Canadian Respiratory Journal

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Lead Guest Editor: Vijay Hadda
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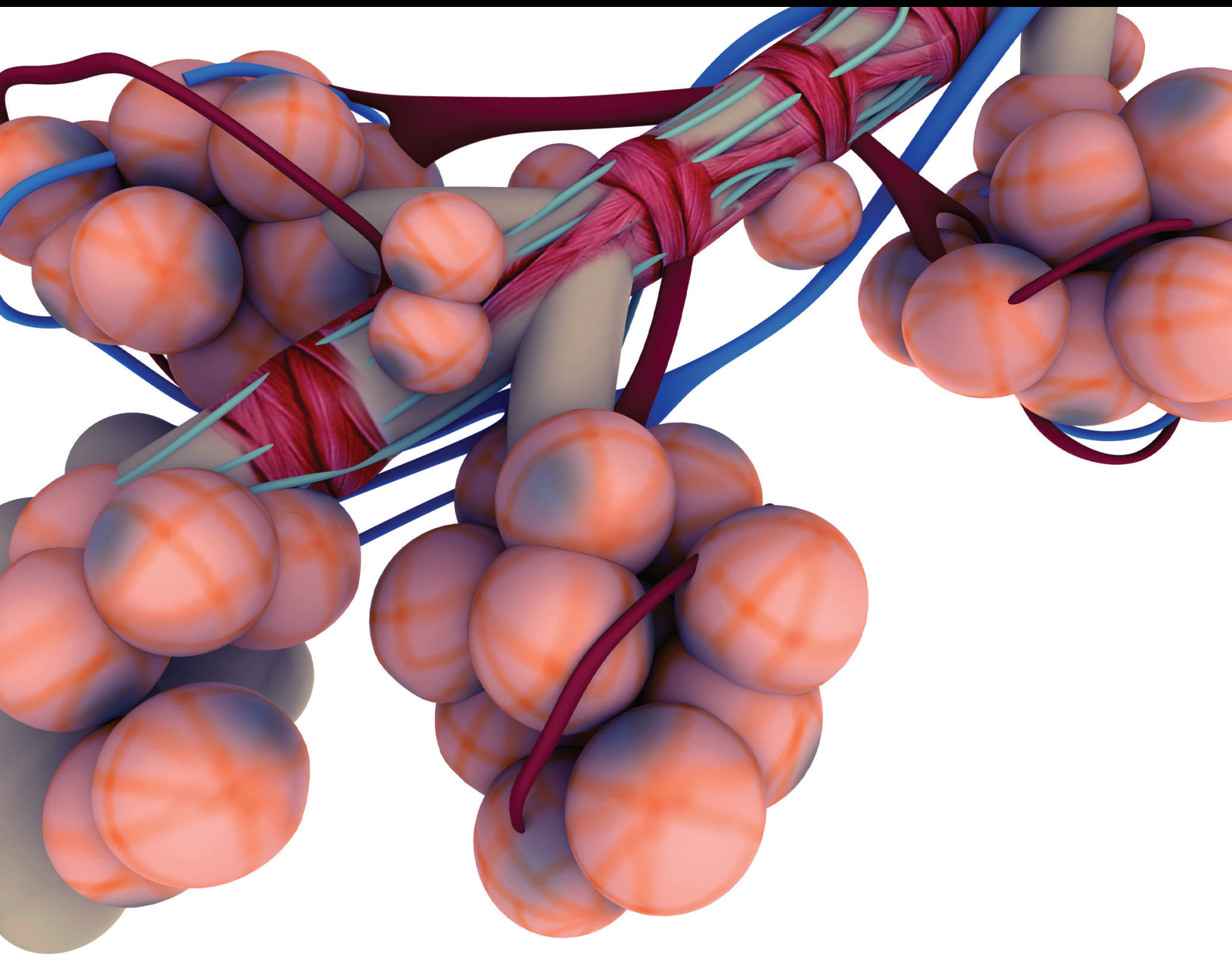

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Review Article

Noninvasive Ventilation in Treatment of Respiratory Failure-Related COVID-19 Infection: Review of the Literature

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The recently diagnosed coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in December 2019 commonly affects the respiratory system. The incidence of acute hypoxic respiratory failure varied among epidemiological studies with high percentage of patients requiring mechanical ventilation with a high mortality. Noninvasive ventilation is an alternative tool for ventilatory support instead of invasive mechanical ventilation, especially with scarce resources and intensive care beds. Initially, there were concerns by the national societies regarding utilization of non-invasive ventilation in acute respiratory failure. Recent publications reflect the gained experience with the safe utilization of noninvasive mechanical ventilation. Noninvasive ventilation has beneficiary role in treatment of acute hypoxic respiratory failure with proper indications, setting, monitoring, and timely escalation of therapy. Patients should be monitored frequently for signs of improvement or deterioration in the clinical status. Awareness of indications, contraindications, and parameters reflecting either success or failure of noninvasive ventilation in the management of acute respiratory failure secondary to COVID-19 is essential for improvement of outcomes.

1. Introduction

The recently diagnosed coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially recognized in Wuhan City, Hubei Province, China, in December 2019. The WHO declared COVID-19 as a global health emergency on January 31, 2020, and subsequently, a pandemic on March 11, 2020. Globally, the disease has been reported in more than 210 countries with 512,225,941 confirmed cases and 6,230,957 mortalities till April 28, 2022. Since the first wave of COVID-19, many countries have already seen the third wave of the spread of this virus (e.g., India, Germany, USA, and others), and a few countries (e.g., India, South Africa, and Zimbabwe) are now witnessing the fourth and higher waves of the COVID-19 pandemic. Different variants of the SARS-CoV-2 virus have been identified since the initial pandemic. The variants are different in rate of infectibility and fatality. The Omicron variant is more infectious than the Delta variant but less fatal, and consequently, less hospitalization.

Disease manifestation varies from mild flu like symptoms to severe respiratory failure with multiple organ involvement. The risk of death among individuals infected with COVID-19 was found to be in the range of 0.3% to 0.6%, which is comparable to that of a previous Asian influenza pandemic (1957 to 1958) [1]. It is now well recognized that the severe pulmonary involvement manifested as acute respiratory failure and adult respiratory distress syndrome is strongly associated with worse outcomes.

1.1. Pulmonary Manifestations of COVID-19. The respiratory system is the most common organ affected by the COVID-19. The common symptoms of the COVID-19 include fever (82–91%), cough (57–72%), dyspnea (21–45%), and sputum production (26–28%) which are usually mild [2, 3]. In severe

cases, the clinical course can progress to pneumonia with hypoxic respiratory failure and acute respiratory distress syndrome (ARDS).

There are studies which have described the patterns of lung involvement on computer tomography (CT) scan of the thorax by COVID-19. In fact, CT findings can be diagnostic of COVID-19 among patients with RT-PCR-negative patients. The common radiological abnormalities on CT scans included ground glass opacity (14–98%), consolidation (2–64%), consolidation plus GGO (19–59%), interlobular septal thickening (1–75%), reticular pattern (1–22%), crazy paving (5–36%), air bronchogram (21–80%), and bronchial wall thickening (11–23%) [4].

1.2. Incidence of Acute Respiratory Failure (ARF). Incidence of acute respiratory failure and need for mechanical ventilation varied among published studies due to different timings in the pandemic, among countries, age groups, resources, and variation in severity of disease at time of presentation [5]. Acute hypoxic respiratory failure was defined as (1) respiratory rate of 30 breaths per minute or greater; (2) oxygen saturation of 93% or less in a resting state; (3) arterial oxygen tension (Pa_{O_2})/inspiratory oxygen fraction (Fi_{O_2}) of 300 mm·Hg or less (1 mm·Hg = 0.133 kPa); or (4) need for mechanical ventilation [6]. A study from China reported that 5.0% of patients required admission in the ICU and 2.3% underwent invasive mechanical ventilation [2]. Another epidemiological study reported 25% of patients with severe or critical disease required mechanical ventilation [7]. In USA, 2.3% of hospitalized patients were admitted to ICU [8].

ARDS, the most severe for hypoxemia, is defined according to Berlin definition into mild, moderate, and severe, depending on the degree of PaO_2/FiO_2 ratio [9]. The frequency of ARDS in COVID-19 varied between studies. A retrospective analysis reported incidence of ARDS of 74.1%, whereas Lai and colleagues identified that among hospitalized patients, about 20% developed ARDS and >25% of patients required ICU admission [10, 11]. A meta-analysis of observational studies and case reports has reported an incidence of ARDS as high as 32.8% of patients during their hospital admission [12]. Another study by Tzotzos et al. and colleagues reported the weighted averages for the incidence of ARDS among published studies. They reported that among hospitalized patients, approximately 33% developed ARDS, 26% required ICU admission, 16% received invasive mechanical ventilation, and 16% died. They also reported that two-third (63%) of patients who required ICU admission received mechanical ventilation; the indication of mechanical ventilation was ARDS in 75% of patients. COVID-19-associated ARDS mortality rate was 40% and 59% among who received invasive mechanical ventilation (IMV) [13].

1.3. Pathophysiology of COVID-19 ARDS. Marini described two distinct subsets of ARDS in COVID-19 patients. "Type L" early in the process of the disease is related to interstitial rather than alveolar edema with relatively good compliance despite poor oxygenation, low elastance, lower lung weight, and low response to PEEP. That stage can progress to stage "type H" (similar to typical ARDS) with poor compliance, higher elastance, higher lung volume, and low response to PEEP. "Type L" ARDS stabilizes easily with just increasing the FiO_2 and may benefit from high flow nasal cannula or noninvasive ventilation (NIV) depending on the respiratory drive. Targeting a lower PEEP (8–10 cm H_2O) is recommended for "type L" ARDS to avoid ventilator-induced lung injury (VILI) and avoiding patient self-induced ventilator lung-induced injury (P-SILI). Larger tidal volume can be applied for "type L" (7–8 ml/kg ideal body weight). Lung protective ventilation protocol should be applied to "type H" ARDS with low tidal volume (6 ml/kg ideal body weight) and higher PEEP (<15 cm H_2O) [14].

Invasive mechanical ventilation (IMV) is essential therapeutic modality in the management of acute respiratory failure but is associated with potentially preventable complications such as atelectrauma, barotrauma, volutrauma, biotrauma, and infection [15, 16]. Use of NIV may reduce many of these complications without adversely affecting the outcomes. Currently, NIV has been recommended for the treatment of ARF due to acute exacerbation COPD, acute cardiogenic pulmonary edema, in immunocompromised patients, and de novo ARF [17]. De novo respiratory failure is defined as respiratory failure occurring without prior chronic respiratory disease with significant hypoxemia ($PaO_2/FiO_2 \leq 200$), tachypnea (respiratory rate >30–35 breaths/min), and a non-COPD diagnosis (e.g., pneumonia and/or ARDS). NIV can decrease mortality (RR 0.83, 95% CI 0.65–1.05) and the need for intubation (*RR* 0.75, 95% CI 0.63–0.89). Patients should be carefully selected, closely monitored in the ICU, and reassessed early after starting NIV for evidence of worsening respiratory failure and escalation to invasive mechanical ventilation [17].

ARF secondary to COVID-19 remains a serious cause of morbidity and mortality as we are experiencing the fourth wave of COVID-19 with mutated variant with a different infectivity. Despite significant increase in our understanding of the pathophysiology of ARDS in COVID-19, the best pharmacological and nonpharmacological therapeutic modalities for this disease are yet not known. However, the management of hypoxemia is pivotal for good outcome. As critical care resources remain scarce, NIV remains a tool that can be utilized in the treatment of ARF in COVID-19. Recent publication addressed previous concerns in regard to utilization of NIV in treatment of ARF related to COVID-19 [18–23]. However, there are still many unanswered questions. The objective of the article is to review the current literature and explore the effectiveness and safety of NIV in treatment of COVID-19-related acute hypoxic respiratory failure.

2. Methodology

The literature review was focused on the topics of NIV and treatment of ARF in COVID-19 with critical analysis of the data for exploring the strengths and weaknesses. We complete an extensive literature search to ensure a

comprehensive review of existing studies on the topic of our document. We identified new and additional research by performing targeted keyword searches (NIV, acute respiratory failure, COVID-19, and pulmonary complications of COVID-19) through PubMed and Google Scholar. We identified and selected a total of 68 peer-reviewed, scholarly sources, in particular the research topics, as our guide. For the literature review, we ensured discussion of all literature is presented in past tense.

3. Results

3.1. Application of NIV. Initially, the indications and contraindications of NIV in COVID-19 were extrapolated from the general recommendation of NIV in the management of ARF and published literature from previous pandemic (such as H1N1) [18]. The recent literature provides data related to the application of NIV which is COVID-19-related ARF [24–28]. Recommended criteria for application of NIV in selected patients are shown in Table 1.

NIV is contraindicated under certain situations in COVID-19 patients as listed in Table 2.

3.2. Modalities, Interfaces, and Settings of NIV. Noninvasive ventilation can be in the form of bilevel NIV or CPAP primarily with escalation to NIV. Among interfaces, full-face mask or helmet (preferable) is recommended but not nasal masks. Monitor for full fit of the full-face mask and any evidence of air leak. Recommended settings for NIV are given as follows:

(i) CPAP for hypoxemic respiratory failure, commencing at 10 cm H_2O pressure and an FiO_2 of 0.6, with potential to increase to 12–15 cm H_2O and FiO_2 1.0

(ii) BiPAP may be used for hypercapnic acute on chronic respiratory failure

(iii) Recommended high peep (8–12 cm H_2O) and low-pressure support in order to obtain tidal volume <9 ml/kg ideal body weight

(iv) Titrate FiO_2 to achieve target SpO_2 94–96% or 88–92% for patients with acute on chronic respiratory failure

3.3. Monitoring Response to NIV. Response to NIV should be monitored every 1–2 hours for either improvement or deterioration in the respiratory and clinical status. It is prudent to identify patients for potential failure of NIV and escalation to mechanical ventilation, without delay in endotracheal intubation. Also, the patient should be monitored for possible mask intolerance and mask malposition, with possible air leak with limitation of PEEP and decruitment leading to deterioration is gas exchange and increase in work of breathing [17, 19–23, 29–33].

The following parameters should be monitored as a standard practice:

(i) Oxygen saturation or arterial blood gas analysis

(ii) Tidal volume

(iii) Respiratory rate

(iv) Accessory respiratory muscles

(v) Hemodynamics (blood pressure, heart rate, arrhythmias)

(vi) Mental status

(vii) Gastric distension and aspiration risk

(viii) Organ failure

(ix) Noncompliance

3.4. Indications of NIV Failure. The incidence of NIV failure in moderate and severe ARDS is reported in >50% of cases, with almost 50% mortality rates [31]. Indicators of NIV failure include deterioration of clinical and respiratory status, worsening of oxygenation with increase in respiratory effort, within 1–2 hour of initiation of NIV (Table 3) [29, 34–37]. ROX index is a useful tool to guide physicians in treating patients with moderate acute respiratory failure especially in a non-ICU setting. A ROX value <5.99 was associated with an increased risk of failure ($p = 0008$ log-rank test) [38].

Factors that are associated with increased mortality with NIV are moderate and severe ARDS, simplified acute physiology score [SAPS] >37, degree of hypoxemia with PaO_2/FiO_2 ratio <150 mm·Hg, high tidal volumes (>9.2 or 9.5 mL/kg), presence of bilateral pneumonia, and progressive worsening of the chest CT scan [10, 29, 34–40].

High tidal volumes (>9.2 or 9.5 mL/kg) under NIV are associated with increased mortality related to high spontaneous respiratory drive, with high volume resulting in transpulmonary pressure variation which can lead to volutrauma and patient self-induced lung injury (P-SILI) [34–37, 41, 42].

3.5. Effectiveness of NIV. Faranone et al. assessed the effectiveness and safety of NIV in treatment of acute hypoxemic respiratory failure (AHRF) among 50 patients with COVID-19. Authors reported a success rate of 64% among who received NIV without limitation. Successful weaning from NIV was predicted by use of corticosteroids (OR 15.4, CI 1.79–132.57; $p = 0.013$) and the increase in the PaO_2/FiO_2 ratio measured 24–48 h after NIV initiation (OR 1.02, CI 1–1.03; $p = 0.015$), while it was inversely correlated with the presence of a DNI order (OR 0.03, CI 0.001–0.57; $p = 0.020$) [43]. Menzella et al. evaluated outcomes of 79 patients who required NIV for AHRF secondary to COVID-19 infection. NIV was successful in 48.1%, and 25.3% required invasive mechanical ventilation after a trial of NIV of whom 57% were discharged alive. The authors concluded that NIV can be applied safely, and invasive mechanical ventilation can be avoided in 50% of cases [44]. In another study, authors reported that heart rate, acidosis (assessed by pH), consciousness (assessed by GCS), oxygenation, and respiratory rate (HACOR) at 1 hr were independent risk factors for NIV failure. The HACOR ranged from 1 to 25, and each point increase in score was associated with odds ratio (OR) of NIV failure 1.73 (95% CI 1.58–1.95) [39].

Table 1: Criteria for application of NIV in selected patients.

(1) Clinical criteria:
(i) Moderate to severe dyspnea with signs of respiratory effort and use of accessory muscles or paradoxical abdominal movement (increase work of breathing) or staccato speech.
(ii) Tachypnea over 30 bpm.
(iii) No multi-organ failure (APACHE<20)
(iv) Known patient history of OSA, COPD, congestive heart failure, or cardiogenic pulmonary edema and neuromuscular disorders with acute or exacerbated hypercapnic respiratory failure.
(v) Availability of an expert team and continuous monitoring.
(vi) Early intubation (within the hour) if there is no improvement.
(vii) Patients with do-not-intubate status.
(viii) Postextubation phase of ARDS.
(2) Blood gas criteria:
(i) Need for FiO_2 greater than 0.4 to achieve an SpO_2 of at least 92%, or SpO_2 <94%, $RR > 20$ with poor response to oxygen 10–15 l/min.
(ii) Acute hypercapnic respiratory failure (pH < 7.35 with $PaCO_2 > 45$ mm·hg).
(iii) $PaO_2/FiO_2 > 150$ but <300, or $SpO_2 < 90$–94% on non-rebreather.

Table 2: Contraindications for NIV in COVID patients.

Indication for invasive mechanical ventilation
Limited personnel experience with HFNC/NIV
Lack of capability of monitoring
Lack of infectious control and control of aerosolized transmission
Hemodynamic instability and cardiac arrhythmias
Multiple organ failure
Abnormal mental status or encephalopathy
Over-ventilation and "patient-induced lung injury" (PILI)
Cardiopulmonary arrest
Uncooperative patients
Inability to protect airways
Anatomical and/or subjective difficulties gaining access to the airway
Gastrointestinal bleeding, ileus, or risk for aspiration
Severe hypoxemia or acidosis (pH < 7.1)
Excessive secretions
Recent upper airway or upper gastrointestinal surgery
Severe hypoxemia on admission defined as $PaO_2/FiO_2 < 150$
Pneumothorax, pleural effusion, or pulmonary embolism
Recent facial trauma or facial surgery
SOFA score >5 is predictive of NIV failure
CXR/CT showing evidence of bilateral, multi-lobar involvement

Table 3: Indicators of NIV failure.

Simplified acute physiology score [SAPS] >37
High APACHE score
PaO_2/FiO_2 ratio <150 mm·Hg
High tidal volumes (>9.2 or 9.5 mL/kg)
Respiratory rate >30/min
HACOR score >5 [34]
Acute respiratory acidosis with rise in $PaCO_2$
ROX index <3 at 2 hours

NIV (CPAP) has been compared with high flow oxygen by nasal cannula (HFNC) and conventional oxygen for management of AHRF due to COVID-19 [45]. The study reported a significant reduction in the need for mechanical ventilation among patients managed with CPAP. Escalation to invasive mechanical ventilation was significantly lower with CPAP (36.3%) vs. conventional oxygen therapy (44.4%) (absolute difference, −8% [95% CI, −15% to −1%]; $p = 0.03$). ICU admission was less in the CPAP group compared with the conventional oxygen therapy group (55.4% vs. 62.9%, respectively: absolute difference, −7% [95% CI, −15% to −3%]). CPAP, compared to conventional oxygen therapy, was associated with more frequent adverse events in 34.2% vs. 13.9%, respectively [45].

Helmet noninvasive respiratory support has been suggested as alternative to avoid droplet dispersion and healthcare worker contamination. The benefit of CPAP application by means of helmet can improve patient comfort level and increase tolerability. The CO_2 rebreathing is of concern and depends on two factors: the fresh gas passing through the helmet and the amount of CO_2 produced by the patient. The recommendation is to initiate CPAP at 5 cm H_2O and to titrate according to blood gas analysis and respiratory mechanics. PEEP should not exceed 12–13 cm H_2O in order to avoid VAE and effect on hemodynamic due to increase in intrathoracic pressure. Weaning from the helmet should be initiated by incremental decrease in PEEP while maintaining PO_2/FiO_2 ratio with FiO_2 not higher than 50%. A proposed algorithm for the management of helmet CPAP in ARF was recently published [26].

A recent review on mortality and clinical outcomes of patient with COVID-19 pneumonia treated with NIV concluded that CPAP and NIV appeared equally and frequently applied in patients with COVID-19 pneumonia but associated with higher mortality. Utilization rate of CPAP and NIV was 48.4% and 46%, respectively. Noninvasive respiratory support was unsuccessful in 47.7%, of which 26.5% were intubated with 40.9% mortality. NIV was associated with a higher in-hospital mortality compared to CPAP (35.1% vs. 22.2%). The indications for endotracheal intubation and invasive mechanical ventilation were decreased level of consciousness, exhaustion, refractory hypoxemia, sepsis, and hemodynamic instability [46].

Factors that are associated with increased mortality with NIV are moderate and severe ARDS, simplified acute physiology score [SAPS] >37, degree of hypoxemia with PaO_2/FiO_2 ratio <150 mm·Hg, high tidal volumes (>9.2 or 9.5 mL/kg), presence of bilateral pneumonia, and progressive worsening of the chest CT scan [10, 29, 34–37, 41, 42]. Reported total mortality rate ranged between 24.6% and 25.3% [45, 47]. Chacko et al. reported overall mortality in

patients who required NIV was 30.1%. On adjusted analysis, mortality was associated with older age (OR, 1.08; 95% CI, 1.04 to 1.12), severe ARDS (OR, 4.04; 95% CI, 1.08 to 15.1), and higher peak D-dimer level (OR, 2.75; 95% CI, 1.19 to 6.37), requirement for intubation (OR, 9.36; 95% CI, 3.38 to 25.94), and need for inotropes and/or dialysis (OR, 9.19; 95% CI, 2.83 to 29.9) (3.1%) [48].

3.6. Alternatives to NIV. HFNC can be utilized safely in acute hypoxic respiratory failure associated with severe COVID-19 pneumonia. A prospective study from two tertiary care hospitals evaluated the incidence of successful weaning from HFNC as a primary outcome; in addition, study reported the incidence of failure and need for escalation and endotracheal intubation, and overall mortality. Study showed that HFNC was successful in 47% and 93% of patients who were discharged home. Predictors of success of HFNC, at the time of application, were higher oxygen saturation, lower respiratory rate, lower oxygen requirement within 6 hours of HFNC, higher ROX-6 and mROX-6 score, and no steroid usage. The authors concluded that HFC was feasible in the treatment of AHRF associated with severe COVID-19 pneumonia, but mortality was high in patients who failed HFNC trial [49].

HFNC can improve dyspnea scores in patients with AHRF and be applied in non-ICU areas [50–52]. In a prospective randomized trial, HFNC was compared to conventional oxygen therapy (COT) in the treatment of hypoxic respiratory failure. HFNC significantly improved dyspnea (2.0 ± 1.8 vs. 3.8 ± 2.3, $p = 0.01$) compared with COT. The HFNC decreased the respiratory frequency within 5 minutes of its application. Roca et al. reported improvement in dyspnea ($p = 0.001$) and overall comfort ($p < 0.001$) with HFNC compared to conventional face mask 50 [51]. HFNC can be utilized during breaks from NIV with significantly lower dyspnea scores compared to standard oxygen therapy [53]. HFNC may be an alternative method for palliative patients with hypoxic respiratory failure and do-not-intubate status in improving dyspnea within the first hour of treatment [54].

3.7. Healthcare Worker Risks and Environmental Protections. Safety of the delivery of the ventilatory support is one major concern for healthcare worker regarding bio-aerosolization and nosocomial SARS-CoV-2 transmission. Menzella and Avdeev et al. reported low risk of healthcare worker contracting COVID-19 infection (1.6%) [44, 55].

Invasive ventilation and helmet ventilation with a PEEP valve were found to be associated with the lowest bacteriophage concentrations in the air, and HFNO and nasal prongs were associated with the highest concentrations in the environment [56]. In another study performed on healthy subjects, neither humidified HFNC nor NIV increased aerosol generation from the respiratory tract measured in a negative pressure room. Aerosol generation is influenced more by breathing pattern and coughing [57]. Personal protective equipment and environmental control (negative pressure rooms) should be the initial concern and consideration when managing patients with COVID-19. There should be emphasis on adherence with infection control protocols among healthcare workers to decrease the incidence of infection [47].

3.8. Application of NIV outside of ICU Settings. There was an increase in the utilization of NIV outside the ICU area due to lack of ICU resources and bed availability. Nava reported feasibility of out-of-ICU noninvasive respiratory support in the treatment of patients with COVID-19 pneumonia and favorable outcomes. Majority of patients were treated with CPAP. The 30-day unadjusted mortality was 30% for both CPAP and NIV. Incidence of endotracheal intubation for CPAP and NIV was 25% and 28%, respectively. Mortality was related to age and comorbidities but not to noninvasive respiratory support after adjustment for cofounders. There was 11.4% incidence of healthcare workers tested positive for infection [58].

In a prospective single-day observational study from 31 hospitals in Lombardy, Italy, 10% of patients received NIV outside the ICU, and 68% were treated with CPAP delivered by helmet. Failure rate was 37.6%; on the contrary, 62.4% patients were discharged alive without need for intubation. In-hospital mortality was 25% [59].

NIV can be applied on regular wards as a viable ceiling treatment option in patients with underlying severe comorbidities, such as CAD and hematological diseases, with acute hypoxic respiratory failure secondary to severe COVID-19 pneumonia. Reported survival rate was 29%. Worsening hemodynamic and vital signs within 48 hours of initiating NIV were poor indicators [60].

4. Discussion

Around 5% of COVID-19 patients develop a critical form of the disease with AHRF necessitating ICU admission, and delaying intubation may prove fatal among these patients. Adding to the controversy, early intubation, and mechanical ventilation, within 2 days of ICU admission, for patients with COVID-19 with AHRF was associated with increased 60-day mortality as compared to initial use of noninvasive oxygen support [42.7% versus 21.9% ($p < 0.01$)]. In addition, delayed intubation group (intubation after the first 2 days after ICU admission) had a similar outcome to those in the early IMV group, with a 60-day mortality of 42.2% and 42.7%, respectively. Patients without any IMV intervention had the highest survival rate with 60-day mortality of 10.8% [61].

Data for the Lombardy region in Italy support the above data. Patients who subsequently intubated after a trial of unsuccessful NIV had a significantly lower chance of survival compared with the patients who continued NIV and did not require IMV (HR, 1.69; 95% CI, 1.43–1.98; $p < 0.001$). The mortality of the patients who undergone subsequent intubation was similar to the group of patients who were treated with IMV at the time on admission to ICU (HR for IMV vs. NIV failure, 1.20; 95% CI, 0.95–1.53; $p = 0.12$). The mortality rate and mortality rate per 1000 patient-days were lower in the NIV group compared to IMV group [62].

Data from the interim analysis of the international, multicenter HOPE COVID-19 registry concluded that NIV can be a feasible alternative to IMV especially when ICU resources are limited. NIV was indicated in 20% of their study population. NIV was successful in 50% of cases. In-hospital death was 37.7%, while 15.9% of patients needed invasive ventilation and were associated with high rate of in-hospital death. Those requiring invasive ventilation had the lowest survival rate (41.9%). Both NIV and IMV groups were associated with an increased risk of mortality (HR 1.26, 95% CI 1.04 to 1.53 and HR 1.91, 95% CI 1.45 to 2.53, respectively). The population treated with IMV at any point had increased mortality risk compared to those who only received NIV (HR 1.52, 95% CI 1.11 to 2.06, $p = 0.008$). 37.7%) [63].

Recommendations and consensus statements by medical societies (NIH, Australian and New Zealand Intensive Care Society, WHO, Surviving Sepsis Guidelines SCCM, and Austrian Society of Pneumatology) [20–23, 31] regarding NIV in management of ARF have been published based on published studies with variability of level of evidence, absence of randomization, and a different methodology. Most observational studies suggested that NIV can be utilized with caution in selected patients with ARF, in particular mild ARDS, and to be treated under close observation and readiness to escalate to IMV. NIV could be utilized to avoid intubation or re-intubation postextubation. Ideally, NIV should be applied in negative pressure rooms with minimum six air exchanges per hour or 12 as recommended by WHO, or in a single occupancy neutral pressure room (if negative pressure room is unavailable) with proper adherence to wearing personal protective equipment (PPE) [18–23, 29–33].

Different medical societies were cautious in their recommendations for high flow nasal cannula (HFNC) and noninvasive mechanical ventilation (NIV) in the management of acute respiratory failure related to COVID-19, especially, in the absence of indication for endotracheal intubation and mechanical ventilation. The concern is delaying endotracheal intubation and increasing mortality. Data from non-COVID-19 trials showed reduction in the requirement of invasive mechanical ventilation when HFNC or NIV, compared to conventional oxygen therapy, was utilized with decrease in the endotracheal intubation rates and escalation of respiratory support [64, 65]. NIH recommended HFNC oxygen over NIV; NIV is recommended only in controlled setting when HFNC is unavailable. Panel also recommended the close monitoring of patients for worsening of the respiratory failure and avoiding delay intubation [66].

Several factors contribute to failure of NIV such as type of interface, ventilatory modality (i.e., continuous positive airway pressure (CPAP) vs. bilevel), and lower or higher positive pressures, and pathophysiological characteristics of COVID-19-related interstitial pneumonia and ARDS [14, 67].

NIV is an option for respiratory management of COVID-19-related acute hypoxic respiratory failure. Proper selection of patients, application of proper setting with fitting of face mask or helmet in proper setting, close monitoring for elements of worsening of respiratory status, and readiness for escalation of care are essential in the management of those patients.

5. Conclusion

NIV is feasible in the treatment of AHRF secondary to COVID-19 infection both in the ICU and out-of-ICU setting. NIV is expected to improve oxygenation and decrease the work of breathing. It can reduce the need for mechanical ventilation and complications associated with it. Helmet noninvasive respiratory support is as alternative to oronasal/full-face mask during NIV. Close monitoring and early identification of NIV failure are key to avoid delayed intubation-associated mortality. Well-designed studies are needed to find the best protocol, including initial settings and weaning, and interface to be used. Also, further studies are required to define the exact role of NIV, especially when it is compared with HFNC.

Data Availability

The review article data were obtained from PubMed.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] K. Dhama, S. Khan, R. Tiwari et al., "Coronavirus disease 2019-COVID-19," *Clinical Microbiology Reviews*, vol. 33, October, 2020 4.

[2] W. J. Guan, Z. Y. Ni, Y. Hu et al., "For the China medical treatment expert group for COVID-19 Clinical characteristics of coronavirus disease," *New England Journal of Medicine*, vol. 382, pp. 1708–1720, 2019.

[3] K. D. Johnson, C. Harris, J. K. Cain et al., "Pulmonary and extra-pulmonary clinical manifestations of COVID-19," *Frontiers of Medicine*, vol. 7, p. 526, 2020.

[4] Z. Ye, Y. Zhang, Y. Wang, and B. Song, "Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a practical review," *European Radiology*, vol. 30, no. 8, pp. 4381–4389, 2020 Aug.

[5] P. Manifestations, "COVID-19 real-time learning network," 2020, https://www.idsociety.org.

[6] National Health Commission of the People's Republic of China, "Diagnosis and treatment protocols of pneumonia caused by a novel coronavirus (trial version 5)," 2020, https://www.nhc.gov.cn/yzygj/s7653p/202002/3b09b894ac9b4204a79db5b8912d4440.shtml.

[7] Z. Wu and J. M. McGoogan, "Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China," *JAMA*, vol. 323, no. 13, pp. 1239–1242, 2020.

[8] E. K. Stokes, L. D. Zambrano, K. N. Anderson et al., "Coronavirus disease 2019 case surveillance—United States," *Morbidity and Mortality Weekly Report*, vol. 69, no. 24, pp. 759–765, 2020.

[9] ARDS Definition Task Force, G. D. Rubenfeld, B. T. Thompson et al., "Acute respiratory distress syndrome:

the Berlin Definition," *JAMA*, vol. 307, no. 23, pp. 2526–2533, 2012.

[10] Y. Du, L. Tu, P. Zhu et al., "Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study," *American Journal of Respiratory and Critical Care Medicine*, vol. 201, no. 11, pp. 1372–1379, 2020.

[11] C. C. Lai, T. P. Shih, W. C. Ko, H. J. Tang, and P. R. Hsueh, "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges," *International Journal of Antimicrobial Agents*, vol. 55, no. 3, Article ID 105924, 2020.

[12] A. J. Rodriguez-Morales, J. A. Cardona-Ospina, E. Gutierrez-Ocampo et al., "Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis," *Travel Medicine and Infectious Disease*, vol. 34, Article ID 101623, 2020.

[13] S. J. Tzotzos, B. Fischer, H. Fischer, and M. Zeitlinger, B. Fischer and H. Fischer, Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey," *Critical Care*, vol. 24, no. 1, p. 516, 2020.

[14] J. J. Marini and L. Gattinoni, "Management of COVID-19 respiratory distress," *JAMA*, vol. 323, no. 22, pp. 2329-2330, 2020.

[15] A. S. Slutsky and V. M. Ranieri, "Ventilator-induced lung injury," *New England Journal of Medicine*, vol. 369, no. 22, pp. 2126–2136, 2013.

[16] S. S. Magill, B. Rhodes, and M. Klompas, "Improving ventilator-associated event surveillance in the national healthcare safety network and addressing knowledge gaps: update and review," *Current Opinion in Infectious Diseases*, vol. 27, no. 4, pp. 394–400, 2014 Aug.

[17] B. Rochwerg, L. Brochard, M. W. Elliott et al., "Official ERS/ATS clinical practice guidelines: non-invasive ventilation for acute respiratory failure," *European Respiratory Journal*, vol. 50, no. 2, Article ID 1602426, 2017 Aug.

[18] C. Cinesi Gómez, Ó Peñuelas Rodríguez, M. Lujan Torne et al., "Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to SARS-CoV-2 infection," *Medicina Intensiva*, vol. 44, no. 7, pp. 429–438, 2020 Oct.

[19] J. Phua, L. Weng, L. Ling et al., "Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations," *Lancet Respiratory Medicine*, vol. 8, no. 5, pp. 506–517, 2020 May.

[20] NHS, "Guidance for the role and use of non-invasive respiratory support in adult patients with COVID-19 (confirmed or suspected)," 2020, https://www.eng-land.nhs.uk/coronavirus/wp-content/up-loads/sites/52/2020/03/CLEARED_Special-ty-guide_-NIV-respiratory-support-and-coronavirus-v2-26-March-003.pdf.

[21] "Australian and New Zealand intensive care society," *ANZICS COVID-19 Guidelines Version 1*, ANZICS, Melbourne, Australia, 2020.

[22] WHO, *Clinical Management of Severe Acute Respiratory Infection (SARI) When COVID-19 Disease is Suspected: Interim Guidance V1.2*, World Health Organisation, Geneva, Switzerland, 2020.

[23] W. Alhazzani, M. H. Møller, Y. M. Arabi et al., "Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19)," *Intensive Care Medicine*, vol. 46, no. 5, pp. 854–887, 2020.

[24] S. Raoof, S. Nava, C. Carpati, and N. S. Hill, "High-flow, non-invasive ventilation and awake (nonintubation) proning in patients with coronavirus disease 2019 with respiratory failure," *Chest*, vol. 158, no. 5, pp. 1992–2002, 2020.

[25] S. Piva, M. Filippini, F. Turla et al., "Clinical presentation, and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia Italy," *Journal of Critical Care*, vol. 58, pp. 29–33, 2020.

[26] D. Radovanovic, M. Rizzi, S. Pini, M. Saad, D. A. Chiumello, and P. Santus, "Helmet CPAP to treat acute hypoxemic respiratory failure in patients with COVID-19: a management strategy proposal," *Journal of Clinical Medicine*, vol. 9, no. 4, p. 1191, 2020.

[27] S. Gupta, S. Ramasubban, S. Dixit et al., "ISCCM guidelines for the use of non-invasive ventilation in acute respiratory failure in adult ICUs," *Indian Journal of Critical Care Medicine*, vol. 24, no. S1, pp. S61–S81, 2020.

[28] J. R. Masclans, M. Perez, J. Almirall et al., "Early non-invasive ventilation treatment for severe influenza pneumonia," *Clinical Microbiology and Infections*, vol. 19, no. 3, pp. 249–256, 2013.

[29] M. Pfeifer, S. Ewig, T. Voshaar et al., "Position paper for the state-of-the-art application of respiratory support in patients with COVID-19," *Respiration*, vol. 99, no. 6, pp. 521–542, 2020.

[30] S. A. Harari, M. Vitacca, F. Blasi et al., "Managing the respiratory care of patients with COVID-19," *Italian Thoracic Society-Associazione Italiana Pneumologi Ospedal-ieri-Societa Italiana Di Pneumologia*, 2020, http://www.aiponet.it.

[31] H. Flick, B. M. Arns, J. Bolitschek et al., "Management of patients with SARS-CoV-2 infections and of patients with chronic lung diseases during the COVID-19 pandemic (as of 9 May 2020). Statement of the Austrian society of pneumology (ASP)," *Wiener Klinische Wochenschrift*, vol. 132, no. 13-14, pp. 365–386, 2020.

[32] B. Schonhofer, R. Kuhlen, P. Neumann, M. Westhoff, C. Berndt, and H. S. Schon, "Non-invasive mechanical ventilation as treatment of acute respiratory failure," *Deutsches Ärzteblatt International*, vol. 105, no. 24, pp. 424–433, 2008 Jun.

[33] S. Nava and N. Hill, "Non-invasive ventilation in acute respiratory failure," *The Lancet*, vol. 374, no. 9685, pp. 250–259, 2009.

[34] G. Bellani, J. G. Laffey, T. Pham et al., "Non-Invasive ventilation of patients with acute respiratory distress syndrome. Insights from the lung safe study," *American Journal of Respiratory and Critical Care Medicine*, vol. 195, no. 1, pp. 67–77, 2017 Jan.

[35] J. P. Frat, S. Ragot, R. Coudroy et al., "Predictors of intubation in patients with acute hypoxemic respiratory failure treated with a non-invasive oxygenation strategy," *Critical Care Medicine*, vol. 46, no. 2, pp. 208–215, 2018 Feb.

[36] J. P. Frat, A. W. Thille, A. Mercat et al., "High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure," *New England Journal of Medicine*, vol. 372, no. 23, pp. 2185–2196, 2015 Jun.

[37] G. Carteaux, T. Millán-Guilarte, N. De Prost et al., "Failure of non-invasive ventilation for *de novo* acute hypoxemic respiratory failure: role of tidal volume," *Critical Care Medicine*, vol. 44, no. 2, pp. 282–290, 2016 Feb.

[38] M. L. Vega, R. Dongilli, G. Olaizola et al., "COVID-19 pneumonia and ROX index: time to set a new threshold for patients admitted outside the ICU," *Pulmonology*, vol. 28, no. 1, pp. 13–17, 2022.

[39] J. Duan, X. Han, L. Bai, L. Zhou, and S. Huang, "Assessment of heart rate, acidosis, conscious-ness, oxygenation, and respiratory rate to predict non-invasive ventilation failure in hypoxemic patients," *Intensive Care Medicine*, vol. 43, no. 2, pp. 192–199, 2017 Feb.

[40] H. Shi, X. Han, N. Jiang et al., "Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study," *The Lancet Infectious Diseases*, vol. 20, no. 4, pp. 425–434, 2020 Apr.

[41] L. Gattinoni, S. Coppola, M. Cressoni, M. Busana, S. Rossi, and D. Chiumello, "COVID-19 does not lead to a "typical" acute respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 201, no. 10, pp. 1299-1300, 2020 May.

[42] L. Brochard, A. Slutsky, and A. Pesenti, "Mechanical ventilation to minimize progression of lung injury in acute respiratory failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 195, no. 4, pp. 438–442, 2017 Feb.

[43] A. Faraone, A. Faraone, C. Beltrame et al., "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," *Internal and Emergency Medicine*, vol. 16, no. 5, pp. 1183–1190, 2020 Nov 22.

[44] F. Menzella, C. Barbieri, M. Fontana et al., "Effectiveness of non-invasive ventilation in COVID-19 related-acute respiratory distress syndrome," *Clinical Research J*, vol. 15, no. 7, pp. 779–787, 2021 Mar 23.

[45] G. D. Perkins, C. Ji, B. A. Connolly et al., "Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19 the RECOVERY-RS randomized clinical trial," *JAMA*, vol. 327, no. 6, pp. 546–558, 2022.

[46] D. Radovanovic, S. Coppola, E. Franceschi et al., "Mortality and clinical outcomes in patients with COVID-19 pneumonia treated with non-invasive respiratory support: a rapid review," *Journal of Critical Care*, vol. 65, pp. 1–8, 2021.

[47] J. C. Winck and N. Ambrosino, "COVID-19 pandemic and non-invasive respiratory management: every goliath needs a David. An evidence-based evaluation of problems," *Pulmonology*, vol. 26, no. 4, pp. 213–220, 2020.

[48] B. Chacko, T. L. Lovely, J. P. Peter et al., "Noninvasive ventilation in the management of respiratory failure due to COVID-19 infection: experience from a resource-limited setting," *Mayo Clinic Proceedings*, vol. 97, no. 1, pp. 35–45, Article ID 100570, 2022.

[49] G. L. Calligaro, U. Lalla, G. Audley et al., "The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study," *EClinicalMedicine*, vol. 28, Article ID 100570, 2020.

[50] N. Rittayamai, J. Tscheikuna, N. Praphruetkit, and S. Kijpinyochai, "Use of high flow nasal canula for acute dyspnea and hypoxemia in the emergency department," *Respiratory Care*, vol. 60, no. 10, pp. 1377–1382, 2015.

[51] O. Roca, J. Riera, F. Torres, and J. R. Masclans, "High-flow oxygen therapy in acute respiratory failure," *Respiratory Care*, vol. 55, no. 4, pp. 408–413, 2010.

[52] N. Rittayamai, J. Tscheikuna, and P. Rujiwit, "High-flow nasal cannula versus conventional oxygen therapy after endotracheal extubation: a randomized crossover physiologic study," *Respiratory Care*, vol. 59, no. 4, pp. 485–490, 2014.

[53] G. Spoletini, C. Mega, L. Pisani et al., "High-flow nasal therapy vs. standard oxygen during breaks off non-invasive ventilation for acute respiratory failure: a pilot randomized controlled trial," *Journal of Critical Care*, vol. 48, pp. 418–425, 2018 Dec.

[54] O. Ruangsomboon, T. Dorongthom, T. Chakorn et al., "High-flow nasal cannula versus conventional oxygen therapy in relieving dyspnea in emergency palliative patients with do-not-intubate status: a randomized crossover study," *Annals of Emergency Medicine*, vol. 75, no. 5, pp. 615–626, 2020.

[55] S. N. Avdeev, A. I. Yaroshetskiy, N. A. Tsareva et al., "Non-Invasive ventilation for acute hypoxemic respiratory failure in patients with COVID-19," *The American Journal of Emergency Medicine*, vol. 39, pp. 154–157, 2021 Jan.

[56] H. Avari, R. J. Hiebert, A. A. Ryzynski et al., "Quantitative assessment of viral dispersion associated with respiratory support devices in a simulated critical care environment," *American Journal of Respiratory and Critical Care Medicine*, vol. 203, no. 9, pp. 1112–1118, May 1, 2021.

[57] N. T. Gaeckle, J. Lee, Y. Park, G. Kreykes, M. D. Evans, and C. J. Hogan, "Aerosol generation from the respiratory tract with various modes of oxygen delivery," *American Journal of Respiratory and Critical Care Medicine*, vol. 202, no. 8, pp. 1115–1124, Oct 15, 2020.

[58] C. Franco, N. Facciolongo, R. Tonelli et al., "Feasibility and clinical impact of out-of-ICU non-invasive respiratory support in patients with COVID-19 related pneumonia," *European Respiratory Journal*, vol. 56, no. 5, Article ID 2002130, 2020.

[59] G. Bellani, G. Grasselli, M. Cecconi et al., "Non-invasive ventilatory support of patients with COVID-19 outside the intensive care units (WARd-COVID)," *Annals of the American Thoracic Society*, vol. 18, pp. 1020–1026, June 2021.

[60] G. A. Ramirez, E. P. Bozzolo, A. Gobbi et al., "Outcomes of non-invasive ventilation as the ceiling of treatment in patients with COVID-19," *Panminerva Medical*, 2021 Apr 16.

[61] C. Dupuis, L. Bouadma, E. de Montmollin et al., "Association between early invasive mechanical ventilation and day-60 mortality in acute hypoxemic respiratory failure related to coronavirus disease-2019 pneumonia," *Critical Care Explorations*, vol. 3, Article ID e0329, January 2021.

[62] G. Grasselli, M. Greco, A. Zanella et al., "Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy," *JAMA Internal Medicine*, vol. 180, no. 10, pp. 1345–1355, 2020.

[63] M. Bertaina, I. J. Nuñez-Gil, L. Franchin et al., "Non-invasive ventilation for SARS-CoV-2 acute respiratory failure: a subanalysis from the hope COVID-19 registry," *Emergency Medicine Journal*, vol. 38, no. 5, pp. 359–365, 2021.

[64] X. P. Xu, X. C. Zhang, S. L. Hu et al., "Non-Invasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis," *Critical Care Medicine*, vol. 45, no. 7, pp. e727–e733, 2017.

[65] H. Zhao, H. Wang, F. Sun, S. Lyu, and Y. An, "High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to non-invasive mechanical ventilation on intubation rate: a systematic review and meta-analysis," *Critical Care*, vol. 21, no. 1, p. 184, 2017.

[66] Coronavirus Disease, "(COVID-19)-Treatment guidelines," 2019, https://www.COVID19treatmentguidelines.nih.gov/.

[67] J. R. Beitler, R. L. Owens, and A. Malhotra, "Unmasking a role for non-invasive ventilation in early acute respiratory distress syndrome," *JAMA*, vol. 315, no. 22, pp. 2401–2403, 2016.

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Research Article

Intermittent Abdominal Pressure Ventilation: An Alternative for Respiratory Support

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Intermittent abdominal pressure ventilation is a positive pressure ventilation technique that works with abdominal compressions. It has been known since 1938; however, for many years, it was out of production. In recent years, a new device has been produced that has captured the attention to this old respiratory support technique. We considered eight patients with respiratory failure secondary to a neuromuscular disease (congenital myopathy, Duchenne dystrophy, and amyotrophic lateral sclerosis) intolerant to daytime noninvasive ventilation (NIV). IAPV was proposed as an alternative to NIV. We performed baseline and post-IAPV respiratory function assessment. All patients, two years later, are still using intermittent abdominal ventilation. Intermittent positive abdominal mechanical ventilation can be a valid alternative to noninvasive mechanical ventilation with a nasal or face mask. It improves gas exchange, symptoms, and quality of life, decreases the incidence of pneumonia, and can avert the need for intubation and tracheotomy.

1. Background

We are used to thinking of noninvasive mechanical ventilation as positive pressure ventilation using a nasal or face mask. This type of interface interferes with the patient's quality of life who has to start using NIV, and often, the patient rejects it. Intermittent abdominal pressure ventilation is a positive pressure ventilation technique that works with abdominal compressions. It is a system of noninvasive respiratory care known since 1938 [1], individually modified to the cure of postdiphtheritic respiratory paralysis or respiratory paralysis due to anterior poliomyelitis [2]. In 1987, a marginal approach to NIV with IAPV was described in patients with spinal cord injury [3].

In 1988, Miller et al. described a rehabilitative practice in high quadriplegic patients with tracheostomy about speech capability and safe respiratory management with an optimal patient tolerance of treatment [4]. Later, in 1991, Bach described long-term use of IAPV in patients diagnosed with different neuromuscular diseases (myopathy, Duchenne dystrophy, and spinal cord injury). In this paper, only 54 out of 209 initially undergoing the trial were long-term adapted to IAPV [2].

IAPV facilitates diaphragmatic motion and may be particularly useful in patients with bilateral diaphragmatic weakness or paralysis and permits plugging of the tracheostomy tube with cuff deflation for several hours during the day, with the prevention of tracheal damage. However, it was out of production for many years, until 1990. It led to a loss of knowledge of the method, and only in recent years, some centres have begun to have an interest in this old, renewed technology again. The device available today is the LunaBelt (Dima Italia Inc., Bologna, Italy); it is a transportable ventilator.

Along with the PBAir™ corset, it is easy to utilize the intermittent abdominal pressure ventilation (IAPV) device. The LunaBelt is a portable ventilator explicitly designed to operate the IAPV through dedicated software and a new abdominal interface called PBAir®. Recently, case reports have been published on its use in patients with late-onset Pompe disease, postischemic cervical myelopathy, and ALS [5–7]. IAPV has been reported to facilitate good mechanical ventilation adaptation with an efficient ventilation pattern and good peripheral oxygenation. We describe the use of IAPV in our respiratory pathophysiology unit.

2. Materials and Methods

We evaluated 8 patients (Pt) diagnosed with neuromuscular disease who presented with ventilatory insufficiency with dyspnea and reduced tidal volume on spirometry and with an indication for NIV. One congenital myopathy patient (Pt 1, female, 32 ys), two Duchenne muscular dystrophy patients (Pt 2, 3, males, 22 and 20 ys), and two ALS patients (Pt 4, 5, males, 62 and 63 ys) had previously refused noninvasive mechanical ventilation due to claustrophobia, interface intolerance, and emotional and psychological factors. Pt 2, affected by Duchenne muscular dystrophy, also complained of gastric and colonic distension. Two patients with ALS (Pt 6, 7, males, 68 and 25 ys) and one patient with Duchenne muscular dystrophy (Pt 8, male, 19 ys) were treated with noninvasive mechanical ventilation with a nasal mask, with poor compliance of gastric hyperdistention and severe skin decubitus (Table 1). All patients agreed to carry out a trial with IAPV with LunaBelt (Dima Italia Inc., Bologna, Italy). The LunaBelt has internal battery power that can also, eventually, be used for noninvasive respiratory support for sleep. It provides a dedicated IAPV mode. The IAPV corset is lightweight, comfortable, and fitted with Velcro fasteners (Figure 1). Like earlier IAPV, cyclical inflation of a rubber bladder inside the corset pushes the diaphragm upwards to eject air from the residual volume. It allows air to enter the lungs via the upper airway as gravity moved the diaphragm back to its resting position [8, 9]. We set the following IAPV parameters: pressure (pressure inside the bladder), inspiratory time (an adequate inspiratory time when the diaphragm returns), frequency (respiratory rate), and rise time (time to pump up the bladder). The parameters were adjusted for each patient (Table 2).

A functional respiratory assessment (tidal volume measurement, peak expiratory flow, and oxygen saturation) was performed during spontaneous breathing and using the IAPV. Inspiratory volume, expiratory volume, and peak expiratory flow were evaluated. Tidal volume was assessed in the inspiratory phase (the diaphragm's prevalent muscular activity) and the expiratory phase (elastic return of the lung and chest wall compliance). A day hospital training session was carried out before use at home.

3. Results

All patients performed the baseline assessment and tolerated the IAPV treatment. Pt 1 (congenital myopathy), Pt 2 and 3 (Duchenne patients), and two ALS patients (Pt 4 and 5) had previously refused NIV, while they tolerated and adapted well to IAPV. Pt 6 presented with deep nasal, frontal, and retronucal pressure sores, which interfered with the use of NIV; he therefore enthusiastically accepted IAPV. Pt 2, 7, and 8 presented with aerophagia and gastric overdistension. IAPV, thanks to abdominal compressions, allowed us to counteract the air retention that occurred during noninvasive positive pressure ventilation that Pt 7 and 8 used at night. The mean spontaneous tidal volume at baseline was 316.375 ± 146.80 mL, increased to 678 ± 334 mL using the IAPV. The tidal volume was doubled for all patients during IAPV use. The parameters for each patient are shown in Table 1. Peak expiratory flow measured in baseline conditions was 29.5 ± 10.9 mL. During IAPV, the average peak flow was 54 ± 18.04 mL. Pt 4, 5, 6, 7, and 8 performed air staking during IAPV use. All patients are still using IAPV after three years. Three patients (Pt 1, 2, and 3) rely on the IAPV as their sole method of ventilatory support 24 hours a day. The IAPV, as the only respiratory support, became ineffective for two patients (Pt 4 and 5) after 2 years of use, and these patients then switched to daytime IAPV and nocturnal positive pressure ventilation with a nasal mask due to the appearance of obstructive sleep apnea syndrome. Pt 6, 7, and 8 associated IPAV with nocturnal noninvasive mechanical ventilation with a nasal (Pt 8) or facial (Pt 6 and 7) mask, which they already used (Figures 2 and 3).

4. Discussion

We know that the lungs dilate, thanks to the expansion of the thoracic cavity that is realized by two mechanisms: the contraction of the internal intercostal muscles, which raise the ribs and widen the chest (rib or thoracic breathing) and the contraction of the diaphragm, which expands downwards (abdominal or diaphragmatic breathing) [10]. When the diaphragm is weak, a manual or mechanical thrust to the abdominal wall can force the diaphragm upward to expel air below the patient's average resting lung volume or functional residual capacity. Tidal volume improves through several mechanisms: it increases the chest wall elastance because the elastic recoil pressure of the chest wall is negative at this lower lung volume; inspiration takes this increased elastic energy and improves tidal volumes. Also, enhanced length-contraction characteristics of the diaphragm can enhance the force of diaphragmatic contraction. In addition to this, gravity augments both. The patient can further increase tidal volumes and add to ventilator-derived intermittent abdominal pressure ventilation through the respiratory muscles' voluntary activity or by glossopharyngeal breathing.

The LunaBelt device is simple to use, and the corset is quick to put on. It helps to carry out a training period for family members, as for all devices, with particular attention to patients who will have to use noninvasive mechanical ventilation with the mask. The IAPV only operates effectively when the subject is in the sitting posture [2, 5] at an angle of 30° or more and is ideal at 75° [11] because the increase in lung volume is generated by gravity. For severely obese patients or patients with severe chest wall deformity, it

Table 1: Patient's characteristics and slow vital capacity (SVC) at baseline and during IAPV.

Disease	Gender	Age	SVC (ml)	Basal RR	NIV adherence	Pbelt, Ti, FR (cm H_2O, sec, bpm)	IAPV vital capacity (ml)
Myopathy	F	32	340	15.6	Refused	30, 1.8, 13	748
Duchenne	M	22	270	18.9	Refused	60, 1.5, 15	648
Duchenne	M	20	320	22.2	Refused	50, 1.4, 15	578
ALS	M	62	440	15.4	Refused	30, 1.5, 13	962
ALS	M	63	780	16.9	Refused	50, 1.5, 12	1484
ALS	M	68	250	19.8	Poor compliance	60, 1.2, 18	514
ALS	M	25	280	19.8	Poor compliance	60, 1.5, 14	524
Duchenne	M	19	150	26.2	Poor compliance	50, 1.5, 16	475

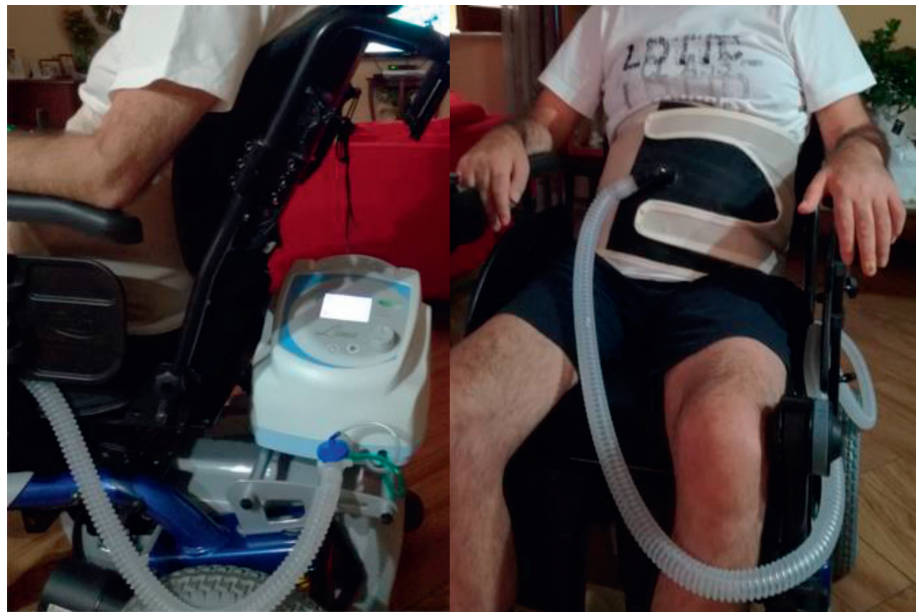

Figure 1: Patient during ventilation with LunaBelt.

Table 2: IAPV parameters: we suggest starting with Pbelt of 0–70 Hpa (at the beginning: 30–40 Hpa); select desired Ti (during Ti set, PBAir will be deflated, while the patient will be able to inhale); backup rate as desired; rise time usually 1.0 s; expiratory time (abdominal compression) will be linked to the backup rate and inspiratory time set. For example, set inspiratory time: 1.5 sec, Fr: 15 bpm, and derivative expiratory time: 2.5 sec.

Intermittent abdominal pressure ventilator (LunaBelt)		
Mode	Timed	Spontaneous/timed
Pressure belt	0–70 hPa	0–70 hPa
Time inspiratory	0.3–5.0 sec	Na
Time inspiratory minimum	Na	0.3–3.0 sec
Time inspiratory maximum	[(60/Freq) – 0.6 sec]	[(60/Freq – 0.6 sec)]
Time expiratory minimum	Na	0–1.5 sec
Backup frequency	1–60 bpm	1–60 bpm
Frequency maximum	[60/(Tinsp + 0.6 sec)]	[60/(Tinsp + 0.6 sec)
Rise time	0.1–1.0 sec	0.1–1.0 sec
Trigger inspiratory (nasal cannula)	Na	Auto
Trigger expiratory (nasal cannula)	Na	Auto

may be ineffective. However, there have been reports of patients using IAPV even during sleep with excellent comfort and adherence to treatment [2, 9].

Bach, in 1991, described an extensive series of patients using the IAPV for many years. They suggested that IAPV is a safe and helpful technique of long-term daytime ventilatory support for paralytic/restrictive respiratory deficiency subjects [2]. Its use is enhanced in combination with other noninvasive methods of ventilatory support, thus eliminating the need for tracheostomy and improving the use of glossopharyngeal breathing. Several authors have described follow-up as essential because the IAPV can become less effective over time [2, 5]. We found an improvement in the cough peak, which, in some patients, allowed a better

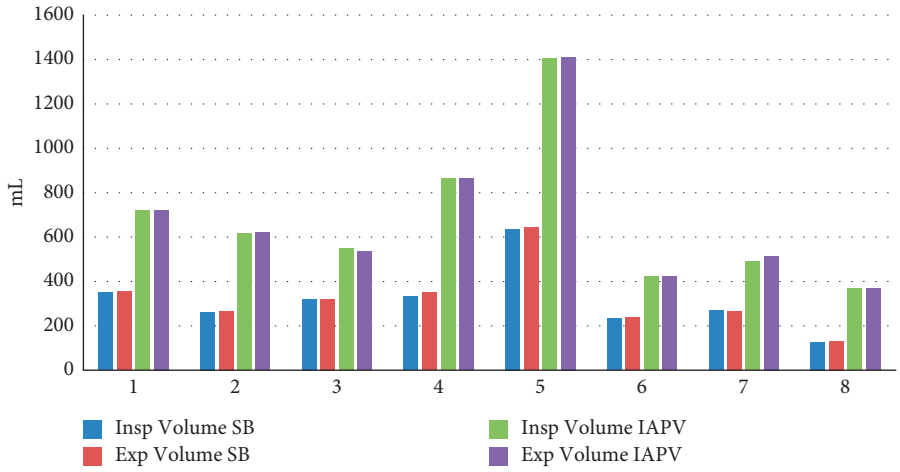

Figure 2: Inspiratory and expiratory volume measurement at baseline and during IAPV.

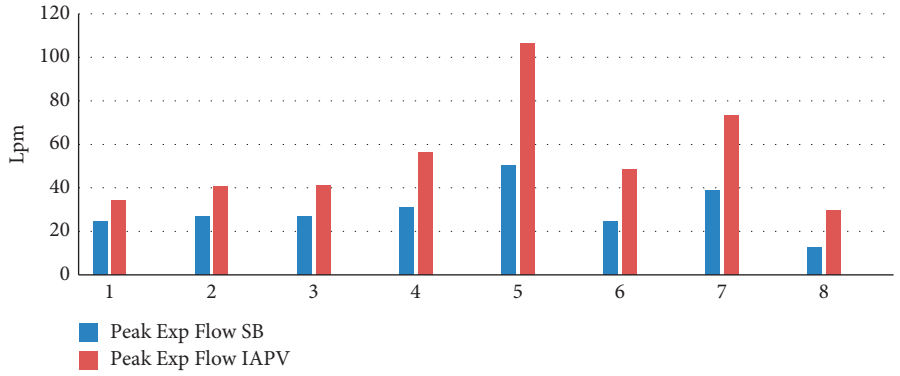

Figure 3: Peak flow at baseline and during IAPV.

clearance of secretions, even during air staking manoeuvres. Bach and Alba stressed that regular follow-up is essential because IAPV can become less effective with time [2].

Our experience agreed with previous suggestions and results described in recent case reports that patients with severe restrictive syndrome adjusted well to and were successfully ventilated by the IAPV, using it for several years. In our population, IAPV has been well tolerated for over two years. The average time of IAPV use was 10–12 hours per day. In some patients, due to the progression of neurodegenerative disease, it was necessary to integrate the treatment with positive pressure ventilation with a mask during the night hours due to obstructive sleep apnea syndrome. IAPV facilitates diaphragmatic motion and may be particularly useful in patients with bilateral diaphragmatic weakness or paralysis and permits plugging of the tracheostomy tube with cuff deflation for several hours during the day, with the prevention of tracheal damage. IAPV permits patients to speak and provides an effective daytime ventilatory pattern; it also allows the maintenance of an excellent peripheral saturation without dyspnea, a significant improvement in salivary secretion management, and a decrease in the need for tracheal aspiration. IAPV can be used in patients who require NIV many hours a day alternatively or alternating NIV with a mask. NIV can be a cause of severe gastric insufflation. Patients with neuromuscular pathology may have altered intestinal smooth muscle, leading to air retention in the stomach and colonic [12]. In particular, dystrophin is expressed in the smooth muscle of the gastrointestinal tract. The disruption of protein expression can lead to functional disturbances of the gastrointestinal tract, including acute gastric dilatation, gastroparesis, and intestinal pseudo-obstruction [13].

Moreover, aerophagia is a significant NIV-related problem that appears in up to half of patients with NIV and may lead to the discontinuation of treatment. Patients with gastric distension may benefit from the device's abdominal compression during the exhalation phase [9, 10]. Regurgitation of food during meals, catching of clothing on straps and Velcro fasteners, redness of bony prominences, and inability to shower or bathe during use have been reported as possible disadvantages [11]. In the past, sacral decubitus has been described in patients that used IAPV constantly [2].

5. Conclusion

The use of IAPV is limited to a few centres, likely due to the long time required to adapt and monitor the patient. It is necessary to have different possibilities for noninvasive mechanical ventilation to guarantee the optimal interface for

the patient. IAPV is a comfortable alternative to NIV with a mask, and it is significant for patients requiring daytime support and patients with chronic disease to be considered for NIV. Patients with the need for continuous noninvasive ventilation often present pressure ulcers from the mask, aerophagia, and intolerance to the mask due to interference with social life. These complications can lead to the failure of NIV [14, 15]. IAPV maintains good ventilation and oxygenation and reduces complications related to positive pressure ventilation with a mask. It can also be used often in addition to or alternating NIV with a mask [16]. It can be helpful to alternate the interface in patients who need ventilator support 24 h a day and to carry out daily life activities without interference related to the use of masks.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] C. J. McSweeney, "Bragg-Paul pulsator for respiratory paralysis," *BMJ*, vol. 1, no. 4039, pp. 1206-1207, 1938.

[2] J. R. Bach and A. S. Alba, "Intermittent abdominal pressure ventilator in a regimen of noninvasive ventilatory support," *Chest*, vol. 99, no. 3, pp. 630–636, 1991.

[3] S. I. Weingarden and J. G. Belen, "Alternative approach to the respiratory management of the high cervical spinal cord injury patient," *International Disability Studies*, vol. 9, no. 3, pp. 132-133, 1987.

[4] H. J. Miller, E. Thomas, and C. B. Wilmot, "Pneumobelt use among high quadriplegic population," *Archives of Physical Medicine and Rehabilitation*, vol. 69, no. 5, pp. 369–372, 1988.

[5] P. I. Banfi, E. Volpato, and J. R. Bach, "Efficacy of new intermittent abdominal pressure ventilator for post-ischemic cervical myelopathy ventilatory insufficiency," *Multidisciplinary Respiratory Medicine*, vol. 14, no. 1, p. 4, 2019.

[6] E. De Mattia, M. Iatomasi, B. Garabelli, C. Lunetta, V. A. Sansone, and F. Rao, "Use of the intermittent abdominal pressure ventilation to guarantee speech in a tracheostomized amyotrophic lateral sclerosis patient," *Revista Portuguesa de Pneumologia*, vol. 23, no. 4, pp. 236–239, 2017.

[7] P. Pierucci, J. R. Bach, V. Di Lecce Valentina, P. Banfi, G. E. Carpagnano, and O. Resta, "Daytime non-invasive ventilatory support via intermittent abdominal pressure for a patient with Pompe disease," *Pulmonology*, vol. 27, no. 2, pp. 182–184, 2021.

[8] J. R. Bach, M. R. Gonçalves, I. Hamdani, and J. C. Winck, "Extubation of patients with neuromuscular weakness," *Chest*, vol. 137, no. 5, pp. 1033–1039, 2010.

[9] G. F. Yang, A. Alba, M. Lee, and A. Khan, "Pneumobelt for sleep in the ventilator user: clinical experience," *Archives of Physical Medicine and Rehabilitation*, vol. 70, no. 9, pp. 707–709, 1989.

[10] D. R. Hess, "Noninvasive ventilation in neuromuscular disease: equipment and application," *Respiratory Care*, vol. 51, no. 8, pp. 896–911, 2006.

[11] J. R. Bach, "Pathophysiology of paralytic/restrictive pulmonary syndromes," in *Pulmonary Rehabilitation: The Obstructive and Paralytic Conditions*, J. R. Bach, Ed., pp. 275–283, Hanley and Belfus, Philadelphia, PA, USA, 1996.

[12] A. Vianello, G. Arcaro, P. Peditto, S. Iovino, and R. Marchese-Ragona, "Acute colonic distension in a patient with severe muscular dystrophy receiving non-invasive positive pressure ventilation," *Neuromuscular Disorders*, vol. 28, no. 1, pp. 60-61, 2018.

[13] G. Fiorentino and A. M. Esquinas, "Colonic distension treatment in Duchenne muscular dystrophy," *Neuromuscular Disorders*, vol. 29, no. 2, pp. 157-158, 2019.

[14] G. Fiorentino, A. Annunziata, A. Annunziata, R. Cauteruccio, G. S. d. Frega, and A. Esquinas, "Mouthpiece ventilation in Duchenne muscular dystrophy: a rescue strategy for non-compliant patients," *Jornal Brasileiro de Pneumologia*, vol. 42, no. 6, pp. 453–456, 2016.

[15] M. Antonelli, G. Conti, M. Moro et al., "Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study," *Intensive Care Medicine*, vol. 27, no. 11, pp. 1718–1728, 2001.

[16] P. Banfi, P. Pierucci, E. Volpato et al., "Daytime noninvasive ventilatory support for patients with ventilatory pump failure: a narrative review," *Multidisciplinary Respiratory Medicine*, vol. 14, no. 1, p. 38, 2019.

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Research Article

Impact of HACOR Score on Noninvasive Ventilation Failure in Non-COPD Patients with Acute-on-Chronic Respiratory Failure

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Background. A rating scale that takes into account heart rate, acidosis, consciousness, oxygenation, and respiratory rate (the HACOR score) has been used to predict noninvasive ventilation (NIV) failure in patients with chronic obstructive pulmonary disease (COPD). However, the HACOR score has not been used to predict NIV failure in non-COPD patients with acute-on-chronic respiratory failure. *Methods*. This study was performed in the respiratory intensive care unit of a teaching hospital. Data had been collected prospectively between June 2011 and January 2019. We enrolled non-COPD patients who received NIV due to acute-on-chronic respiratory failure, pH < 7.35, and $PaCO_2$ >45 mmHg. NIV failure was defined as requiring intubation or dying during NIV. The HACOR score was determined at initiation and after 1-2, 12, and 24 h of NIV. Scores can range from 0 to 27, with higher scores indicating a higher risk of NIV failure. *Results*. A total of 148 patients were enrolled in the study, 52 with sleep apnea-hypopnea syndrome, 34 with chronic thoracic sequelae, 31 with bronchiectasis, 14 with chest wall deformity, 5 with obesity-hypoventilation syndrome, and 12 with other conditions. Of the patients, 19 (13%) experienced NIV failure. From initiation to 24 h of NIV, the HACOR scores of patients who experienced NIV failure were much higher than those of patients who received successful NIV. The area under the receiver operating characteristic curve was 0.69, 0.91, 0.91, and 0.94 when the HACOR score was tested at initiation and after 1-2, 12, and 24 h of NIV, respectively. To obtain the best sensitivity and specificity, the cutoff value at initiation was 7 with a sensitivity of 68% and a specificity of 61%. After 1-2 h of NIV, it was 5 with a sensitivity of 90% and a specificity of 85%. After 12 h of NIV, it was 4 with a sensitivity of 82% and a specificity of 91%. After 24 h of NIV, it was 2 with a sensitivity of 100% and a specificity of 76%. *Conclusions*. The HACOR score has high sensitivity and specificity for predicting NIV failure among non-COPD patients who receive NIV due to acute-on-chronic respiratory failure with respiratory acidosis.

1. Introduction

Physiologic research shows that noninvasive ventilation (NIV) increases minute ventilation, improves gas exchange, counterbalances intrinsic positive end-expiratory pressure (PEEP), and decreases the work of breathing [1, 2]. In patients with hypoxemic or hypercapnic respiratory failure, NIV reduces the requirement for intubation for invasive mechanical ventilation [2–5]. As NIV benefits patients with acute respiratory failure, its use increases year by year [6].

Acute-on-chronic respiratory failure is common in patients with chronic obstructive pulmonary disease (COPD), sleep apnea-hypopnea syndrome, chronic thoracic sequelae, bronchiectasis, chest wall deformity, obesity-hypoventilation syndrome, neuromuscular disease, and other conditions. In COPD patients with hypercapnia due to acute-on-chronic respiratory failure, NIV reduces the need for intubation [7, 8]. Guidelines strongly recommend providing NIV to COPD patients [9, 10]. However, evidence of the use of NIV is rare among non-COPD patients with acute-on-chronic respiratory failure.

Although NIV reduces the need for intubation among COPD patients, mortality increases significantly if patients experience NIV failure [11, 12]. Among patients who experience NIV failure, delayed intubation further increases mortality [13]. Therefore, early identification of patients at risk for NIV failure and early intubation may reduce

mortality. In a previous study, we developed a rating scale (the HACOR score) to predict the risk of NIV failure in COPD patients who experienced acute-on-chronic respiratory failure [14]. It takes into account heart rate, acidosis (assessed by pH), consciousness (assessed by Glasgow Coma Scale (GCS) score), oxygenation, and respiratory rate. The HACOR score has high sensitivity and specificity for predicting NIV failure in COPD patients. As the pathophysiologic mechanism of acute-on-chronic respiratory failure is similar in COPD and non-COPD patients, we hypothesized that the HACOR score would also have high sensitivity and specificity for predicting NIV failure among non-COPD patients with acute-on-chronic respiratory failure.

2. Methods

This study was performed in the respiratory intensive care unit (ICU) of a teaching hospital. Data had been collected prospectively between June 2011 and January 2019. The study protocol was approved by the local ethics committee of the First Affiliated Hospital of Chongqing Medical University. As the study was observational nature, informed consent was waived. Patients who received NIV due to hypercapnic respiratory failure were candidates for inclusion in the study. The inclusion criteria were (1) acute-on-chronic respiratory failure with respiratory acidosis, (2) use of NIV as a first-line therapy, (3) $PaCO_2$ >45 mmHg, and (4) pH < 7.35. The exclusion criteria were (1) respiratory failure caused by exacerbation of COPD, (2) prophylactic use of NIV after extubation, (3) rescue use of NIV due to respiratory failure after extubation, (4) accidental extubation and use of NIV, and (5) use of a high-flow nasal cannula before or after NIV.

NIV (BiPAP Vision or V60; Philips Respironics, Carlsbad, CA, USA) was managed by attending physicians, respiratory therapists, and nurses in charge. The ventilator settings were based on the previously published protocols [14, 15]. Bilevel positive airway pressure (S/T mode) was used for all patients. PEEP was initially set at 4 cmH_2O and titrated to counterbalance the intrinsic PEEP. Support pressure was set at 8 cmH_2O and was increased by 2 cmH_2O at a time to obtain a tidal volume >6 mL/kg or to reach the maximum level tolerated by the patient. The fraction of inspired oxygen was titrated to maintain SpO_2 around 95%. The ventilator settings were adjusted based on $PaCO_2$ and the severity of the patient's distress.

If respiratory failure abated, weaning from NIV was considered. NIV was used intermittently until the patient could breathe normally without ventilation. However, if respiratory failure worsened and escalation therapy was required, intubation was performed. The criteria for intubation were persistent respiratory distress with a respiratory rate >35 breaths/min, failure to correct respiratory acidosis, an inability to maintain PaO_2/FiO_2 above 100 mmHg, the development of conditions necessitating intubation to protect the airway (coma or seizure disorders) or to manage copious tracheal secretions, hemodynamic instability without response to fluids and vasoactive agents, and respiratory or cardiac arrest [14]. If a patient met the criteria for intubation but the attending physician did not think they would benefit from it, NIV was continued. NIV failure was defined as requiring intubation or dying during NIV [14].

Demographic data, including data on age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, diagnosis, and underlying disease, were collected before the use of NIV. Data on respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, consciousness, and arterial blood gas were collected at initiation and after 1-2, 12, and 24 h of NIV. Data on the support pressure and PEEP of the ventilator were collected after 1-2, 12, and 24 h of NIV. Patients were followed up to discharge or death, whichever came first. Data on the duration of NIV, the length of stay in the ICU, and the length of stay in the hospital were also collected.

The HACOR score was determined before and after 1-2, 12, and 24 h of NIV [14]. Heart rate <100, 100–119, 120–139, and >139 beats per minute was given 0, 1, 2, and 3 points, respectively. Acidosis was assessed by pH. pH ≥ 7.35, 7.30–7.34, 7.25–7.29, 7.20–7.24, and <7.20 was given 0, 2, 3, 5, and 8 points, respectively. Consciousness was assessed with the GCS score. GCS score of 15, 14, 13, 12, and <12 was given 0, 2, 4, 6, and 11 points, respectively. Oxygenation was assessed with PaO_2/FiO_2. PaO_2/FiO_2 ≥150, 101–149, and ≤100 was given 0, 1, and 2 points, respectively. Respiratory rate <30, 31–34, 35–39, and ≥40 breaths per minute was given 0, 1, 2, and 3 points, respectively. The HACOR score was the sum of the points for the five variables. Scores can range from 0 to 27, with higher scores indicating a higher risk of NIV failure.

In our study, 3 out of 148 patients (2%) had missing data for at least one variable. Multiple imputations were performed. The imputed value was the average of five imputations. Continuous variables were expressed as means and standard deviations or medians and interquartile ranges when appropriate. Differences between groups were tested with independent samples t tests or Mann–Whitney U tests. Qualitative variables were expressed as numbers of events (%), and differences between groups were tested with chi-square or Fisher exact probability tests. The ability to predict NIV failure was tested with the area under the receiver operating characteristic curve (AUC). The optimal cutoff value was determined when the maximal Youden index was reached [16]. We ran 1000 bootstrap samples to estimate the odds ratio (OR) and 95% confidence interval (CI) of NIV failure per 1-point increment for internal validation. A two-sided $p < 0.05$ was considered significant.

3. Results

A total of 1954 NIV patients with hypercapnic respiratory failure were screened (Figure 1). Ultimately, 148 non-COPD patients with acute-on-chronic respiratory failure were enrolled, 52 with sleep apnea-hypopnea syndrome, 34 with chronic thoracic sequelae, 31 with bronchiectasis, 14 with chest wall deformity, 5 with obesity-hypoventilation syndrome, and 12 with other conditions. Of the 148 cases, 19 (13%) experienced NIV failure, including 2 who died during

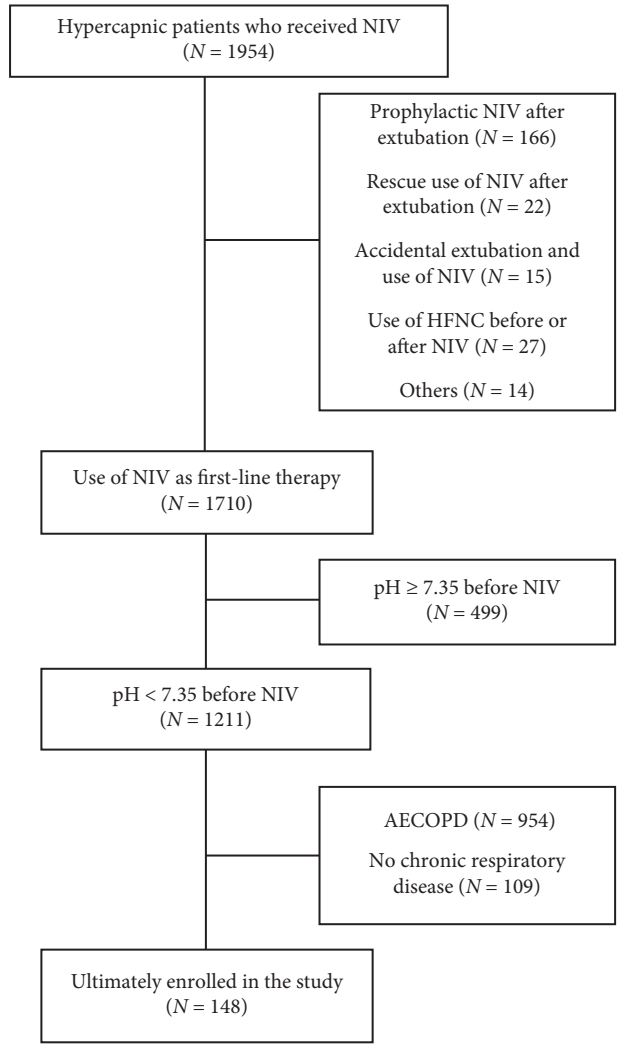

Figure 1: Flowchart of patient enrollment. NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; AECOPD, acute exacerbation of COPD.

NIV (Table 1). Among the overall cohort, the median duration of NIV was 96 h, and hospital mortality was 10%.

There were no differences in age, sex, diagnosis, underlying disease, or prevalence of chronic respiratory conditions between patients who experienced successful NIV and NIV failure (Table 1). Support pressure and PEEP were also not different when recorded after 1-2, 12, and 24 h of NIV (Table 2). Before NIV, however, patients who later experienced NIV failure had a higher APACHE II score (20 ± 7 vs. 16 ± 5), a higher heart rate (122 ± 23 vs. 107 ± 22 bpm), and a lower pH (7.22 ± 0.07 vs. 7.26 ± 0.07) than those who experienced successful NIV. They also had a higher heart rate, a lower GCS score, a lower pH, and a lower PaO_2/FiO_2 after 1-2, 12, and 24 h of NIV.

The HACOR score was much lower in patients who experienced successful NIV than in patients with NIV failure when it was measured at initiation and after 1-2, 12, and 24 h of NIV (Figure 2). The OR for NIV failure was 1.15, 1.99, 2.14, and 1.53 per 1-point increment when the HACOR score was assessed at initiation and after 1-2, 12, and 24 h of NIV, respectively (Table 3). To predict NIV failure, the AUC was 0.69, 0.91, 0.91, and 0.94 when the HACOR score was assessed at initiation and after 1-2, 12, and 24 h of NIV, respectively (Figure 3). To obtain the best sensitivity and specificity, the cutoff value at initiation was 7 with a sensitivity of 68% and a specificity of 61%. After 1-2 h of NIV, it was 5 with a sensitivity of 90% and a specificity of 85%. After 12 h of NIV, it was 4 with a sensitivity of 82% and a specificity of 91%. After 24 h of NIV, it was 2 with a sensitivity of 100% and a specificity of 76%.

4. Discussion

The rate of NIV failure was low in this sample of non-COPD patients with acute-on-chronic respiratory failure with respiratory acidosis. The HACOR score, which takes into account heart rate, acidosis, consciousness, oxygenation, and respiratory rate, had high sensitivity and specificity for predicting NIV failure when it was measured within 24 h of NIV. A higher HACOR score was associated with an increased risk of NIV failure.

Table 1: Baseline data for patients who experienced successful NIV and NIV failure.

	Overall cohort, $N = 148$	Successful NIV, $N = 129$	NIV failure, $N = 19$	P
Age, years	64 ± 16	64 ± 16	67 ± 11	0.49
Sex, male	83 (56%)	71 (55%)	12 (63%)	0.62
APACHE II score	16 ± 5	15 ± 4	20 ± 7	<0.01
Diagnosis				
Sleep apnea-hypopnea syndrome	52 (35%)	48 (37%)	4 (21%)	0.12
Chronic thoracic sequelae	34 (23%)	28 (22%)	6 (32%)	
Bronchiectasis	31 (21%)	25 (19%)	6 (32%)	
Chest wall deformity	14 (10%)	14 (11%)	0 (0%)	
Obesity-hypoventilation syndrome	5 (3%)	3 (2%)	2 (11%)	
Others	12 (8%)	11 (9%)	1 (5%)	
Underlying disease				
Hypertension	68 (46%)	62 (48%)	6 (32%)	0.22
Chronic heart disease	29 (20%)	25 (19%)	4 (21%)	>0.99
Diabetes mellitus	28 (19%)	23 (18%)	5 (26%)	0.36
Chronic renal failure	11 (7%)	9 (7%)	2 (11%)	0.63
Liver cirrhosis	4 (3%)	2 (2%)	2 (11%)	0.08
Duration of NIV (h)	96 (42–143)	103 (50–166)	29 (3–77)	<0.01
Length of stay in the ICU (days)	5.8 (3.7–10.8)	5.5 (3.7–10.4)	6.6 (3.4–13.2)	0.79
Length of stay in the hospital (days)	11.8 (6.8–19.0)	11.8 (6.8–18.9)	12.1 (7.6–21.8)	0.88
Hospital mortality	14 (10%)	4 (3%)	10 (53%)	<0.01

NIV, noninvasive ventilation; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

NIV is widely used in patients with acute-on-chronic respiratory failure. The spectrum of disease includes COPD, sleep apnea-hypopnea syndrome, chronic thoracic sequelae, bronchiectasis, chest wall deformity, obesity-hypoventilation syndrome, neuromuscular disease, and other conditions [17]. The use of NIV is strongly recommended for patients with COPD regardless of patients' stability or acute-on-chronic respiratory failure [9, 10, 17]. However, the effect of NIV in non-COPD populations is lacking. To the best of our knowledge, this is the largest study to describe the characteristics of non-COPD patients who received NIV due to acute-on-chronic respiratory failure with respiratory acidosis. Our study showed a rate of NIV failure of only 13%, which indicates that NIV can be used successfully with the majority of non-COPD patients who experience acute-on-chronic respiratory failure with respiratory acidosis.

The HACOR score was developed by our team with COPD patients who received NIV due to acute-on-chronic respiratory failure [14]. It takes into account heart rate, acidosis, consciousness, oxygenation, and respiratory rate. It has excellent power to predict NIV failure in COPD patients. However, its accuracy at predicting NIV failure in non-COPD patients with acute-on-chronic respiratory failure with respiratory acidosis is not known. The current study validated the use of the HACOR score with these patients and found very good sensitivity and specificity for predicting NIV failure. Therefore, the HACOR score can be used to predict NIV failure in both COPD and non-COPD patients who experience acute-on-chronic respiratory failure with respiratory acidosis.

NIV failure significantly increases the risk of death [11, 12]. Our study confirms this. We found that mortality was 53% in patients who experienced NIV failure but only 3% in patients who had successful NIV. Reducing mortality is challenging. Our previous study showed that patients with a high risk of NIV failure identified by the HACOR score who were intubated early had lower mortality than those whose intubation was delayed [14]. Therefore, early identification of the risk of NIV failure and early intubation in non-COPD patients with acute-on-chronic respiratory failure may help reduce mortality. The current study shows that the HACOR score is a simple and reproducible tool for predicting NIV failure. The optimal cutoff values to obtain the best sensitivity and specificity were 7, 5, 4, and 2 at initiation and after 1-2, 12, and 24 h of NIV, respectively. The HACOR score is a good tool for clinical staff to use to manage non-COPD patients who require NIV due to acute-on-chronic respiratory failure.

Our study has several limitations. First, we screened hypercapnic patients admitted to our ICU within the past 8 years, and only 148 non-COPD patients with acute-on-chronic respiratory failure were enrolled. The characteristics of the non-COPD patients in the study varied greatly. It was impossible to describe the characteristics of each subgroup given the small sample sizes. A larger sample is needed to perform subgroup analyses. Second, this was an observational study performed in a single center. The results must be validated for other centers. Third, COPD is frequently underdiagnosed in the real word [18]. We were unable to exclude all cases of COPD from our study because of a lack of data on patients' smoking history, previous hospitalizations due to respiratory failure, and pulmonary function. Further study with stricter assessment is required to exclude cases of underdiagnosed COPD.

Table 2: Vital signs and ventilator parameters from initiation to 24 h of NIV for patients who experienced successful NIV and NIV failure.

	Successful NIV	NIV failure	*P*
Before NIV			
Heart rate (bpm)	107 ± 22	122 ± 23	<0.01
Respiratory rate (bpm)	29 ± 6	28 ± 5	0.68
Mean arterial blood pressure (mmHg)	101 ± 16	103 ± 22	0.76
GCS score	14.5 ± 1.2	14.2 ± 1.2	0.38
pH	7.26 ± 0.07	7.22 ± 0.07	0.01
$PaCO_2$ (mmHg)	81 ± 18	77 ± 17	0.28
PaO_2/FiO_2, (mmHg)	199 ± 99	173 ± 79	0.28
1-2 h of NIV			
Heart rate (bpm)	96 ± 18	111 ± 26	<0.01
Respiratory rate (bpm)	23 ± 5	25 ± 6	0.07
Mean arterial blood pressure (mmHg)	91 ± 13	103 ± 19	<0.01
GCS score	14.7 ± 0.7	13.7 ± 1.3	<0.01
pH	7.35 ± 0.05	7.26 ± 0.10	<0.01
$PaCO_2$ (mmHg)	68 ± 18	74 ± 22	0.25
PaO_2/FiO_2 (mmHg)	223 ± 63	169 ± 70	<0.01
Support pressure (cmH_2O)	17 ± 4	17 ± 4	0.58
PEEP (cmH_2O)	6 ± 2	6 ± 2	0.47
12 h of NIV			
Heart rate (bpm)	89 ± 16	113 ± 31	<0.01
Respiratory rate (bpm)	22 ± 4	22 ± 3	0.85
Mean arterial blood pressure (mmHg)	88 ± 11	91 ± 14	0.48
GCS score	14.8 ± 0.5	14.5 ± 0.7	0.02
pH	7.38 ± 0.05	7.27 ± 0.12	<0.01
$PaCO_2$ (mmHg)	65 ± 15	71 ± 22	0.19
PaO_2/FiO_2 (mmHg)	241 ± 86	182 ± 64	0.03
Support pressure (cmH_2O)	18 ± 4	18 ± 3	0.89
PEEP (cmH_2O)	7 ± 3	6 ± 2	0.53
24 h of NIV			
Heart rate (bpm)	87 ± 17	105 ± 30	<0.01
Respiratory rate (bpm)	23 ± 4	25 ± 6	0.11
Mean arterial blood pressure (mmHg)	90 ± 12	92 ± 23	0.61
GCS score	14.9 ± 0.9	14.2 ± 0.8	0.02
pH	7.40 ± 0.07	7.29 ± 0.14	<0.01
$PaCO_2$ (mmHg)	59 ± 15	73 ± 33	0.01
PaO_2/FiO_2 (mmHg)	256 ± 80	171 ± 68	<0.01
Support pressure (cmH_2O)	19 ± 4	20 ± 3	0.78
PEEP (cmH_2O)	7 ± 3	6 ± 2	0.32

NIV, noninvasive ventilation; GCS, Glasgow Coma Scale; PEEP, positive end-expiratory pressure. Differences between the two groups were analyzed with independent samples *t* tests.

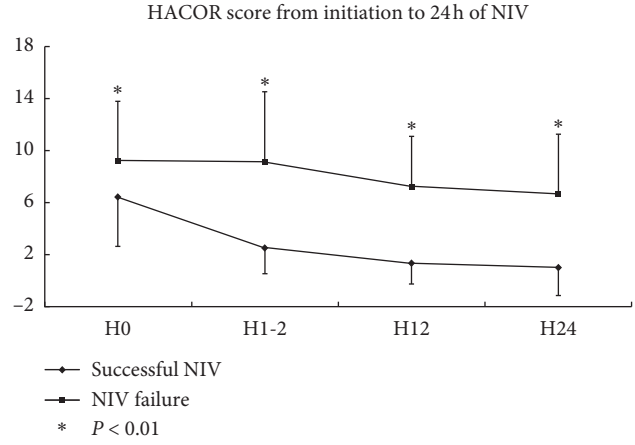

Figure 2: Differences in the HACOR score from initiation to 24 h of NIV between patients who experienced successful NIV and NIV failure. HACOR, heart rate, acidosis, consciousness, oxygenation, and respiratory rate; NIV, noninvasive ventilation; H0, initiation; H1-2, 1-2 h of NIV; H12, 12 h of NIV; H24, 24 h of NIV.

Table 3: Odds ratios for NIV failure tested by the HACOR score (per 1-point increment).

	OR (95% CI)	OR (95% CI) under 1000 bootstraps
Before NIV	1.15 (1.04–1.28)	1.15 (1.04–1.31)
1-2 h of NIV	1.99 (1.50–2.64)	1.99 (1.59–3.28)
12 h of NIV	2.14 (1.52–3.02)	2.14 (1.60–6.19)
24 h of NIV	1.53 (1.18–1.98)	1.53 (1.15–3.85)

HACOR, heart rate, acidosis, consciousness, oxygenation, and respiratory rate; OR, odds ratio; CI, confidence interval; NIV, noninvasive ventilation.

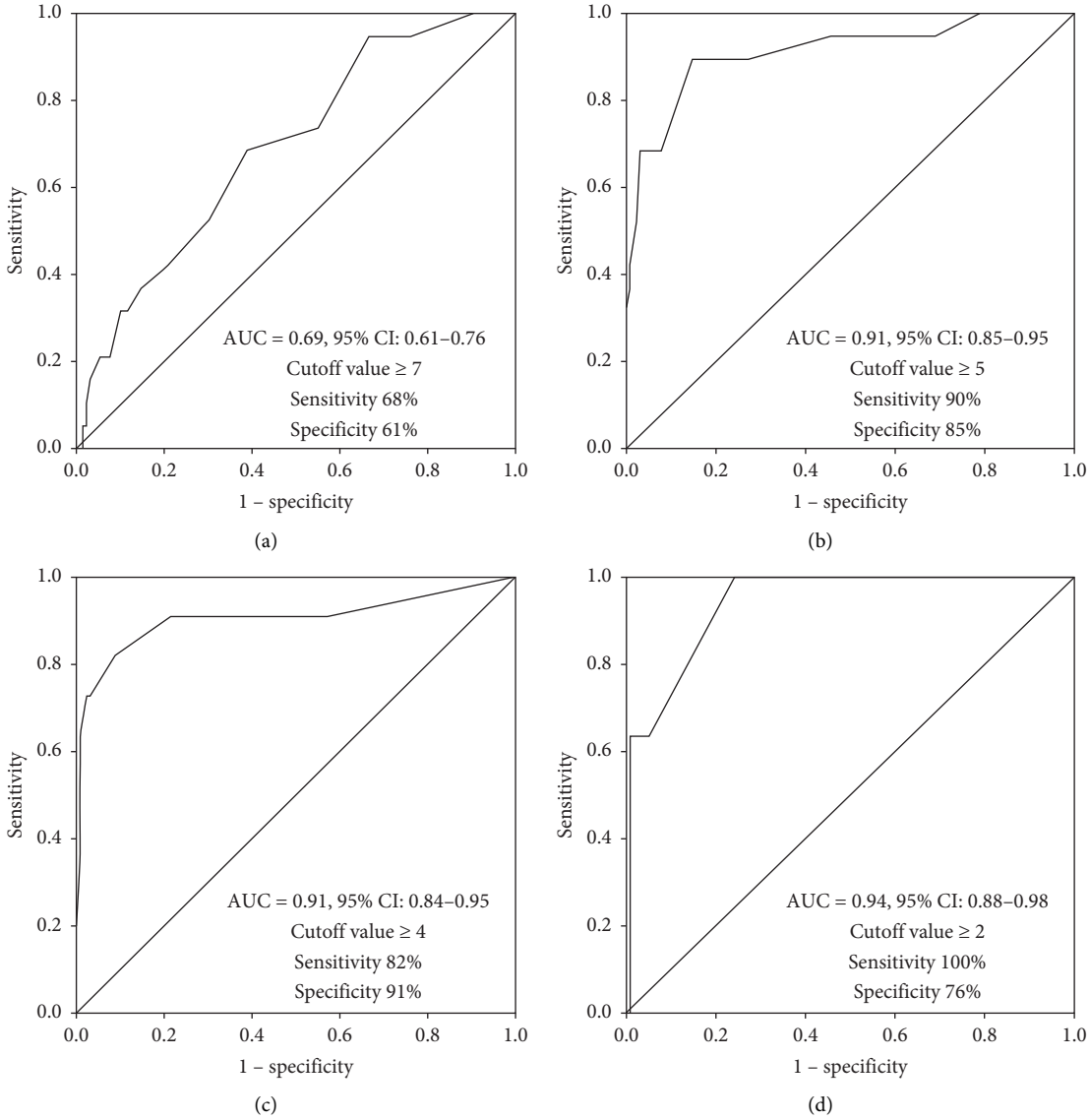

Figure 3: The predictive power of NIV failure assessed by the HACOR score from initiation to 24 h of NIV. HACOR, heart rate, acidosis, consciousness, oxygenation, and respiratory rate; NIV, noninvasive ventilation; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

5. Conclusions

The rate of NIV failure is low in non-COPD patients who experience acute-on-chronic respiratory failure with respiratory acidosis. Among these patients, the HACOR score has high sensitivity and specificity for predicting NIV failure.

Abbreviations

COPD: Chronic obstructive pulmonary disease
AECOPD: Acute exacerbation of COPD
NIV: Noninvasive ventilation
GCS: Glasgow Coma Scale

OR: Odds ratio
CI: Confidence interval
ICU: Intensive care unit
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate
HFNC: High-flow nasal cannula
AUC: Area under the receiver operating characteristic curve.

Data Availability

The datasets analyzed during this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Jun Duan conceived the study, joined in study design, study management, data collection, data analysis, and manuscript revision. Min Ding participated in study design, study management, data collection, data analysis, and manuscript preparation. Xiaoli Han, Linfu Bai, and Shicong Huang participated in study design, data collection, and manuscript revision. All authors read and approved the final version.

References

[1] L. Appendini, A. Patessio, S. Zanaboni et al., "Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 149, no. 5, pp. 1069–1076, 1994.

[2] E. L'Her, N. Deye, F. Lellouche et al., "Physiologic effects of noninvasive ventilation during acute lung injury," *American Journal of Respiratory and Critical Care Medicine*, vol. 172, no. 9, pp. 1112–1118, 2005.

[3] C. R. Osadnik, V. S. Tee, K. V. Carson-Chahhoud, J Picot, J. A. Wedzicha, and B. J Smith, "Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease," *The Cochrane Database of Systematic Reviews*, vol. 7, Article ID CD004104, 2017.

[4] P. G. David-João, M. H. Guedes, Á. Réa-Neto, V. B. d. O. Chaiben, and C. P. Baena, "Noninvasive ventilation in acute hypoxemic respiratory failure: a systematic review and meta-analysis," *Journal of Critical Care*, vol. 49, pp. 84–91, 2019.

[5] B. L. Ferreyro, F. Angriman, L. Munshi et al., "Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure," *JAMA*, vol. 324, no. 1, pp. 57–67, 2020.

[6] A. Demoule, S. Chevret, S. Chevret et al., "Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries," *Intensive Care Medicine*, vol. 42, no. 1, pp. 82–92, 2016.

[7] L. Brochard, J. Mancebo, M. Wysocki et al., "Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease," *New England Journal of Medicine*, vol. 333, no. 13, pp. 817–822, 1995.

[8] P. Plant, J. Owen, and M. Elliott, "Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial," *The Lancet*, vol. 355, no. 9219, pp. 1931–1935, 2000.

[9] B. Rochwerg, L. Brochard, M. W Elliott et al., "Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure," *The European Respiratory Journal*, vol. 50, 2017.

[10] T. Akashiba, Y. Ishikawa, H. Ishihara et al., "The Japanese respiratory society noninvasive positive pressure ventilation (NPPV) guidelines (second revised edition)," *Respiratory Investigation*, vol. 55, no. 1, pp. 83–92, 2017.

[11] D. Chandra, J. A. Stamm, B. Taylor et al., "Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008," *American Journal of Respiratory and Critical Care Medicine*, vol. 185, no. 2, pp. 152–159, 2012.

[12] M. S. Stefan, B. H. Nathanson, T. L. Higgins et al., "Comparative effectiveness of noninvasive and invasive ventilation in critically ill patients with acute exacerbation of chronic obstructive pulmonary disease," *Critical Care Medicine*, vol. 43, no. 7, pp. 1386–1394, 2015.

[13] M. Moretti, C. Cilione, A. Tampieri et al., "Incidence and causes of non-invasive mechanical ventilation failure after initial success," *Thorax*, vol. 55, no. 10, pp. 819–825, 2000.

[14] J. Duan, S. Wang, P. Liu et al., "Early prediction of noninvasive ventilation failure in COPD patients: derivation, internal validation, and external validation of a simple risk score," *Annals of Intensive Care*, vol. 9, no. 1, p. 108, 2019.

[15] L. Fan, Q. Zhao, Y. Liu, L. Zhou, and J. Duan, "Semiquantitative cough strength score and associated outcomes in noninvasive positive pressure ventilation patients with acute exacerbation of chronic obstructive pulmonary disease," *Respiratory Medicine*, vol. 108, no. 12, pp. 1801–1807, 2014.

[16] W. J. Youden, "Index for rating diagnostic tests," *Cancer*, vol. 3, no. 1, pp. 32–35, 1950.

[17] A. C. Davidson, S. Banham, M. Elliott et al., "BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults," *Thorax*, vol. 71, no. Suppl 2, pp. i–35, 2016.

[18] C. Wang, J. Xu, L. Yang et al., "Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study," *The Lancet*, vol. 391, no. 10131, pp. 1706–1717, 2018.

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Research Article

Effects of Continuous Positive Airway Pressure on Sleep EEG Characteristics in Patients with Primary Central Sleep Apnea Syndrome

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This study aimed to investigate the effects of continuous positive airway pressure (CPAP) on the electroencephalographic (EEG) characteristics of patients with primary central sleep apnea syndrome (CSAS). Nine patients with primary CSAS were enrolled in this study. The raw sleep EEG data were analyzed based on two main factors: fractal dimension (FD) and zero-crossing rate of detrended FD. Additionally, conventional EEG spectral analysis in the delta, theta, alpha, and beta bands was conducted using a fast Fourier transform. The FD in patients with primary CSAS who underwent CPAP treatment was significantly decreased during nonrapid eye movement (NREM) sleep but increased during rapid eye movement (REM) sleep ($p < 0.05$). Regarding the EEG spectral analysis, the alpha power increased, while the delta/alpha ratio decreased during REM sleep in patients with CSAS ($p < 0.05$). In conclusion, CPAP treatment can reduce FD in NREM sleep and increase FD during REM sleep in patients with primary CSAS. FD may be used as a new biomarker of EEG stability and improvement in brain function after CPAP treatment for primary CSAS.

1. Introduction

Central sleep apnea syndrome (CSAS) is a respiratory disorder that occurs when the respiratory center fails to issue the respiratory drive effectively due to various causes [1]. CSAS encompasses a wide range of diseases and covers eight categories according to the International Classification of Sleep Disorders-Third Edition (ICSD-3) [2], such as central sleep apnea (CSA) associated with Cheyne–Stokes respiration, CSA due to drugs or substances, and primary CSA. Except for primary CSA, most CSAs are caused by various underlying diseases or other medical conditions, for example, the most common is Cheyne–Stokes respiration caused by heart failure or stroke.

Compared with obstructive sleep apnea (OSA), CSAS has a lower prevalence in the general population [1]. Both OSA and CSA are characterized by recurrent nocturnal hypoxia and arousals, which are associated with daytime sleepiness, inattention, memory loss, and other signs of impaired brain function. Meanwhile, continuous positive airway pressure (CPAP) has been shown to improve brain function in patients with OSA [3]. Electroencephalography (EEG) is a tool for evaluating brain function. Quantitative EEG analysis has become an important method for assessing brain function in various populations [4, 5]. Previous studies have shown that CPAP can improve sleep EEG features in patients with OSA [6–9], such as correcting EEG slowing and reducing the complexity and increasing the stability of sleep EEG waves, which may explain the improvement of brain function in patients with OSA who receive CPAP treatment. However, the efficacy of CPAP in treating patients with CSAS and its effects on sleep EEG are not yet known.

The most common method for quantitative EEG analysis is EEG power spectral analysis [6, 7, 10], which includes the analysis of the absolute and relative power of delta, theta,

alpha, and beta frequency bands. Fractal dimension (FD) is a new method for measuring the irregularity and complexity of an object. It was initially introduced as a description of self-similar objects [11] and was subsequently utilized in a variety of scientific disciplines [12, 13]. FD is more suitable for the analysis of nonlinear and nonstationary physiological data, such as EEG [13]. In our previous study [13], we found that FD could reflect the sleep macroarchitecture of each participant. Furthermore, the fast fluctuation of FD, as measured by the zero-crossing rate of detrended FD (zDFD), is a useful indicator of sleep disturbance. CPAP can decrease FD in nonrapid eye movement (NREM) sleep and zDFD in both NREM and rapid eye movement (REM) sleep in patients with OSA [9].

Therefore, the purpose of this study was to explore the effect of CPAP treatment on the sleep EEG of patients with CSAS using FD and conventional EEG spectral analysis. We attempted to identify markers from these EEG signal analyses that could reflect improved brain function in patients with CSAS undergoing CPAP treatment. To avoid the interference of underlying diseases and potential confounding effects, we included only primary CSAS patients.

2. Materials and Methods

2.1. Study Participants. In this retrospective study, patients aged ≥20 years who were diagnosed with primary CSAS in the sleep lab of Peking University First Hospital and received CPAP pressure titration were enrolled.

According to ICSD-3, the diagnosis criteria of primary CSAS were as follows:

(A) At least one of the following:
  (1) Sleepiness
  (2) Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep
  (3) Awakening with shortness of breath
  (4) Snoring
  (5) Witnessed apneas

(B) PSG demonstrates all of the following:
  (1) Five or more central apneas and/or central hypopneas per hour of sleep
  (2) The number of central apneas and/or central hypopneas is >50% of the total number of apneas and hypopneas
  (3) Absence of Cheyne–Stokes breathing

(C) No evidence of daytime or nocturnal hypoventilation

(D) The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder

Finally, nine patients with primary CSAS, in accordance with the above criteria, who underwent full-night CPAP titration were included.

This retrospective study was approved by the ethics committee of Peking University First Hospital, and the requirement for obtaining informed consent was waived (Ethics Approval No. 2017 [1363]). The study adhered to the Declaration of Helsinki, and patient confidentiality was maintained.

2.2. Study Methods

2.2.1. Overnight PSG. Sleep apnea was confirmed by overnight PSG (Compumedics, E-Series, Australia). Six channels of EEG signals (C3-M2, C4-M1, F3-M2, F4-M1, O1-M2, and O2-M1), two channels of electrooculography signals (E1-M2 and E1-M2), and chin EMG (EMG1–EMG2, EMG1–EMG3), electrocardiography, respiration (nasal pressure, airflow), oxygen saturation, abdominal and chest movement, and leg movements were recorded according to the American Academy of Sleep Medicine (AASM) scoring manual (version 2.4) [14].

Sleep stage and respiratory events were analyzed according to the guidelines of the AASM [14]. Sleep stages were divided into *N*1, *N*2, *N*3, *R*, and *W* stages. Respiratory events were divided into obstructive apnea, central apnea, mixed apnea, and hypopnea. The apnea-hypopnea index (AHI) was defined and calculated as the sum of the number of apneas and hypopneas per hour.

2.3. CPAP Titration. CPAP titration was conducted according to the CPAP titration guidelines [15].

2.4. Calculation and Analysis of FD and zDFD. The FD and zDFD indices of the EEG before and after CPAP titration were analyzed. Briefly, FD is an engineering index used to describe the complexity of an EEG. Furthermore, the fast fluctuation of FD was measured using zDFD.

All raw FD and zDFD data were analyzed by the Academy for Advanced Interdisciplinary Studies, Peking University, and the single channel of C3-M2 was used for analysis. The FD and zDFD were calculated using custom programming in MATLAB (MathWorks, Inc., Natick, MA).

The general calculation processing is as follows: (1) the local FD of sleep EEG signals in each 30 s epoch was estimated for all patients using a standard "box-counting" algorithm. FD was defined as the following equation.

$$\mathrm{FD} = -\lim_{r \longrightarrow 0} \frac{\log_2 [N(r)]}{\log_2 (r)}. \quad (1)$$

By covering a structure such as an EEG signal with boxes of side length r, the FD is given, where $N(r)$ is the number of nonempty boxes needed to completely cover the structure, and FD corresponds to the slope of the plot versus $\log 2N(r)$. An FD time series was generated by sequentially moving the 30 s window forward in time. We applied an adaptive data analysis technique, called the empirical mode decomposition (EMD) algorithm, to detrend the FD sequence. In this study, the EMD algorithm was employed to smooth the FD sequences of the full-night EEG in an adaptive manner. The detailed processing method has been described in our previous reports [10].

2.5. EEG Spectral Analysis. Quantitative EEG analysis was conducted [16, 17]. All EEG study sampling rates were >200 Hz. A standard fast Fourier transform (FFT) with a Hamming window was performed. The FFT was applied to contiguous 30 s segments, and periodograms were calculated from one successive segment to obtain the absolute power in every stage lasting 30 s for the delta (0.1–3.99 Hz), theta (4–7.99 Hz), alpha (8–13 Hz), and beta (13–32 Hz) frequency bands of the central (C3-M2) EEG. Relative power was also calculated.

2.6. Statistical Methods. The SPSS software package, version 17.0 (SPSS, Inc., Chicago, IL, USA), was used for statistical analyses. Normality tests were also performed. Data conforming to a normal distribution were described as mean ± standard deviations. The FD, zDFD, and relative power percentages of the delta, theta, alpha, and beta waves before and after CPAP treatment were compared using a t-test of two related samples. A p value <0.05 was considered statistically significant.

3. Results

Nine CSAS patients (male:female ratio of 8 : 1; age, 60.2 ± 10.8 years; body mass index, $28.4 \pm 4.0\,\text{kg/m}^2$) were enrolled. After the initial monitoring, the nine CSAS patients underwent manual CPAP titration within 1 month. CPAP decreased the AHI effectively for patients with CSAS (from 60.0 ± 17.0 times/h to 6.0 ± 7.1 times/h; $p < 0.05$). The demographic and basic data are given in Table 1.

CPAP had a significant effect on sleep architecture in patients with CSAS. After the application of CPAP, the proportion of light sleep ($N1 + N2$ sleep) decreased, and slow-wave sleep ($N3$ sleep) and REM sleep increased (Table 2); however, some of the changes showed no statistical differences probably owing to the relatively small sample size.

After CPAP treatment, the FD decreased significantly during NREM sleep but increased significantly during REM sleep in patients with CSAS ($p < 0.05$; Figure 1). The zDFD in these patients showed a downward trend, although this difference was not statistically significant (Figure 1). The data are presented in Table 3.

Regarding the EEG spectral analysis results, the alpha power increased and delta/alpha ratio decreased during REM sleep in patients with CSAS after CPAP treatment ($p < 0.05$). There were no significant changes in delta, theta, and beta activities in patients with CSAS after CPAP treatment, although delta activity tended to decrease, while theta and alpha activities increased (Figure 2; $p > 0.05$).

4. Discussion

This study investigates the efficacy of CPAP on primary CSAS from the EEG perspective. Engineering parameters, FD and zDFD, and conventional EEG spectral analysis were used to analyze sleep EEG before and after CPAP. Based on the results, CPAP treatment could reduce the FD of NREM sleep in patients with primary CSAS, thereby reducing the complexity of EEG and stabilizing the EEG. On the other hand, CPAP could increase the FD of REM sleep, which may increase the EEG activity and improve the brain function. Conventional spectral power analysis showed that with CPAP treatment, the alpha power increased while the delta/alpha ratio decreased during REM sleep, suggesting increased EEG activity, which is consistent with the results of FD.

The impairment of brain function in patients with sleep breathing is an evident and prominent problem. Patients with sleep apnea often complain of daytime sleepiness, memory loss, and attention deficit, and CPAP is an effective treatment method for these patients. Until now, there has been limited research regarding the mechanism of CPAP efficacy on central sleep apnea [1, 15]. Since the central sleep apnea is very complicated and include a variety of diseases, the present study chose patients with primary CSAS to exclude the potential confounding effect.

Researchers have shown that EEG, assessed by quantitative analysis, is a tool to evaluate brain dysfunctions [10]. The most common method used in these quantitative analyses of EEG studies is power spectral analysis [6, 7, 10]. FD is a new parameter more suitable for the analysis of nonlinear and nonstationary physiological data, such as EEG [13]. In our previous study, we showed that the variation in FD reflects the macrostructure of sleep and that the fast fluctuation of FD, as measured by the zDFD, is a useful indicator of sleep disturbance; hence, it correlates with the AHI [13]. Sleep stages were divided into $N1$, $N2$, $N3$, R, and W stages. NREM sleep stage included $N1$, $N2$ (light sleep), and $N3$ (deep sleep). During deep sleep, the synchronization of EEG activity is significantly enhanced. The REM period is a period of paradoxical sleep, with weak muscle activity and active EEG. In our previous study [13], we showed that the FD value decreased from W to $N1$, $N2$, and $N3$ but increased during REM sleep, which showed that FD is a good indicator of the complexity of EEG. The zDFD reflects the fast fluctuation of FD in a certain period, which indicates the variability of EEG complexity. We used the FD and zDFD to analyze the effects of CPAP therapy on sleep EEG in patients with OSAS [9]. After CPAP treatment, the FD of EEG decreased significantly in NREM sleep, while the FD of EEG increased significantly in REM sleep.

Similar to the effect of CPAP on OSA patients, the present study showed that FD of EEG decreased significantly during NREM sleep in CSAS patients with CPAP. As mentioned earlier, the FD can reflect the complexity of the EEG. Thus, the results suggest that CPAP therapy can reduce the complexity of sleep EEG in patients with CSAS to achieve a more stable EEG pattern. On the other hand, the FD of sleep EEG increased during REM sleep in patients with CSAS. The EEG slowing in REM sleep is associated with the cognitive decline [18]. The increase in EEG activity during REM sleep may indicate the improvement of brain function.

This conclusion from the FD analysis was supported by conventional EEG spectral analysis. In the present study, we showed that the alpha power increased and the delta/alpha ratio of EEG decreased for REM sleep with CPAP treatment. Previous studies have shown that alpha power belongs to

Table 1: The demographic and basic data for the nine CSAS participants.

Number of CSAS participants	Age (y)	Gender	BMI (kg/m^2)	BP before bedtime (mmHg)	BP after sleep (mmHg)	AHI (hr)	AHI on CPAP (hr)
1	40	Male	30	120/90	140/100	37.3	7.2
2	51	Male	35.9	120/85	138/100	84.7	1.3
3	56	Male	26	130/70	140/70	67.5	7.5
4	57	Male	30.8	130/85	140/100	64.8	7.8
5	59	Female	27.8	130/80	150/100	76.5	1.6
6	67	Male	31.1	140/57	160/56	63.9	1.2
7	68	Male	23.4	140/85	120/85	33.9	0.6
8	69	Male	26.4	130/90	130/90	68.5	23.3
9	75	Male	23.8	144/86	160/80	51	3.5

BP, blood pressure; AHI, apnea and hypopnea index; CPAP, continuous positive airway pressure.

Table 2: The proportion of sleep in different stages of patients with CSAS before and after continuous positive airway pressure (CPAP) treatment.

	REM%	*N*1%	*N*2%	*N*3%
Before CPAP	8.40 ± 5.32	26.66 ± 16.62	55.13 ± 10.42	9.81 ± 10.62
After CPAP	23.60 ± 9.76*	7.38 ± 5.56*	49.93 ± 14.40	19.13 ± 15.17

* $p < 0.05$ vs. before CPAP. CSAS, central sleep apnea syndrome; CPAP, continuous positive airway pressure; REM, rapid eye movement.

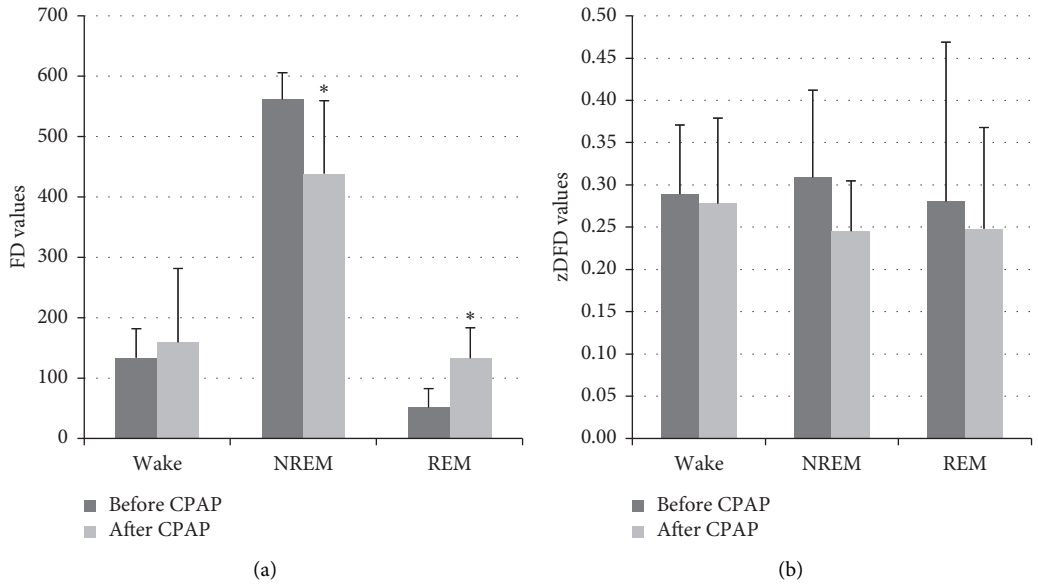

Figure 1: The changes of fractal dimension (FD) and zero-crossing rate of detrended FD (zDFD) in patients with primary central sleep apnea syndrome (CSAS) before and after continuous positive airway pressure (CPAP) treatment. (a) The FD significantly decreased in nonrapid eye movement (NREM) sleep but increased in rapid eye movement (REM) sleep with CPAP treatment (* $p < 0.05$; before CPAP). (b) There were no significant changes in zDFD before and after CPAP treatment in either NREM or REM sleep.

Table 3: The data of FD and zDFD before and after continuous positive airway pressure (CPAP) treatment in patients with central sleep apnea syndrome (CSAS).

CSAS	NREM		REM	
	Before CPAP	After CPAP	Before CPAP	After CPAP
FD	561.67 ± 44.19	438.67 ± 120.83*	51.55 ± 31.02	132.81 ± 50.54*
zDFD	0.31 ± 0.10	0.25 ± 0.60	0.28 ± 0.19	0.25 ± 0.12

* $p < 0.05$ vs. data before CPAP. FD, fractal dimension; zDFD, zero-crossing rate of detrended FD; CPAP, continuous positive airway pressure; CSAS, central sleep apnea syndrome.

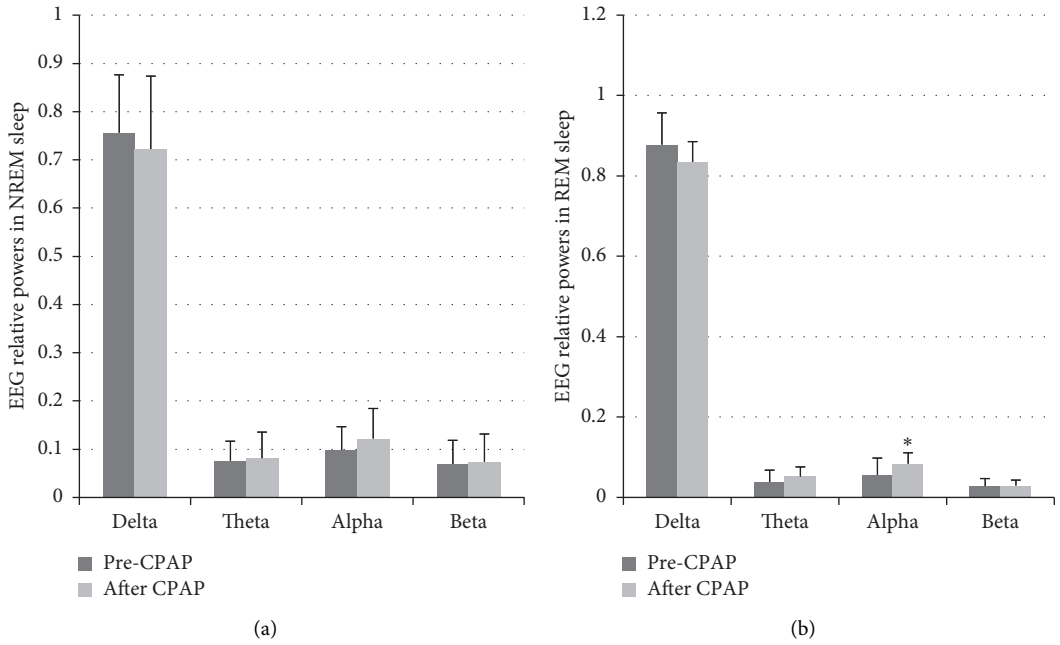

Figure 2: The changes of sleep EEG spectral power before and after CPAP in patients with CSAS in nonrapid eye movement (NREM) sleep (a) and rapid eye movement (REM) sleep. (b) $^{*}p < 0.05$ vs. before CPAP.

relatively active EEG frequency [6]. And the delta/alpha ratio of EEG has been used to reflect the level of EEG activation [18]. The present study showed the increased alpha power and decreased delta/alpha ratio of EEG, suggesting the increase of EEG activation and improvement of the brain function.

With respect to the zDFD, there were no significant changes after CPAP treatment during both NREM and REM sleep in patients with CSAS, although there was a downward trend. The zDFD is a useful parameter that reflects the variability in EEG complexity. In our previous research, we showed that zDFD decreased remarkably after CPAP therapy in patients with OSAS [9]. The effect of CPAP on the zDFD was different between patients with CSAS and those with OSAS, which may be due to the fact that primary CSAS is a rare disease [15]. Only nine cases of primary CSAS were enrolled in this study, which is a relatively small number of cases. It may also be related to the different impact of CPAP on central and obstructive apnea events, which may require further exploration.

The main limitation of our study was the small sample number of primary CSAS patients due to its low prevalence. In addition, the overall results of the effect of CPAP on CSAS EEG were similar to those of OSA. Whether this result suggests a similar effect of CPAP on OSA and CSAS EEG or a bias due to the small sample size remains to be determined.

5. Conclusions

In this study, we have explored, for the first time, the effect of CPAP therapy on sleep EEG characteristics in patients with primary CSAS using FD. With CPAP treatment, the FD significantly decreased in NREM sleep but increased in REM sleep in patients. This suggests that CPAP could reduce the sleep EEG complexity in NREM sleep and increase the sleep EEG activity in REM sleep in patients with CSAS, which may be one of the mechanisms by which CPAP improves brain function in patients with CSAS. Therefore, FD may be used as a new biomarker of electroencephalographic stability and improvement in brain function with CPAP treatment for primary CSAS.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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References

[1] S. Baillieul, B. Revol, I. Jullian-Desayes, M. Joyeux-Faure, R. Tamisier, and J.-L. Pépin, "Diagnosis and management of central sleep apnea syndrome," *Expert Review of Respiratory Medicine*, vol. 13, no. 6, pp. 545–557, 2019.

[2] M. J. Sateia, "International classification of sleep disorders-third edition," *Chest*, vol. 146, no. 5, pp. 1387–1394, 2014.

[3] M. Dalmases, C. Solé-Padullés, M. Torres et al., "Effect of CPAP on cognition, brain function, and structure among elderly patients with OSA," *Chest*, vol. 148, no. 5, pp. 1214–1223, 2015.

[4] U. Smailovic and V. Jelic, ""Neurophysiological markers of Alzheimer's disease: quantitative EEG Approach," *Neurology and Therapy*, vol. 8, no. 2, pp. 37–55, 2019.
[5] A. Parekh, A. E. Mullins, and K. Kam, "Slow-wave activity surrounding stage N2 K-complexes and daytime function measured by psychomotor vigilance test in obstructive sleep apnea," *Sleep*, vol. 42, no. 3, Article ID 30561759, 2019.
[6] F. Morisson, A. Décary, D. Petit, G. Lavigne, J. Malo, and J. Montplaisir, "Daytime sleepiness and EEG spectral analysis in apneic patients before and after treatment with continuous positive airway pressure," *Chest*, vol. 119, no. 1, pp. 45–52, 2001.
[7] A. G. Xiromeritis, A. A. Hatziefthimiou, G. M. Hadjigeorgiou, K. I. Gourgoulianis, D. N. Anagnostopoulou, and N. V. Angelopoulos, "Quantitative spectral analysis of vigilance EEG in patients with obstructive sleep apnoea syndrome," *Sleep and Breathing*, vol. 15, no. 1, pp. 121–128, 2011.
[8] S. D. Lee, G. Ju, J.-W. Kim, and I.-Y. Yoon, "Improvement of EEG slowing in OSAS after CPAP treatment," *Journal of Psychosomatic Research*, vol. 73, no. 2, pp. 126–131, 2012.
[9] C. Zhang, J. Lv, J. Zhou et al., "The effect of CPAP treatment on EEG of OSAS patients," *Sleep and Breathing*, vol. 19, no. 4, pp. 1121–1124, 2015.
[10] J. Taillard, P. Sagaspe, and C. Berthomier, "Non-REM sleep characteristics predict early cognitive impairment in an aging population," *Frontiers in Neurology*, vol. 10, p. 197, 2019.
[11] G. A. Losa, "The fractal geometry of life," *Rivista di Biologia*, vol. 102, no. 1, pp. 29–59, 2009.
[12] F. Grizzi, A. Castello, D. Qehajaj, C. Russo, and E. Lopci, "The complexity and fractal geometry of nuclear medicine images," *Molecular Imaging and Biology*, vol. 21, no. 3, pp. 401–409, 2019.
[13] J. Zhang, X. C. Yang, L. Luo et al., "Assessing severity of obstructive sleep apnea by fractal dimension sequence analysis of sleep EEG," *Physica A: Statistical Mechanics and its Applications*, vol. 388, no. 20, pp. 4407–4414, 2009.
[14] R. B. Berry, R. Brooks, C. Gamaldo et al., "AASM scoring manual updates for 2017 (version 2.4)," *Journal of Clinical Sleep Medicine*, vol. 13, no. 5, pp. 665-666, 2017.
[15] R. N. Aurora, S. Chowdhuri, K. Ramar et al., "The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses," *Sleep*, vol. 35, no. 1, pp. 17–40, 2012.
[16] A. L. D'Rozario, N. E. Cross, and A. Vakulin, "Quantitative electroencephalogram measures in adult obstructive sleep apnea - potential biomarkers of neurobehavioural functioning," *Sleep Medicine Reviews*, vol. 36, pp. 29–42, 2017.
[17] H. Alshaer, A. Pandya, I. Zivanovic, C. G. Carvalho, and C. M. Ryan, "The effect of continuous positive airway pressure on spectral encephalogram characteristics in stroke patients with obstructive sleep apnea," *Respiratory Physiology & Neurobiology*, vol. 249, pp. 62–68, 2018.
[18] D. Wang, A. J. Piper, B. J. Yee et al., "Hypercapnia is a key correlate of EEG activation and daytime sleepiness in hypercapnic sleep disordered breathing patients," *Journal of Clinical Sleep Medicine*, vol. 10, no. 5, pp. 517–522, 2014.

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Research Article

Head-To-Head Comparison of Treatment Failure and Costs among COPD Patients Who Used Noninvasive Ventilation in the Ward versus in the ICU: A Propensity-Matched Cohort Study

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Background. Head-to-head comparison of treatment failure and costs among chronic obstruct pulmonary disease (COPD) patients who used noninvasive ventilation (NIV) in the ward versus in the ICU is lacking. *Methods*. This retrospective study was performed in a department of respiratory and critical care medicine in a teaching hospital. COPD patients who used NIV in the respiratory ward or respiratory ICU were screened. We enrolled patients with $PaCO_2$ more than 45 mmHg and pH less than 7.35 before the use of NIV. *Results*. We enrolled 83 patients who initiated NIV in the ward and 319 patients in the ICU. Only 5 (6%) patients in the ward were required to transfer to ICU for intensive care. The vital signs were worse but improved faster within 24 h of NIV among patients in the ICU than those in the ward. The NIV failure, hospital mortality, and the length of stay in hospital did not differ between the two groups. However, the duration of NIV was shorter (median 4.0 vs. 6.1 days, $p < 0.01$) and hospital costs were higher (median 4638 vs. 3093 $USD, $p < 0.01$) among patients in the ICU than those in the ward. After propensity matching, 42 patients were left in each group, and the baseline data were comparable between the two groups. The findings in the overall cohort were confirmed again in the propensity-matched cohort. *Conclusions*. Among COPD patients, the use of NIV in the ward leads to longer duration of NIV, but lower hospital costs, and similar NIV failure and mortality compared with those in the ICU.

1. Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) is 8.6% in adult population and 13.7% in those aged 40 years or older [1]. It leads to high morbidity and mortality and becomes the third leading cause of death in China [2, 3]. Also, the cost burden in COPD patients is much higher than non-COPD subjects [4]. At the end stage, shortness of breath and hypercapnia are the main clinical features in COPD patients. Therefore, relief of dyspnea and reduction of $PaCO_2$ are two main therapeutic regimens.

In COPD patients, noninvasive ventilation (NIV) improves minute ventilation and decreases the work of breathing [5]. NIV also reduces the need of intubation and mortality in this population [6, 7]. Guidelines have strongly recommended the use of NIV in hospitalized patients due to COPD exacerbations [8–10]. Also, the use of NIV in hospitalized COPD patients is increasing year by year [11].

Among COPD patients, the use of NIV in the intensive care unit (ICU) is common [12–14]. As ICU beds are limited, not all COPD patients can admit to ICU for application of NIV. The ward is another place where the NIV can be used. Several studies have reported that use of NIV in the ward is feasible [15–17]. However, head-to-head comparison of treatment failure and costs among COPD patients who used noninvasive ventilation (NIV) in the ward versus in the ICU is lacking. Here, we aimed to explore the optimal location to use of NIV in COPD patients.

2. Methods

This was a retrospective observational study performed in a teaching hospital from March, 2015, to June, 2018. We screened all the patients who used NIV as first-line therapy due to COPD exacerbation in the respiratory ward or respiratory ICU and enrolled the patients with pH less than 7.35 and $PaCO_2$ more than 45 mmHg. However, the patients with refusal of intubation were excluded. The diagnosis of COPD was based on the criteria published by Chinese Medical Association [18]. The study protocol was approved by our ethics committee (the First Affiliated Hospital of Chongqing Medical University). As this was a retrospective study, the informed consent was waived.

In the respiratory ward, the bed nurse ratio was 1 : 0.4 and the bed physician ratio was 1 : 0.5. In the respiratory ICU, the bed nurse ratio was 1 : 2.5 and the bed physician ratio was 1 : 0.6. Use of NIV in the ward or in the ICU was decided by the attending physicians based on the volume of ICU beds, ability to pay, and patients' wishes. In our hospital, the indications of NIV in patients with COPD exacerbation were as follows: (1) respiratory rate more than 25 breaths/min, (2) $PaCO_2$ more than 45 mmHg, (3) pH less than 7.35, (4) PaO_2/FiO_2 less than 200 mmHg, and (5) vigorous activity of accessory respiratory muscles [19].

The pneumologist took care of the NIV patients in the ward. When the NIV has been used for more than 2 hours, the patients in the ward were considered to be transferred to ICU for escalation therapy if the respiratory failure got worse. The criteria were respiratory rate more than 35 breaths/min, pH less than 7.25, PaO_2/FiO_2 less than 100 mmHg, unstable hemodynamic status, and other causes required intensive care. However, this was decided by the attending physician's discretion.

The management of NIV (BiPAP Vision or V60; Philips Respironics, Carlsbad, CA) in COPD patients was based on our hospital protocol [19–21]. The face mask was the first choice for the interface to connect the ventilator to the patient. The size of the face mask was fitted to the face type. Bilevel positive airway pressure was used for all patients. The expiratory positive airway pressure was initially set at 4 cm H_2O, and it was titrated to diminish the ineffective trigger. Usually, the expiratory positive pressure ventilation was maintained at 4 to 8 cm H_2O. The inspiratory positive airway pressure was initially set at 8 cm H_2O and then gradually increased to achieve the best control of dyspnea or to the tolerance of the patient. Usually, the inspiratory positive airway pressure was maintained at 15 to 20 cm H_2O within 30 minutes. The fractional concentration of inspiratory oxygen (FiO_2) was adjusted to maintain the bedside SpO_2 above 90% and the PaO_2 above 60 mmHg. At the initial phase, continuous use of NIV was encouraged except drinking, eating, and sputum excretion. If the respiratory failure relieved, intermittent use of NIV was performed until the NIV was weaned. However, in those whose respiratory failure progressively deteriorated and required invasive mechanical ventilation, intubation was performed. The NIV failure was defined as requirement of intubation or death during NIV intervention. In addition, the decision to transfer the patient to ICU for escalation therapy was based on the attending physicians' discretion if the respiratory failure progressively deteriorated.

We collected the age, gender, underlying disease, vital signs, and arterial blood gas tests. The disease severity was assessed by the acute physiology and chronic health evaluation II (APACHE II) score. The prognostic outcomes were also collected including the rate of NIV failure and hospital mortality. The resource consumption was assessed including the duration of NIV, length of stay in hospital, and hospital cost. All the data we collected were extracted from the medical records.

2.1. Statistical Analysis. The continuous variable was reported as mean value and standard deviation or median value and interquartile range (IQR) when appropriate. Differences between two groups were analyzed with the use of Student's *t*-test or the Mann–Whitney *U* test. Categorical variable was reported as numbers and percentages, and the differences between groups were analyzed with the use of Chi-square or Fisher's exact tests. p values less than 0.05 were considered statistically significant.

Propensity scores were estimated using multiple logistic regression analyses, with adjustments for age, gender, underlying disease, APACHE II score, GCS, respiratory rate, heart rate, mean arterial pressure, pH, $PaCO_2$, and PaO_2/FiO_2. After calculating propensity scores, we matched the patients who initiated the NIV in the ward and those in the ICU with similar propensity scores at a 1 : 1 ratio, using the nearest neighbor method, no replacement, and a 0.05 caliper width.

3. Results

In the overall cohort, 83 patients initiated NIV as first-line therapy in the ward and 319 patients in the ICU (Table 1). Compared with the subjects in the ICU, the patients who initiated the NIV in the ward had lower respiratory rate (24 ± 3 vs. 28 ± 6 breaths/min, $p < 0.01$), lower heart rate (98 ± 19 vs. 108 ± 22, beats/min), higher pH (7.29 ± 0.05 vs. 7.26 ± 0.06, $p < 0.01$, higher PaO_2/FiO_2 (228 ± 70 vs. 208 ± 90 mmHg, $p = 0.05$), and higher Glasgow coma scale (14.8 ± 0.7 vs. 14.4 ± 1.5, $p = 0.02$) at the beginning of NIV.

Five (6%) patients in the ward were transferred to the ICU for intensive care (3 for continuous use of NIV and 2 for intubation) due to progressive deterioration (Table 2). Of the 5 patients, only one died in hospital. The rate of NIV failure, hospital mortality, and the length of stay in hospital did not differ between the two groups. The duration of NIV was longer in the patients who initiated NIV in the ward than those in the ICU (6.1, IQR: 3.0–9.1 vs. 4.0, 2.1–6.6 days, $p < 0.01$). But, their hospital cost was much lower (3093, IQR: 2214–4352 vs. 4638, 3259–7712 $USD, $p < 0.01$). Also, the vital signs from initiation to 24 h of NIV improved faster among the patients in the ICU than those in the ward (Figure 1).

After propensity matching, 42 patients were left in each group (Table 3). The baseline data were comparable between the two groups. The rate of NIV failure and hospital

Table 1: Clinical characteristics of the patients who used NIV in the ward versus those in the ICU.

	In the ward $N = 83$	In the ICU $N = 319$	p
Age, years	71 ± 8	73 ± 9	0.10
Male/female	63/20	243/76	>0.99
Underlying disease			
Hypotension	27 (33%)	110 (35%)	0.80
Diabetes mellitus	16 (19%)	61 (19%)	>0.99
Chronic heart disease	13 (16%)	63 (20%)	0.44
Chronic kidney disease	0 (0%)	14 (4%)	0.08
Chronic liver disease	1 (1%)	10 (3%)	0.47
Data collected at initiation of NIV			
APACHE II score	15 ± 2	16 ± 4	0.09
GCS	14.8 ± 0.7	14.4 ± 1.5	0.02
Respiratory rate, breaths/min	24 ± 3	28 ± 6	<0.01
Heart rate, beats/min	98 ± 19	108 ± 22	<0.01
Mean arterial pressure, mmHg	91 ± 11	100 ± 18	<0.01
pH	7.29 ± 0.05	7.26 ± 0.06	<0.01
$PaCO_2$, mmHg	80 ± 13	83 ± 17	0.08
PaO_2/FiO_2, mmHg	228 ± 70	208 ± 90	0.05

NIV = noninvasive ventilation, ICU = intensive care unit, GCS = Glasgow coma scale, APACHE II = acute physiology and chronic health evaluation II.

Table 2: Outcomes in patients who used NIV in the ward versus those in the ICU.

	In the ward $N = 83$	In the ICU $N = 319$	p
NIV failure	4 (5%)	35 (11%)	0.10
Hospital mortality	3 (4%)	31 (10%)	0.08
Transfer to the ICU	5 (6%)	–	–
Duration of NIV, days	6.1 (3.0–9.1)	4.0 (2.1–6.6)	<0.01
The length of stay in hospital, days	10.2 (8.0–15.0)	10.2 (6.7–15.0)	0.40
Hospital cost, $	3093 (2214–4352)	4638 (3259–7712)	<0.01

NIV = noninvasive ventilation, ICU = intensive care unit.

mortality did not differ between the two groups (Table 4). Similar with the overall cohort, we also found that the duration of NIV was longer and hospital cost was lower in patients who initiated the NIV in the ward than those in the ICU. Also, the respiratory rate, heart rate, pH, $PaCO_2$, and PaO_2/FiO_2 improved faster within the first 24 h of NIV in patients who initiated NIV in the ICU than those in the ward (Figure 2). In addition, there was another new finding that the length of stay in hospital was shorter among the patients in the ICU than those in the ward (median 8.8 vs. 10.9 day, $p = 0.04$).

4. Discussion

To our knowledge, this is the first head-to-head comparison of treatment failure and costs among COPD patients who used NIV in the ward versus in the ICU. Slower improvement of vital signs and arterial blood gas tests, longer duration of NIV, but lower cost were observed in patients who used NIV in the ward than those in the ICU. Also, the rate of NIV failure and hospital mortality did not differ between the two groups.

A landmark paper published at 2000 has reported that the early use of NIV in the ward among patients with COPD exacerbation reduced the need for intubation and hospital mortality compared with standard care [6]. This study only demonstrated that the use of NIV in the ward was feasible. During the following 20 years, many studies also showed the benefits of NIV in the ward among COPD population [17, 22, 23]. However, these studies only demonstrated that patients with COPD exacerbation benefited from NIV in the ward but failed to demonstrate the optimal location where the NIV should be used. To our knowledge, our study is the first one head-to-head comparison on the use of NIV in the ward against those in the ICU. It provides a reference for clinical staffs how to select the location to use NIV.

We found an interesting result that patients who used NIV in the ward had a less severe respiratory acidosis and lower cost but a longer duration of NIV compared with those in the ICU. The potential reasons were as follows. First, the physicians and nurses in the ICU were much more than those in the ward when they managed the same number of patients. Second, the ICU physicians and nurses have managed much more NIV patients than those who managed NIV in the ward. So, the experience on NIV management was much richer in ICU physicians and nurses. Third, the two reasons lead to a faster improvement in vital signs and arterial blood gas tests in the ICU patients. Therefore, these reasons can be explained this interesting result.

Delayed admission to the ICU may be associated with increased mortality. A previous study reported by Valentini et al. showed that the mortality was 18% in patients who directly transferred from the emergency department to respiratory ICU, but it increased to 64% in cases who

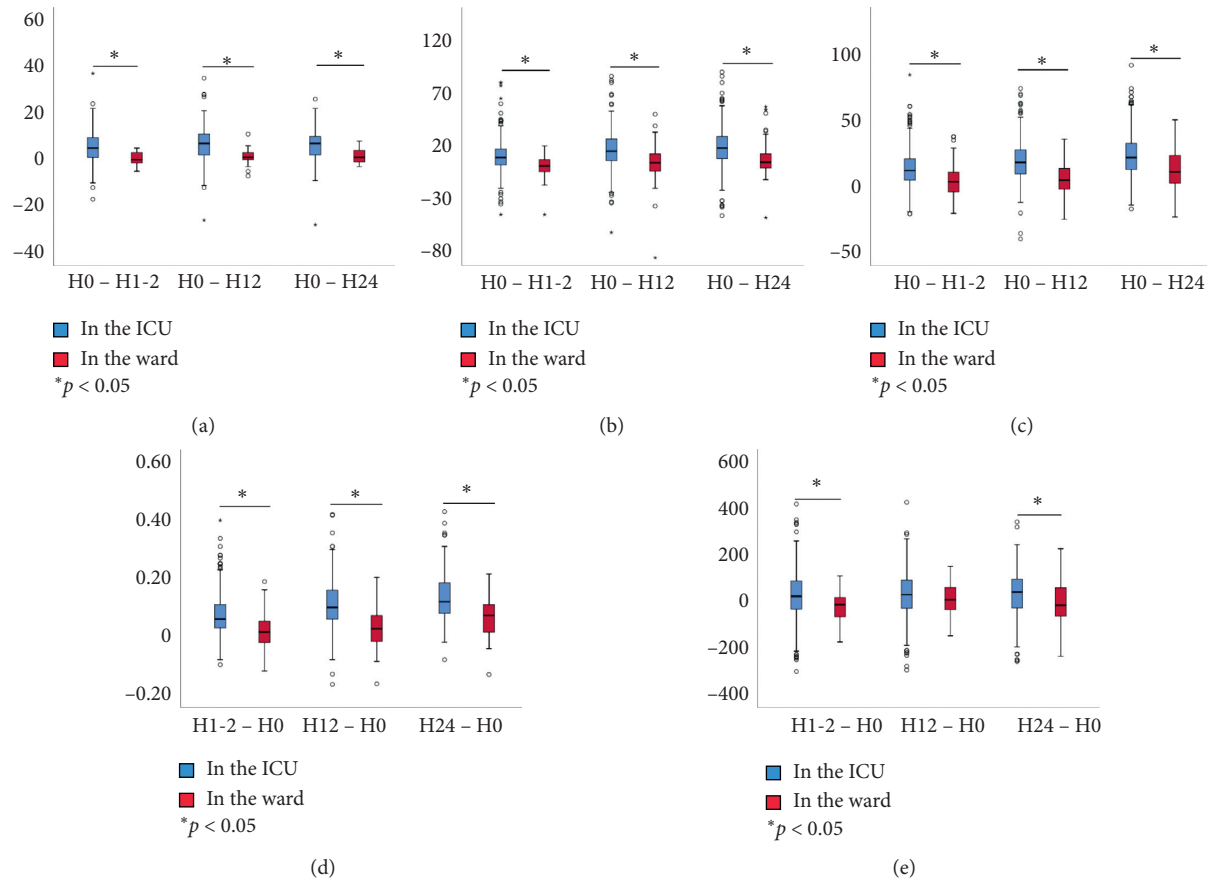

Figure 1: The changes of vital signs and arterial blood gas tests within 24 h of NIV in overall cohort. (a) ΔRespiratory rate, breaths/min. (b) ΔHeart rate, beats/min. (c) $\Delta PaCO_2$, mmHg. (d) ΔpH. (e) $\Delta PaO_2/FiO_2$, mmHg.

Table 3: Clinical characteristics in the propensity-matched cohort.

	In the ward $N = 42$	In the ICU $N = 42$	p
Age, years	72 ± 8	72 ± 9	0.88
Male/female	32/10	33/9	>0.99
Underlying disease			
Hypotension	16 (38%)	12 (29%)	0.48
Diabetes mellitus	10 (24%)	11 (26%)	>0.99
Chronic heart disease	6 (14%)	9 (21%)	0.57
Chronic kidney disease	0 (0%)	1 (2%)	>0.99
Chronic liver disease	0 (0%)	1 (2%)	>0.99
Data collected at initiation of NIV			
APACHE II score	15 ± 3	15 ± 4	0.58
GCS	14.7 ± 0.9	14.5 ± 0.8	0.31
Respiratory rate, breaths/min	25 ± 3	26 ± 8	0.49
Heart rate, beats/min	104 ± 20	106 ± 19	0.31
Mean arterial pressure, mmHg	93 ± 12	95 ± 15	0.47
pH	7.29 ± 0.04	7.29 ± 0.05	0.69
$PaCO_2$, mmHg	77 ± 11	76 ± 16	0.82
PaO_2/FiO_2, mmHg	208 ± 71	214 ± 92	0.73

NIV = noninvasive ventilation, ICU = intensive care unit, GCS = Glasgow coma scale, APACHE II = acute physiology and chronic health evaluation II.

transferred from the respiratory ward [24]. This study enrolled all the patients who used NIV in the ICU due to various reasons. However, we only enrolled patients who used the NIV due to COPD exacerbation, and only 5 (6%) patients in the ward were transferred to ICU due to progressive deteriorations. Among the 5 cases, only one died in hospital. Therefore, the need to transfer to the ICU for escalation therapy is low among COPD patients who used NIV in the ward. Also, the mortality is not high among those who transferred to the ICU. We believe the use of NIV in the ward among COPD patients is an alternative place.

Table 4: Outcomes in the propensity-matched cohort.

	In the ward $N=42$	In the ICU $N=42$	p
NIV failure	1 (2%)	4 (9%)	0.36
Hospital mortality	2 (5%)	2 (5%)	>0.99
Transfer to the ICU	2 (5%)	–	–
Duration of NIV, days	7.1 (4.1–10.6)	4.2 (1.8–5.7)	<0.01
The length of stay in hospital, days	10.9 (8.6–16.1)	8.8 (6.4–15.6)	0.04
Hospital cost, $	3105 (2286–4443)	3853 (2281–8049)	0.02

NIV=noninvasive ventilation, ICU=intensive care unit.

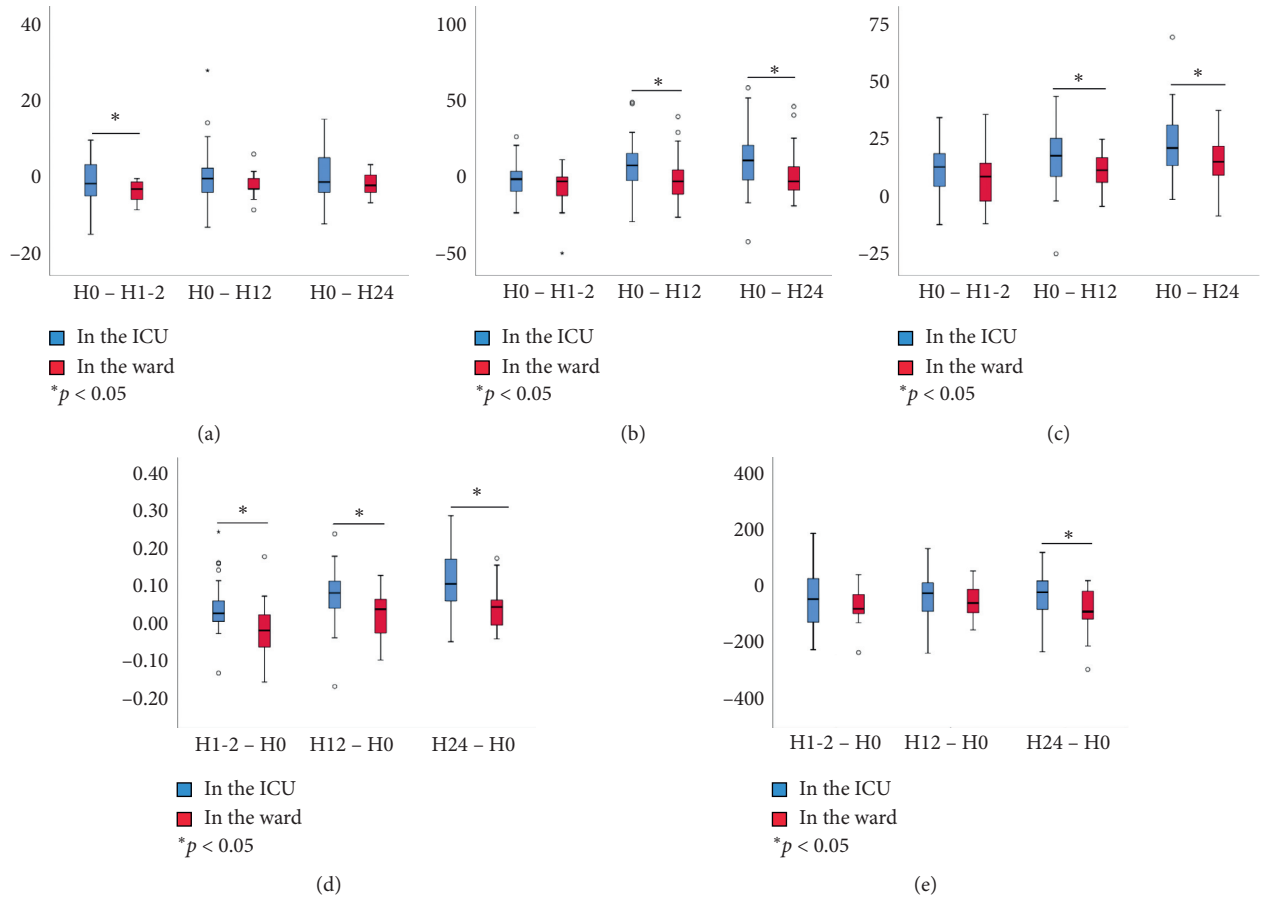

Figure 2: The changes of vital signs and arterial blood gas tests within 24 h of NIV in propensity-matched cohort. (a) ΔRespiratory rate, breaths/min. (b) ΔHeart rate, beats/min. (c). $\Delta PaCO_2$, mmHg. (d) ΔpH. (e) $\Delta PaO_2/FiO_2$, mmHg.

Our study may be limited by the retrospective design. Where to use the NIV was decided by the attending physicians. More serious illness patients were more likely to transfer to the ICU, which lead to unbalanced baseline data between patients in the ICU and those in the ward. However, we performed a propensity-matched analysis to balance the confounders. After propensity matching, the baseline data were comparable. This improves the comparability between the two groups. In addition, the transportation of the patients from the ward to ICU for escalation therapy was also decided by the attending physicians if the respiratory failure progressively deteriorated. Delayed admission to the ICU for escalation therapy may be occurred because the personnel allocation was much lower in the ward than that in the ICU. Therefore, more attention should be paid to the patients who used the NIV in the ward.

5. Conclusions

The use of NIV in the ward is cost effective for COPD patients. The rate of transportation to the ICU for escalation therapy is low. NIV failure rate and mortality did not differ between patients who initiated NIV in the ward and those in the ICU.

Abbreviations

COPD: Chronic obstructive pulmonary disease
NIV: Noninvasive ventilation

GCS: Glasgow coma scale
APACHE II: Acute physiology and chronic health evaluation II
IQR: Interquartile range
ICU: Intensive care unit

Data Availability

The datasets analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest in this study.

Authors' Contributions

Jun Duan and Chuanbo Liu conceived the study, contributed to study design, study management, data acquisition, data interpretation, and manuscript preparation, and took responsibility for the integrity of the whole study. Yueling Hong contributed to study design, data acquisition, data interpretation, and data analysis and drafted the manuscript. Linfu Bai, Lei Jiang, Xiaoli Han, Shicong Huang, and Wenhui Hu contributed to data acquisition, data analysis, data interpretation, and manuscript revision. All of the authors read and approved the final version.

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References

[1] C. Wang, J. Xu, L. Yang et al., "Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study," *The Lancet*, vol. 391, no. 10131, pp. 1706–1717, 2018.

[2] T. Vos, C. Allen, M. Arora et al., "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015," *Lancet*, vol. 388, pp. 1545–1602, 2016.

[3] M. Zhou, H. Wang, J. Zhu et al., "Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013," *The Lancet*, vol. 387, no. 10015, pp. 251–272, 2016.

[4] W. Chen, J. M. FitzGerald, D. D. Sin et al., "Excess economic burden of comorbidities in COPD: a 15-year population-based study," *European Respiratory Journal*, vol. 50, 2017.

[5] L. Appendini, A. Patessio, S. Zanaboni et al., "Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 149, no. 5, pp. 1069–1076, 1994.

[6] P. Plant, J. Owen, and M. Elliott, "Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial," *The Lancet*, vol. 355, no. 9219, pp. 1931–1935, 2000.

[7] Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease, "Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicentre randomized controlled trial," *Chinese Medical Journal*, vol. 118, pp. 2034–2040, 2005.

[8] J. A. Wedzicha, M. Miravitlles, J. R. Hurst et al., "Management of COPD exacerbations: a European respiratory society/American thoracic society guideline," *European Respiratory Journal*, vol. 49, 2017.

[9] A. C. Davidson, S. Banham, M. Elliott et al., "BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults," *Thorax*, vol. 71, no. 2, pp. ii1–35, 2016.

[10] S. P. Keenan, T. Sinuff, K. E. A. Burns et al., "Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting," *Canadian Medical Association Journal*, vol. 183, no. 3, pp. E195–E214, 2011.

[11] M. S. Stefan, M.-S. Shieh, P. S. Pekow, N. Hill, M. B. Rothberg, and P. K. Lindenauer, "Trends in mechanical ventilation among patients hospitalized with acute exacerbations of COPD in the United States, 2001 to 2011," *Chest*, vol. 147, no. 4, pp. 959–968, 2015.

[12] L. C. Myers, M. K. Faridi, P. Currier, and C. A. Camargo, "ICU utilization for patients with acute exacerbation of chronic obstructive pulmonary disease receiving noninvasive ventilation," *Critical Care Medicine*, vol. 47, no. 5, pp. 677–684, 2019.

[13] J. Phua, K. Kong, K. H. Lee, L. Shen, and T. K. Lim, "Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure," *Intensive Care Medicine*, vol. 31, no. 4, pp. 533–539, 2005.

[14] D. Contou, C. Fragnoli, A. Cordoba-Izquierdo, F. Boissier, C. Brun-Buisson, and A. W. Thille, "Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit," *Respiratory Care*, vol. 58, no. 12, pp. 2045–2052, 2013.

[15] S. P. Trethewey, R. G. Edgar, A. M. Turner et al., "Ward-based non-invasive ventilation in acute exacerbations of COPD: a narrative review of current practice and outcomes in the UK," *Healthcare (Basel)*, vol. 6, 2018.

[16] L. Cabrini, M. Antonelli, G. Savoia, and M Landriscina, "Non-invasive ventilation outside of the intensive care unit: an Italian survey," *Minerva Anestesiologica*, vol. 77, no. 3, pp. 313–322, 2011.

[17] S. Fiorino, L. Bacchi-Reggiani, E. Detotto et al., "Efficacy of non-invasive mechanical ventilation in the general ward in patients with chronic obstructive pulmonary disease admitted for hypercapnic acute respiratory failure and pH," *Internal Medicine Journal*, vol. 45, no. 5, pp. 527–537, 2015.

[18] W. Chen and Z. Qing-yuan, "Guideline for mechanical ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease (2007)," *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*, vol. 19, pp. 513–518, 2007.

[19] L. Fan, Q. Zhao, Y. Liu, L. Zhou, and J. Duan, "Semiquantitative cough strength score and associated outcomes in noninvasive positive pressure ventilation patients with acute exacerbation of chronic obstructive pulmonary disease," *Respiratory Medicine*, vol. 108, no. 12, pp. 1801–1807, 2014.

[20] J. Duan, S. Wang, P. Liu et al., "Early prediction of noninvasive ventilation failure in COPD patients: derivation, internal

validation, and external validation of a simple risk score," *Ann Intensive Care*, vol. 9, p. 108, 2019.

[21] J. Duan, X. Tang, S. Huang, J. Jia, and S. Guo, "Protocol-directed versus physician-directed weaning from noninvasive ventilation," *The Journal of Trauma and Acute Care Surgery*, vol. 72, no. 5, pp. 1271–1275, 2012.

[22] K. M. McLaughlin, I. M. Murray, G. Thain, and G. P. Currie, "Ward-based non-invasive ventilation for hypercapnic exacerbations of COPD: a "real-life" perspective," *QJM*, vol. 103, no. 7, pp. 505–510, 2010.

[23] M. Yalcinsoy, C. Salturk, S. Oztas et al., "Can patients with moderate to severe acute respiratory failure from COPD be treated safely with noninvasive mechanical ventilation on the ward?" *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 11, pp. 1151–1160, 2016.

[24] I. Valentini, A. M. G. Pacilli, P. Carbonara et al., "Influence of the admission pattern on the outcome of patients admitted to a respiratory intensive care unit: does a step-down admission differ from a step-up one?" *Respiratory Care*, vol. 58, no. 12, pp. 2053–2060, 2013.

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Research Article

Risk Factors Associated with Late Failure of Noninvasive Ventilation in Patients with Chronic Obstructive Pulmonary Disease

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Background. Risk factors for noninvasive ventilation (NIV) failure after initial success are not fully clear in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). *Methods*. Patients who received NIV beyond 48 h due to acute exacerbation of COPD were enrolled. However, we excluded those whose pH was higher than 7.35 or $PaCO_2$ was less than 45 mmHg which was measured before NIV. Late failure of NIV was defined as patients required intubation or died during NIV after initial success. *Results*. We enrolled 291 patients in this study. Of them, 48 (16%) patients experienced late NIV failure (45 received intubation and 3 died during NIV). The median time from initiation of NIV to intubation was 4.8 days (IQR: 3.4–8.1). Compared with the data collected at initiation of NIV, the heart rate, respiratory rate, pH, and $PaCO_2$ significantly improved after 1–2 h of NIV both in the NIV success and late failure of NIV groups. Nosocomial pneumonia (odds ratio (OR) = 75, 95% confidence interval (CI): 11–537), heart rate at initiation of NIV (1.04, 1.01–1.06 beat per min), and pH at 1–2 h of NIV (2.06, 1.41–3.00 per decrease of 0.05 from 7.35) were independent risk factors for late failure of NIV. In addition, the Glasgow coma scale (OR = 0.50, 95% CI: 0.34–0.73 per one unit increase) and PaO_2/FiO_2 (0.992, 0.986–0.998 per one unit increase) were independent protective factors for late failure of NIV. In addition, patients with late failure of NIV had longer ICU stay (median 9.5 vs. 6.6 days) and higher hospital mortality (92% vs. 3%) compared with those with NIV success. *Conclusions*. Nosocomial pneumonia; heart rate at initiation of NIV; and consciousness, acidosis, and oxygenation at 1–2 h of NIV were associated with late failure of NIV in patients with COPD exacerbation. And, late failure of NIV was associated with increased hospital mortality.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death [1]. Acute exacerbations of COPD are responsible for more than 600,000 hospitalizations annually and result in direct costs of more than $20 billion in the United States [2]. Noninvasive ventilation (NIV) as an effective intervention has been used to manage patients with acute exacerbation of COPD for decades. It improves pH, reduces respiratory rate, reduces $PaCO_2$, and subsequently reduces intubation rate and mortality [3, 4]. Because of these advantages, use of NIV in patients with acute exacerbation of COPD has continuously increased in recent years [5, 6]. Moreover, current guidelines strongly recommend NIV to be used in patients with acute exacerbation of COPD [7, 8].

In spite of benefits from NIV in patients with acute exacerbation of COPD, late failure of NIV after initial improvement is not rare. It ranges from 8% to 23% [9–12]. The reasons for early failure of NIV (failure occurred at initial 48 h of NIV) have been widely discussed in patients with acute exacerbation of COPD [13–18]. However, only few studies have reported the reasons for late failure of NIV [9, 12, 19]. Because of small sample sizes, these studies only identified

poor sleep, delirium, metabolic complications, and functional limitation were associated with late failure of NIV. Thus, we aimed to find other potential risk factors for late failure of NIV in patients with acute exacerbation of COPD.

2. Methods

We performed an observational study in a respiratory ICU of a teaching hospital from January 2012 to December 2015. The study protocol was approved by our ethics committee and the institutional review board (the First Affiliated Hospital of Chongqing Medical University). Because of the observational nature, the informed consents were waived.

Patients who were admitted to our ICU for NIV as a first-line intervention because of acute exacerbation of COPD were screened for eligibility. COPD was diagnosed based on the guideline developed by our Respiratory Disease Committee, Chinese Medical Association in 2002 [20]. We enrolled the patients whose pH was less than 7.35 and $PaCO_2$ was more than 45 mmHg which were measured before NIV. However, we excluded those whose NIV was terminated because of clinical improvement, requirement of intubation, or death within 48 h of NIV. Late failure of NIV was defined as intubation or death during NIV after initial success [9].

In our department, NIV was managed by attending physicians, respiratory therapists, and nurses as the protocol reported previously [21]. The face mask (ZS-MZA Face Mask; Shanghai Zhongshan Medical Technology Co., Shanghai, China) was the first choice for NIV (BiPAP Vision or Respironics V60). Patients were positioned at 30° to 45° to avoid aspiration, if there were no contraindications to this positioning. Bi-level positive airway pressure (S/T mode) was used for all patients. Expiratory positive airway pressure was initially set at 4 cmH_2O and titrated according to the flow curve to ensure that expiratory flow reached zero prior to inspiration or diminished ineffective efforts. However, it was limited to less than 12 cmH_2O. Inspiratory positive airway pressure was set at 8 cmH_2O and increased by increments of 2 cmH_2O to obtain a tidal volume of more than 6 mL/kg or to the maximum tolerated level for each patient. The inspiratory positive airway pressure was limited to less than 25 cmH_2O. The fraction of inspired oxygen was set to maintain SpO_2 at around 95%. Humidification was provided by a heated humidifier. If humidification was inadequate, intermittent drinking was allowed. If respiratory failure was reversed, disconnection of NIV equipment was performed per hospital protocol [22].

Intubation was performed referencing the criteria as follows (one major criterion or at least two minor criteria), but it was determined at the discretion of the attending physicians [21]. Major criteria were (1) respiratory arrest, (2) loss of consciousness, (3) hemodynamic instability without response to fluids and vasoactive agents, (4) inability to correct dyspnea, (5) development of conditions necessitating intubation to protect the airway or to manage copious tracheal secretions, and (6) PaO_2/FiO_2 below 100 mmHg. Minor criteria were (1) respiratory rate more than 35 breaths/min, (2) blood pH less than 7.30, (3) persistent tachycardia, (4) persistent activation of accessory respiratory muscles, and (5) PaO_2/FiO_2 below 150 mmHg.

Nosocomial pneumonia was diagnosed by the methods we reported previously [23]. It was suspected if a patient had a radiographic infiltrate that was new or progressive, along with clinical findings suggesting infection, including new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. In patients with suspected pneumonia, respiratory tract culture was performed. Samples were obtained by coughing, nasotracheal suction, a protected specimen brush, or bronchoalveolar lavage. Nosocomial pneumonia was confirmed by positive culture and clinical presentations.

Data were analyzed by statistical software (SPSS 17.0; SPSS, Chicago, IL, USA) and reported as mean and standard deviation or median and interquartile range when appropriate. Normally distributed continuous variables were analyzed with the independent-sample t-test. Abnormally distributed continuous variables were analyzed with the Mann–Whitney U test. Categorical variables were analyzed by the chi-square or Fisher's exact test when appropriate. Within groups, a paired-sample t-test was used to analyze the data collected at NIV initiation and 1-2 h of NIV. Kaplan–Meier curves were used to analyze the proportions of intubation in patients with late failure of NIV. Independent risk factors for late failure of NIV were identified by multivariate logistic regression analysis. $p < 0.05$ was considered significant.

3. Results

We enrolled 291 patients in this study. After 48 h of NIV, 45 patients experienced intubation. The median time from initiation of NIV to intubation was 4.8 days (interquartile range (IQR): 3.4–8.1) (Figure 1). In addition, 3 patients reached the criteria of intubation. In spite of attending physicians, they did not benefit from intubation and continuous use of NIV. Finally the 3 patients died during NIV. Thus, a total of 48 patients (16%) experienced late NIV failure after initial success.

Patients with NIV success were younger than those with late failure of NIV (71 ± 10 vs. 76 ± 9 years, $p = 0.01$) (Table 1). They also had lower APACHE II score (17 ± 6 vs. 21 ± 5, $p < 0.01$) and lower proportion of nosocomial pneumonia (0.8% vs. 14.6%, $p < 0.01$). At initiation of NIV, there were no differences in respiratory rate, pH, and PaO_2/FiO_2 between patients with NIV success and late failure of NIV. However, the patients with NIV success had lower respiratory rate (23 ± 4 vs. 25 ± 7 breaths/min, $p = 0.02$), higher pH (7.34 ± 0.06 vs. 7.31 ± 0.08, $p = 0.02$), and higher PaO_2/FiO_2 (221 ± 81 vs. 183 ± 76 mmHg, $p < 0.01$) after 1–2 h of NIV compared with those who experienced late failure of NIV. Compared with the variables collected at NIV initiation, respiratory rate, heart rate, pH, and $PaCO_2$ collected at 1–2 h of NIV significantly improved both in NIV success and late failure of NIV groups (Figure 2). However, the respiratory rate, pH, $PaCO_2$, and PaO_2/FiO_2 improved

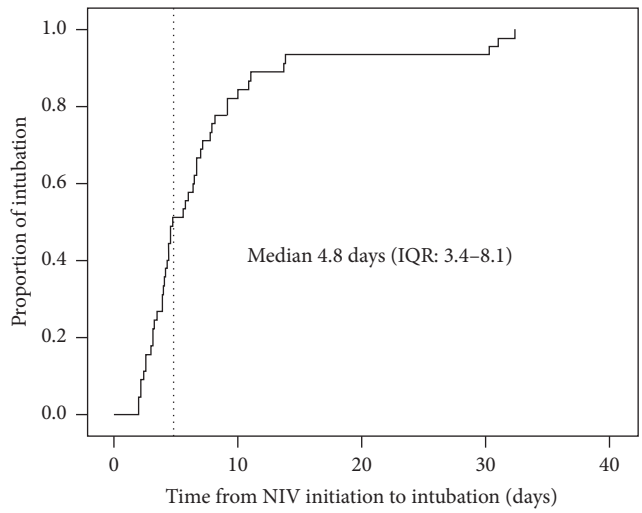

Figure 1: Proportion of intubation in patients with late failure of NIV.

Table 1: Baseline characteristics of patients who had NIV success or late failure of NIV.

	NIV success $N = 243$ (84%)	Late failure of NIV $N = 48$ (16%)	p
Age, years	71 ± 10	76 ± 9	0.01*
Male/female	186/57	33/15	0.27
APACHE II score	17 ± 6	21 ± 5	<0.01*
Nosocomial pneumonia during NIV	2 (0.8%)	7 (14.6%)	<0.01*
Data collected at NIV initiation			
GCS	14.6 ± 1.1	13.8 ± 1.7	<0.01*
Respiratory rate, breaths/min	29 ± 5	29 ± 6	0.85
Heart rate, beats/min	110 ± 19	120 ± 26	<0.01*
MAP, mmHg	102 ± 17	94 ± 18	0.01*
pH	7.26 ± 0.06	7.27 ± 0.06	0.80
$PaCO_2$, mmHg	81 ± 19	73 ± 23	0.01*
PaO_2/FiO_2, mmHg	192 ± 103	188 ± 99	0.79
Data collected at 1–2 h of NIV			
GCS	14.8 ± 0.7	13.9 ± 1.9	<0.01*
Respiratory rate, breaths/min	23 ± 4	25 ± 7	0.02*
Heart rate, beats/min	100 ± 18	109 ± 22	<0.01*
MAP, mmHg	91 ± 14	90 ± 16	0.50
pH	7.34 ± 0.06	7.31 ± 0.08	0.02*
$PaCO_2$, mmHg	70 ± 18	68 ± 21	0.33
PaO_2/FiO_2, mmHg	221 ± 81	183 ± 76	<0.01*

NIV = noninvasive ventilation; GCS = Glasgow coma scale; MAP = mean arterial pressure. * $p < 0.05$ for NIV success vs. late failure of NIV.

faster in the NIV success group than those in the late failure of NIV group (Figure 3).

In the multivariate logistic regression analysis, we identified that nosocomial pneumonia (odds ratio (OR) = 75, 95% confidence interval (CI): 11–537), heart rate at initiation of NIV (1.04, 1.01–1.06 beat per min), and pH at 1–2 h of NIV (2.06, 1.41–3.00 per decrease of 0.05 from 7.35) were independent risk factors for late failure of NIV (Table 2). We also found that the Glasgow coma scale (OR = 0.50, 95% CI: 0.34–0.73 per one unit increase) and PaO_2/FiO_2 (0.992, 0.986–0.998 per one unit increase) were independent protective factors for late failure of NIV.

Outcomes between patients with NIV success and late failure are summarized in Table 3. There were no differences in duration of NIV and the length of stay in the hospital between the two groups. However, the patients with NIV success had shorter length of stay in the ICU (median 6.6, IQR: 4.9–9.8 vs. 9.5, 5.7–13.8, $p = 0.02$) and lower hospital mortality (3% vs. 92%, $p < 0.01$) than those with late failure of NIV.

4. Discussion

The current study found the incidence of late failure of NIV was 16% in patients with acute exacerbation of COPD with a relatively large sample size. Although some clinical variables improved both in the NIV success and late failure of NIV groups, the variables in the NIV success group improved faster than those in the late failure of NIV group. Nosocomial pneumonia; heart rate at initiation of NIV; and

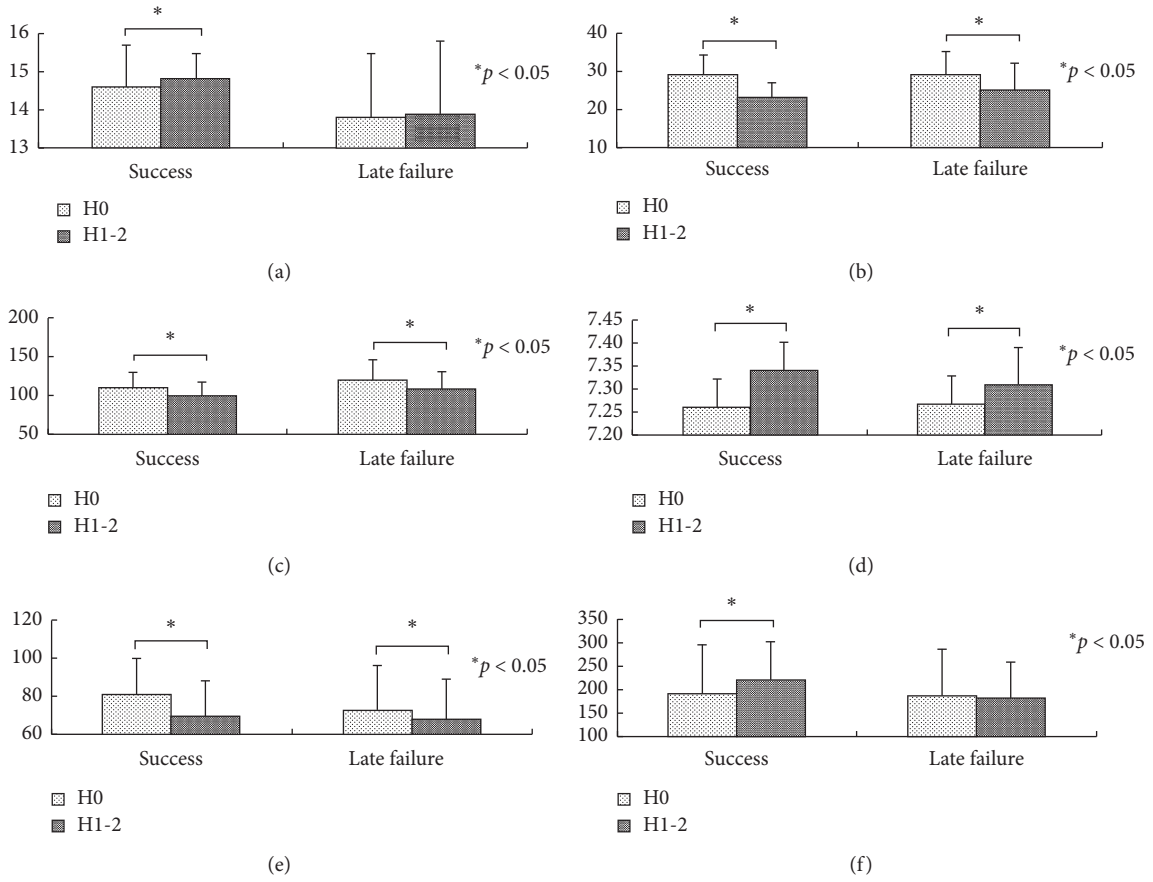

Figure 2: Comparisons between initiation and 1–2 h of NIV: (a) GCS, (b) respiratory rate (breaths/min), (c) heart rate (beats/min), (d) pH, (e) $PaCO_2$ (mmHg), and (f) PaO_2/FiO_2 (mmHg).

consciousness, acidosis, and oxygenation at 1–2 h of NIV were associated with late failure of NIV. In addition, late failure of NIV was associated with increased hospital mortality.

The mortality in patients with late failure of NIV was 68% in Moretti's study and 80% in Carratu's study [9, 12]. In our study, the mortality was 92%, which was higher than the value reported by previous studies. We noted that most of the patients experienced NIV failure within 15 days of NIV in our study. However, some cases experienced NIV failure beyond 30 days. From 15 to 30 days of NIV, there was no NIV failure. It indicates that some patients had significantly impaired respiratory function and required prolonged noninvasive ventilation. In addition, longer exposure in the ICU is associated with a higher incidence of nosocomial pneumonia. These reasons contribute much to hospital mortality.

Previous studies reported that patients with late failure of NIV had higher APACHE II score, higher heart rate, lower GCS, and lower blood pressure compared with successful ones [12, 19, 24]. Our study also found similar results. Different from previous studies, we found nosocomial pneumonia was an independent risk factor for late failure of NIV. It reminds us that nosocomial pneumonia played an important role in late failure of NIV. Among the NIV patients who experienced nosocomial pneumonia in our study, NIV failure occurred in 78% of cases. Thus, prevention of nosocomial pneumonia in NIV patients was as important as in those who received invasive mechanical ventilation.

Both in the NIV success and late failure of NIV groups, most of the clinical variables significantly improved after 1–2 h of NIV. However, the respiratory rate, pH, $PaCO_2$, and PaO_2/FiO_2 improved faster in the NIV success group than those in the late failure of NIV group. These results are new findings compared with previous studies [9, 12, 19, 24]. These data indicate that the patients in the late failure of NIV group responded not so well than those who experienced NIV success. That may be the reason for initial improvement but later failure in the late failure of NIV group.

Our study has several limitations. We found nosocomial pneumonia was associated with late failure of NIV in a patient with acute exacerbation of COPD. However, we only enrolled 9 patients with nosocomial pneumonia. The small sample size may skew this result. Thus, the result is required to be validated with a larger sample size. Secondly, this study was only performed in a respiratory ICU. The single-center study also limited the results to extrapolate to other centers. Thirdly, patients who received intubation later were

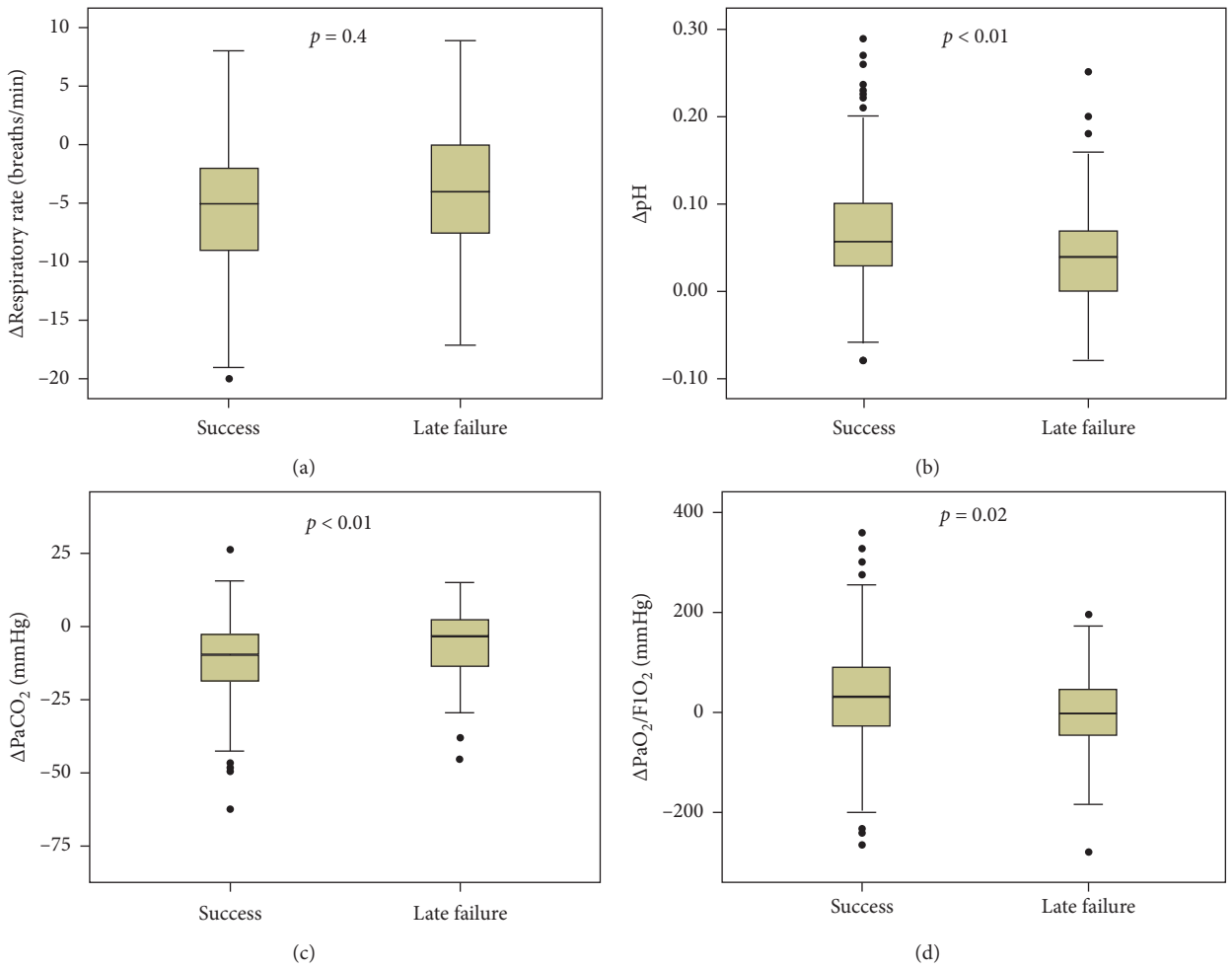

Figure 3: Changes of vital signs from initiation to 1–2 h of NIV.

Table 2: Univariate and multivariate analysis of risk factors associated with late failure of NIV.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.05 (1.01–1.08)	<0.01	—	—
APACHE II score	1.11 (1.05–1.18)	<0.01	—	—
Nosocomial pneumonia during NIV	21 (4–103)	<0.01	75 (11–537)	<0.01
Data collected at NIV initiation				
GCS	0.70 (0.57–0.86)	<0.01	—	—
Heart rate, beats/min	1.02 (1.01–1.04)	<0.01	1.04 (1.01–1.06)	<0.01
MAP, mmHg	0.98 (0.96–0.99)	<0.01	—	—
$PaCO_2$, mmHg	0.98 (0.97–1.00)	0.01	—	—
Data collected at 1–2 h of NIV				
GCS	0.50 (0.36–0.70)	<0.01	0.50 (0.34–0.73)	<0.01
Respiratory rate, breaths/min	1.08 (1.01–1.14)	0.02	—	—
Heart rate, beats/min	1.03 (1.01–1.04)	0.01	—	—
pH at 1–2 h of NIV, per decrease of 0.05 from 7.35	1.67 (1.26–2.25)	<0.01	2.06 (1.41–3.00)	<0.01
PaO_2/FiO_2, mmHg	0.993 (0.988–0.998)	<0.01	0.992 (0.986–0.998)	0.01

OR = odds ratio; CI = confidence interval; NIV = noninvasive ventilation; GCS = Glasgow coma scale; MAP = mean arterial pressure.

Table 3: Outcomes between patients with NIV success and late failure.

	NIV success, $N = 243$ (84%)	Late failure of NIV, $N = 48$ (16%)	p
Duration of NIV (median (IQR)), days	5.0 (3.5–7.7)	5.2 (3.4–9.0)	0.52
Duration of ICU stay (median (IQR)), days	6.6 (4.9–9.8)	9.5 (5.7–13.8)	0.02*
Duration of hospital stay (median (IQR)), days	13.0 (8.3–19.1)	14.1 (9.7–22.7)	0.41
Hospital mortality	8 (3%)	44 (92%)	<0.01*

NIV = noninvasive ventilation; IQR = interquartile range; ICU = intensive care unit. * $p < 0.05$ for NIV success vs. late failure of NIV.

associated with higher mortality [12, 25]. Therefore, early intubation (e.g., 24 h of NIV) is an alternative to reduce mortality.

5. Conclusions

Nosocomial pneumonia; heart rate at initiation of NIV; and consciousness, acidosis, and oxygenation at 1–2 h of NIV were associated with late failure of NIV in patients with COPD exacerbation. In addition, late failure of NIV was associated with increased hospital mortality.

Abbreviations

COPD: Chronic obstructive pulmonary disease
NIV: Noninvasive ventilation
GCS: Glasgow coma scale
MAP: Mean arterial pressure
OR: Odds ratio
CI: Confidence interval
IQR: Interquartile range
ICU: Intensive care unit.

Data Availability

The datasets analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest in this study.

Authors' Contributions

Jun Duan conceived the study and joined in study design, study management, data collection, data analysis, and manuscript revision. Tao Chen participated in study design, study management, data collection, data analysis, and manuscript preparation. Linfu Bai, Wenhui Hu, and Xiaoli Han participated in study design, data collection, and manuscript revision. All authors read and approved the final version.

References

[1] J. Vestbo, S. S. Hurd, A. G. Agustí et al., "Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 187, no. 4, pp. 347–365, 2013.

[2] V. Snow, S. Lascher, C. Mottur-Pilson et al., "Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease," *Annals of Internal Medicine*, vol. 134, no. 7, pp. 595–599, 2001.

[3] J. V. Lightowler, J. A. Wedzicha, M. W. Elliott et al., "Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: cochrane systematic review and meta-analysis," *British Medical Journal*, vol. 326, no. 7382, p. 185, 2003.

[4] F. S. F. Ram, J. Picot, J. Lightowler, and J. A. Wedzicha, "Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease," *The Cochrane Database of Systematic Reviews*, vol. 1, no. 3, Article ID CD004104, 2004.

[5] D. Chandra, J. A. Stamm, B. Taylor et al., "Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008," *American Journal of Respiratory and Critical Care Medicine*, vol. 185, no. 2, pp. 152–159, 2012.

[6] M. S. Mihaela, M.-S. Shieh, P. S. Pekow, N. Hill, M. B. Rothberg, and P. K. Lindenauer, "Trends in mechanical ventilation among patients hospitalized with acute exacerbations of COPD in the United States, 2001 to 2011," *Chest*, vol. 147, no. 4, pp. 959–968, 2015.

[7] W. Hill and Z. Qing-yuan, "Guideline for mechanical ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease (2007)," *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*, vol. 19, pp. 513–518, 2007.

[8] S. P. Keenan, T. Sinuff, K. E. A. Burns et al., "Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting," *Canadian Medical Association Journal*, vol. 183, no. 3, pp. E195–E214, 2011.

[9] P. Carratu, P. Bonfitto, S. Dragonieri et al., "Early and late failure of noninvasive ventilation in chronic obstructive pulmonary disease with acute exacerbation," *European Journal of Clinical Investigation*, vol. 35, no. 6, pp. 404–409, 2005.

[10] A. Carrillo, M. Ferrer, G. Gonzalez-Diaz et al., "Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 186, no. 12, pp. 1279–1285, 2012.

[11] L. Brochard, J. Mancebo, M. Wysocki et al., "Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease," *New England Journal of Medicine*, vol. 333, no. 13, pp. 817–822, 1995.

[12] M. Moretti, C. Cilione, A. Tampieri et al., "Incidence and causes of non-invasive mechanical ventilation failure after initial success," *Thorax*, vol. 55, no. 10, pp. 819–825, 2000.

[13] E. Ozyilmaz, A. O. Ugurlu, and S. Nava, "Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies," *BMC Pulmonary Medicine*, vol. 14, p. 19, 2014.

[14] M. Confalonieri, G. Garuti, M. S. Cattaruzza et al., "A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation," *European Respiratory Journal*, vol. 25, no. 2, pp. 348–355, 2005.

[15] A. Carlucci, J.-C. Richard, M. Wysocki, E. Lepage, and L. Brochard, "Noninvasive versus conventional mechanical ventilation," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 4, pp. 874–880, 2001.

[16] D. Miller, K. Fraser, I. Murray, G. Thain, and G. P. Currie, "Predicting survival following non-invasive ventilation for hypercapnic exacerbations of chronic obstructive pulmonary disease," *International Journal of Clinical Practice*, vol. 66, no. 5, pp. 434–437, 2012.

[17] J. Phua, K. Kong, K. H. Lee, L. Shen, and T. K. Lim, "Non-invasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure," *Intensive Care Medicine*, vol. 31, no. 4, pp. 533–539, 2005.

[18] B. Chakrabarti, R. M. Angus, S. Agarwal, S. Lane, and P. M. A. Calverley, "Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD," *Thorax*, vol. 64, no. 10, pp. 857–862, 2009.

[19] F. R. Campo, X. Drouot, A. W. Thille et al., "Poor sleep quality is associated with late noninvasive ventilation failure in patients with acute hypercapnic respiratory failure," *Critical Care Medicine*, vol. 38, no. 2, pp. 477–485, 2010.

[20] Chinese Medical Association Respiratory Disease Committee, "Guideline for the diagnosis and treatment of chronic obstructive pulmonary disease," *Chinese Journal of Tuberculosis and Respiratory Disease*, vol. 28, pp. 453–460, 2002.

[21] L. Fan, Q. Zhao, Y. Liu, L. Zhou, and J. Duan, "Semiquantitative cough strength score and associated outcomes in noninvasive positive pressure ventilation patients with acute exacerbation of chronic obstructive pulmonary disease," *Respiratory Medicine*, vol. 108, no. 12, pp. 1801–1807, 2014.

[22] J. Duan, X. Tang, S. Huang, J. Jia, and S. Guo, "Protocol-directed versus physician-directed weaning from noninvasive ventilation," *The Journal of Trauma and Acute Care Surgery*, vol. 72, no. 5, pp. 1271–1275, 2012.

[23] Z. Zhang and J. Duan, "Nosocomial pneumonia in non-invasive ventilation patients: incidence, characteristics, and outcomes," *Journal of Hospital Infection*, vol. 91, no. 2, pp. 153–157, 2015.

[24] A. Ciledag, A. Kaya, O. Ercen Diken et al., "The risk factors for late failure of non-invasive mechanical ventilation in acute hypercapnic respiratory failure," *Tuberk Toraks*, vol. 62, pp. 177–182, 2014.

[25] A. Esteban, F. Frutos-Vivar, N. D. Ferguson et al., "Noninvasive positive-pressure ventilation for respiratory failure after extubation," *New England Journal of Medicine*, vol. 350, no. 24, pp. 2452–2460, 2004.