV was defined as intubation or death during the hospital stay.
Results: Between April 8 and June 10, 2020, 61 patients were enrolled into the final cohort. NIV was successful in 44 out of 61 patients (72.1%), 17 patients who failed NIV therapy were intubated, and among them 15 died. Overall mortality rate was 24.6%. Patients who failed NIV were older, and had higher respiratory rate, $PaCO_2$, D-dimer levels before NIV and higher minute ventilation and ventilatory ratio on the 1-st day of NIV. No healthcare workers were infected with SARS-CoV-2 during the study period.
Conclusions: NIV is feasible in patients with COVID-19 and AHRF outside the intensive care unit, and it can be considered as a valuable option for the management of AHRF in these patients.
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1. Introduction

The novel coronavirus disease 2019 (COVID-19) outbreak that began in 2019 and spread rapidly across the world has been observed to cause viral pneumonia and acute hypoxemic respiratory failure (AHRF) [1].

For patients who are unresponsive to conventional oxygen therapy, high-flow nasal cannula (HFNC) oxygen, noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV) may be administered [2]. Several studies suggested high mortality for patients with COVID-19–associated AHRF who received IMV [3], raising the concern that these patients may be particularly vulnerable to ventilator-induced lung injury [4]. Noninvasive oxygenation strategies that could at least safely spare patients of IMV could be of enormous importance. However, there were major concerns that HFNC or NIV may create risks for health care workers (HCWs) because of SARS-CoV-2 transmission via aerosols [5] while the data on the efficacy of noninvasive modalities in COVID-19–associated AHRF are still limited [5-7]. The aim of this study was to assess the outcomes of NIV application in COVID-19 patients with AHRF.

2. Materials & methods

This retrospective cohort study was conducted in COVID-19 care units of two university-affiliated hospitals between April 8 and June 10, 2020. The study was approved by the local ethics committee (approval number 16–20). As this was a retrospective study, the requirement for informed consent was waived. We analyzed all patients aged ≥18 years with the laboratory-confirmed SARS-CoV-2 infection admitted to the general wards (outside intensive care units) for AHRF. The inclusion criteria were the need for oxygen greater than 6 L/min to maintain oxygen saturation (SpO_2) above 92% and symptoms of respiratory distress (dyspnea, tachypnea, and activation of respiratory accessory muscles). The exclusion criteria were as follows: the need for immediate endotracheal intubation (ETI), NIV duration less than 60 min, chronic respiratory diseases (chronic obstructive pulmonary disease, obesity hypoventilation syndrome, etc), and unstable hemodynamics (requiring vasopressor support and/or life-threatening heart rhythm abnormalities). All included patients were managed in isolated neutral pressure rooms. Demographic data, comorbidities and clinical laboratory data were recorded at admission, and respiratory parameters were recorded before NIV start and on the 1st day of NIV.

We used NIV ventilators equipped with air-oxygen blender (Trilogy 202, Philips Respironics, USA) and non-vented oronasal masks; the expiratory limb of the circuit was equipped with an antimicrobial filter.

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The primary NIV mode was the continuous positive airway pressure (CPAP), the pressure was initially set at 10 cm H2O and then adjusted according to SpO_2 and clinical tolerance. A pressure support ventilation (PSV) was considered over CPAP in patients who showed respiratory acidosis (pH < 7.35), tachypnea >30/min or a vigorous activity of respiratory accessory muscles. FiO_2 was adjusted to maintain the arterial oxygen saturation of more than 92% during NIV. Patients with bilateral posterior infiltrates were placed in the prone position for at least 8 h a day.

The failure of NIV was defined as intubation or death during the hospital stay. The criteria for ETI and IMV were worsening respiratory failure with respiratory distress, SpO_2 below 88% without response to NIV, respiratory acidosis with a pH below 7.30, hemodynamic instability and exhaustion.

2.1. Statistical analyses

The statistical analysis was performed using SPSS Statistics v 22.0 (IBM, USA). Continuous variables were reported as the median value and interquartile range. Categorical variables were reported as number and percentage. The differences between success and failure groups were analyzed by Mann–Whitney *U* test and Fisher's exact test. A *p* value < 0.05 was considered significant.

3. Results

A total of 297 patients with COVID-19 and AHRF were admitted to the participating hospitals and 61 patients were enrolled into the final cohort (Fig. 1). Main characteristics of patients are reported in Table 1. Prior to starting NIV the median PaO_2/FiO_2 was 164.0 (131.3–200.0) mmHg. CPAP mode was used in 45 patients (the pressure was set at 10.0 (9.7–12.2) cmH_2O). In 16 patients we used PSV mode (inspiratory pressure was 20.0 (17.8–22.4) cmH_2O and PEEP of 9.9 (9.8–10.3) cmH_2O). NIV was successful in 44 out of 61 patients (72.1%), 17 patients who failed NIV therapy were transferred to ICU and then intubated (Fig. 1). Reasons for ETI were a decreased level of consciousness (11.8%), exhaustion (17.6%) and refractory hypoxemia (70.6%). Among 17 patients who received IMV, 15 died (88.2%). Overall mortality rate was 24.6%. NIV duration was shorter in the NIV failure group – 3.0 (2.5–8.0) days vs 8.0 (6.3–11.0) days in NIV success group ($p = 0.003$). All patients with NIV success were discharged from hospital without need in oxygen support.

Patients who failed NIV were older (68.0 (61.5–71.5) years vs 61.0 (51.0–67.0) years, $p = 0.018$), and had a higher respiratory rate (26 (24–30) breaths/min vs 24 (20–26) breaths/min, $p = 0.049$), $PaCO_2$ (36.0 (30.8–39.8) mmHg vs 31.0 (29.4–33.8) mmHg, $p = 0.048$) and serum D-dimer levels (1832 (1275–1258) ng/mL vs 881 (682–1163) ng/mL, $p < 0.0001$) (Table 1) before NIV. On the 1-st day of NIV patients with NIV failure had higher minute ventilation (15.8 (12.9–17.7) L/min vs 12.9 (10.8–14.2) L/min, $p = 0.008$) and ventilatory ratio (1.88 (1.43–2.37) vs 1.38 (1.10–1.73), $p = 0.005$) (Table 1). D-dimer was the best predictor of NIV failure with the area under the ROC curve of 0.82 (95% CI 0.64–1.00), $p = 0.002$, sensitivity 82% and specificity 80% for D-dimer level > 1190 ng/mL).

All HCWs who were exposed to NIV patients used appropriate personal protection equipment (PPE) composed of FFP2/FFP3 masks, eye and head protections, disposable protective suits, gloves, and overshoes and nobody of HCWs was infected with SARS-CoV-2 during the study period.

4. Discussion

This study suggests that the use of NIV is feasible in acute hypoxemic respiratory failure in patients with COVID-19 outside intensive care unit and can be considered as an effective means to improve oxygenation in patients not responding to conventional oxygen therapy. About 28% of our COVID-19 patients with AHRF failed NIV and required ETI and IMV with an associated mortality of 88%, compared with 0% when NIV

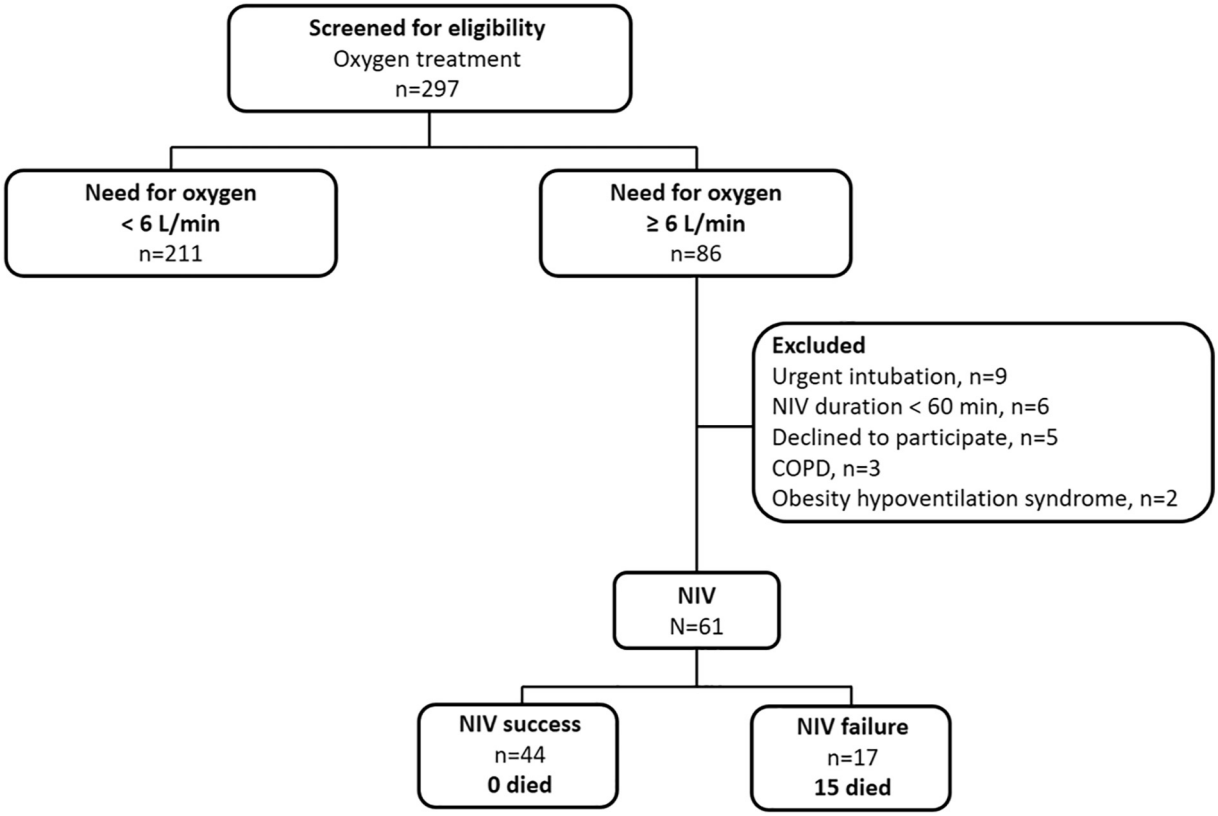

Fig. 1. Study flow chart.

Table 1
Patients' baseline demographic, clinical and laboratory characteristics before NIV initiation.

Variable	All patients ($n = 61$)	NIV success group ($n = 44$)	NIV failure group ($n = 17$)	*P* value
Age, years	62.0 (53.0–70.0)	61.0 (51.0–67.0)	68.0 (61.5–71.5)	0.018
Male, *n* (%)	37 (60.7)	27 (61.4)	10 (58.8)	0.856
BMI, kg/m^2	31.7 (28.9–35.2)	31.3 (28.9–35.0)	33.5 (28.6–36.1)	0.670
Smokers, *n* (%)	30 (49.2)	22 (50.0)	8 (47.1)	0.837
Time from symptoms onset, days	12 (9–14)	12 (9–15)	12 (9–14)	0.840
Comorbidities, *n* (%):				0.856
Hypertension	29 (47.5)	21 (47.7)	8 (47.1)	
Diabetes mellitus	8 (13.1)	5 (11.4)	3 (17.6)	
Congestive heart failure	3 (4.9)	2 (4.5)	1 (5.9)	
Chronic kidney disease	2 (3.3)	1 (2.3)	1 (5.9)	
Before NIV				
CRP, mg/L	134.5 (80.9–214.8)	126.0 (71.5–168.3)	191.5 (102.0–278.0)	0.082
D-dimer, ng/mL	1001 (741–1449)	881 (682–1163)	1832 (1275–1258)	<0.0001
WBC, 10^9/L	7.4 (5.6–9.9)	7.3 (5.8–9.2)	9.7 (4.1–11.3)	0.510
Lymphocytes, 10^9/L	0.9 (0.6–1.3)	0.8 (0.7–1.1)	0.6 (0.4–0.7)	0.153
PaO_2/FiO_2, mmHg	164.0 (131.3–200.0)	161.7 (131.6–210.0)	166.0 (127.3–184.5)	0.367
$PaCO_2$, mmHg	32.0 (29.4–36.0)	31.0 (29.4–33.8)	36.0 (30.8–39.8)	0.048
pH	7.39 (7.35–7.46)	7.40 (7.36–7.47)	7.38 (7.35–7.44)	0.856
Respiratory rate, min^{-1}	25 (20–28)	24 (20–26)	26 (24–30)	0.049
Heart rate, min^{-1}	84 (77–95)	85 (74–85)	87 (75–97)	0.367
1-st day of NIV				
PaO_2/FiO_2, mmHg	198.8 (155.2–242.4)	202.0 (157.6–244.7)	187.9 (149.3–225.2)	0.545
$PaCO_2$, mmHg	37.9 (33.7–42.0)	37.5 (33.6–41.4)	41.5 (34.5–46.3)	0.276
pH	7.38 (7.33–7.43)	7.41 (7.35–7.46)	7.39 (7.35–7.42)	0.367
Respiratory rate, min^{-1}	22 (18–23)	21 (18–22)	22 (22–28)	0.038
V_T, mL/kg IBW	8.0 (6.9–9.3)	8.0 (6.8–8.8)	8.2 (7.1–10.0)	0.226
Minute ventilation, L/min	13.3 (10.9–15.2)	12.9 (10.8–14.2)	15.8 (12.9–17.7)	0.008
Ventilatory ratio	1.47 (1.18–1.96)	1.38 (1.10–1.73)	1.88 (1.43–2.37)	0.005

BMI, body mass index; PaO_2/FiO_2, arterial oxygen tension to inspired oxygen fraction ratio; CRP, C-reactive protein; WBL, whole blood leucocytes; V_T, tidal volume; IBW, ideal body weight.

succeeded. Our results are in accordance with recent reports on the use of NIV in COVID-19-associated AHRF, where the NIV failure rate varied from 23% to 45% [6-8].

No significant difference between the success and failure groups in baseline PaO_2/FiO_2 was found in our study, although a low baseline PaO_2/FiO_2 was shown to be a risk factor of NIV failure in several studies [9]. Interestingly, the median PaO_2/FiO_2 values in our patients were lower than those from a cohort study of mechanically ventilated COVID-19 patients reported by Ziehr et al. (164 vs 182 mmHg) [10]. We identified elevated D-dimer levels as a strong predictor of NIV failure. In a study by Wang et al., describing a nationwide cohort of critically ill COVID-19 patients in China, elevated D-dimer (>1.5 mg/L) at admission was also an indicator of increased possibility of IMV requirement [11]. It was shown that D-dimer elevation in COVID-19 was associated with the progression of the disease [12], so, progressive underlying processes can predispose to prolonged respiratory support and NIV failure [13]. We found that patients who failed NIV had some important characteristics of gas exchange. This concerns minute ventilation and ventilation ratio during NIV, which in general may be associated with increased alveolar dead space and impaired carbon dioxide clearance. Higher minute ventilation in patients with NIV failure was due to slightly higher tidal volume and higher respiratory rate, which, of course, may increase the risk of lung injury [14]. The time to NIV failure and ETI had a very wide range that can be explained by different time from disease onset to NIV start, different volumes of lung injury and different rate of disease progression.

No healthcare workers helping to treat the patients on NIV were infected with SARS-CoV-2 during the study period. These data could be confirmed from other studies. In an observational study by Oranger et al. the proportion of HCWs contaminated by SARS-CoV-2 was similar before and after the implementation of CPAP in the management of COVID-19 patients (6% vs 10%) [6]. In a recent study of Gaeckle et al. there was no observed increase in the concentration of aerosolized viral particles with the use of NIV or HFNC when compared to breathing room air [15]. So, with appropriate PPE, the HCW infections can be avoided even caring for patients with NIV.

5. Limitations

This study has several limitations. First, its retrospective design is susceptible to selection bias, however, all clinical and laboratory parameters were collected prospectively. Second, the small study population precludes subgroup analyses and extensive multivariate analysis due to the limited size of events. Third, our study is a single-center study (although it was performed in two university-affiliated hospitals) with respect to practice of NIV, and so might not be generalizable to other centers.

6. Conclusion

In summary, we have shown that NIV is feasible in patients with COVID-19 with acute hypoxemic respiratory failure outside the intensive care unit, and it can be considered as a valuable option for the management of AHRF in these patients. No healthcare workers helping to treat the patients on NIV were infected with SARS-CoV-2 during the study period.

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Declaration of competing interest

The authors have no competing interests to declare.

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NIV, non-invasive ventilation; COPD, chronic obstructive pulmonary diseases.

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