Impact of ARDS Etiology on the Failure of Noninvasive Ventilation and 28-Day Mortality: A Multicenter Prospective Observational Study

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Research

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Abstract

Background: The failure rate of noninvasive ventilation (NIV) remains high in patients with acute respiratory distress syndrome (ARDS). The etiology of ARDS may play an important role in NIV failure.

Methods: A multicenter prospective observational study was performed in 17 ICUs in China from September 2017 to December 2019. ARDS patients who used NIV as a first-line therapy were enrolled. The etiology of ARDS was recorded at study entry.

Results: A total of 306 patients were enrolled. Of the patients, 146 were classified as having pulmonary ARDS (ARDSp) and 160 were classified as having extrapulmonary ARDS (ARDSexp). NIV improved \( \text{PaO}_2/\text{FiO}_2 \) from initiation to 24 h of NIV in both groups. However, it improved more slowly in patients with ARDSp than in those with ARDSexp (interaction effect: \( p < 0.01 \)). ARDSp patients experienced more NIV failure (55% vs. 28%; \( p < 0.01 \)) and higher 28-day mortality (47% vs. 14%; \( p < 0.01 \)). The multivariate Cox regression also showed that ARDSp was independently associated with NIV failure (hazard ratio [HR] = 2.81, 95% confidence interval [CI]: 1.89-4.18) and 28-day mortality (HR = 7.49, 95% CI: 4.32-13.01). After propensity matching, 62 patients remained in each group. The baseline data were comparable between the two groups. ARDSp was still independently associated with NIV failure and 28-day mortality (HR = 2.62, 95% CI: 1.49-4.61; and 5.70, 2.59-12.55, respectively). Sensitivity analysis also confirmed these results.

Conclusions: Among ARDS patients who used NIV as a first-line therapy, ARDSp was associated with slower improvement in oxygenation, more NIV failure, and higher 28-day mortality than ARDSexp.

Background

Noninvasive ventilation (NIV) reduces the work of breathing, improves oxygenation, and relieves dyspnea in patients with acute respiratory failure [1]. Compared to standard oxygen therapy, NIV reduces the rate of intubation and the length of stay in the intensive care unit (ICU) [2–4]. Moreover, compared to invasive mechanical ventilation, NIV avoids intubation-associated lung injury, reduces ventilator-associated pneumonia, and preserves the ability to cough and communicate verbally [5, 6]. Therefore, the use of NIV in cases of acute respiratory failure increases year after year [7, 8].

A large epidemiologic study of 50 countries showed that 15% of patients with acute respiratory distress syndrome (ARDS) use NIV as a first-line therapy [9]. However, the pooled NIV failure rate is 48% (range: 30–86%) [10]. Among the ARDS population, mortality is 46% in patients who initially receive intubation for invasive mechanical ventilation; however, it increases to 69% in those who experience NIV failure [11]. As NIV failure is associated with increased mortality, identifying ARDS patients who respond well to NIV is important.

The etiologies of ARDS include pneumonia, aspiration, drowning, intra-abdominal infection, urinary infection, pancreatitis, and so on [12, 13]. These causes can be classified as pulmonary ARDS (ARDSp) or...
extrapulmonary ARDS (ARDSexp). In one study, ARDSP patients required a longer duration of mechanical ventilation than ARDSexp patients [14]. Another study with a small sample size reported that ARDSP patients tended to have higher hospital mortality than ARDSexp patients (47.4% vs. 27.9%) [15]. Finally, physiological studies have shown that responses to lung recruitment and prone position differ between patients with ARDSP and ARDSexp [16, 17]. These differences can be explained by the different pathophysiological mechanisms of the two types of ARDS. Based on these data, we hypothesized that the response to NIV would differ in patients with ARDSP and ARDSexp.

Methods

This prospective observational study was performed in 17 ICUs in China from September 2017 to December 2019. We enrolled ARDS patients who used NIV as a first-line therapy. Exclusion criteria were as follows: previous use of NIV > 2 h before admission to participating centers, ventilation support from high-flow nasal cannula to NIV or from NIV to high-flow nasal cannula, NIV carried out within the 48 h after extubation, and transfer to another hospital during NIV. As we aimed to assess the impact of ARDS etiology on NIV failure, we also excluded patients with treatment limitation. The study protocol was approved by our ethics committee (No. 2016150). Informed consent was obtained from patients or their family members. ARDS was determined as follows: 1) the presence of acute hypoxemic respiratory failure with PaO$_2$/FiO$_2$ < 300 mmHg; 2) within 1 week of a clinical insult or the presence of new (within 7 days) or worsening respiratory symptoms; 3) bilateral opacities on computed tomography or chest X-ray not fully explained by effusions, lobar or lung collapse, or nodules; and 4) respiratory failure not fully explained by cardiac failure or fluid overload [18]. The etiology of ARDS was recorded by the attending physician.

The initiation of NIV was based on a protocol we published previously: respiratory rate > 25 breaths/min, or clinical presentation of respiratory distress at rest (such as active contraction of the accessory inspiratory muscles or paradoxical abdominal motion), and PaO$_2$ < 60 mmHg at room air or PaO$_2$/FiO$_2$ < 300 mmHg with supplemental oxygen [19]. However, the use of NIV was at the attending physician’s discretion. A face mask was the first choice for patients with acute respiratory failure, and the size was selected based on the patient’s facial type. The straps of the mask were kept as tight as possible while remaining comfortable for the patient. The parameters of the ventilator were adjusted as follows. The initial positive end-expiratory pressure (PEEP) was 4 cm H$_2$O and was increased gradually to avoid alveolar collapse. The initial inspiratory positive airway pressure (IPAP) was 8 cmH$_2$O (above zero) and was increased gradually to reduce the work of breathing. Usually PEEP was maintained at 6–8 cmH$_2$O and IPAP was maintained at 12–16 cmH$_2$O. The fraction of inspiration oxygen (FiO$_2$) was set to maintain SpO$_2$ around 95%.

Liberation from NIV was considered if the respiratory failure was reversed. The reversal of respiratory failure was defined according to previously published criteria: PaO$_2$/FiO$_2$ > 300 mmHg, respiratory rate < 25 breaths/min, and no clinical symptoms indicating respiratory distress [19]. However, if respiratory
failure deteriorated progressively and required intubation, intubation for invasive mechanical ventilation was performed. Major criteria for intubation were loss of consciousness (such as a sudden change from being awake to being unconscious), respiratory or cardiac arrest, the development of conditions necessitating intubation to protect the airway (coma or seizure disorders) or to manage copious tracheal secretions, heart rate < 50 beats/min with loss of alertness, and hemodynamic instability without response to fluids and vasoactive agents. Minor criteria were respiratory rate > 35 breaths/min, failure to maintain PaO$_2$/FiO$_2$ above 150 mmHg, acidosis with pH < 7.35, inability to correct dyspnea, and lack of improvement in respiratory muscle fatigue. Intubation was recommended if the patient reached one major criterion or more than two minor criteria. NIV failure was defined as requiring intubation [19].

A predefined case report form was used to collect data during the study period. We recorded age, sex, underlying disease, presence of septic shock, organ dysfunction, and etiology of ARDS. Organ dysfunction was assessed with the sequential organ failure assessment (SOFA) score [20]. Septic shock was diagnosed according to the Third International Consensus Definitions for Sepsis and Septic Shock [21]. Data were collected when NIV was performed. ARDS resulting from pneumonia, pulmonary contusion or drowning was classified as ARDSp; that resulting from pancreatitis, intra-abdominal infection, urinary infection, soft tissue infection, non-pulmonary trauma, or other non-pulmonary disease was classified as ARDSexp [12, 13]. All patients were followed to discharge or 28 days.

**Statistical analysis**

We used SPSS (version 25.0) to analyze the data in this study. Missing data were present in 4.6% of cases and multiple imputations were performed. Continuous variables are reported as means and standard deviations or medians and interquartile ranges when appropriate. Normally distributed continuous variables were analyzed by unpaired Student’s t test, and non-normally distributed continuous variables were analyzed by Wilcoxon rank sum test. Proportions are reported as frequencies and percentages and compared with the chi-square test or Fisher’s exact test. Cox regression was used to identify independent risk factors associated with NIV failure or 28-day mortality. Differences in PaO$_2$/FiO$_2$ from initiation to 24 h of NIV between groups were analyzed by two-way repeated measures analysis of variance.

Propensity score matching was used to evaluate possible effects of treatment (ARDSp vs. ARDSexp) on NIV failure and 28-day mortality. We matched patients with similar propensity scores at a 1:1 ratio, using the nearest neighbor method, no replacement, and a caliper width of 0.05. The matched variables included age, sex, non-pulmonary SOFA score, presence of septic shock, underlying disease (chronic heart disease or chronic respiratory disease), severity of ARDS, vital signs collected before NIV (heart rate, respiratory rate, mean arterial blood pressure, pH, PaCO$_2$, and PaO$_2$/FiO$_2$), tidal volume at 1–2 h of NIV, and PEEP at 1–2 h of NIV. We analyzed the cumulative 28-day probability of survival in the overall and propensity-matched cohorts by creating Kaplan-Meier curves, and the difference between the groups was analyzed by log-rank test. Sensitivity analysis in patients with different conditions was used to determine
the effect of ARDS etiology on the failure of NIV and 28-day mortality. A p value less than 0.05 was considered statistically significant.

Results

A total of 306 ARDS patients were enrolled in this study (Fig. 1). The baseline data are summarized in Table 1. Based on etiology, 146 (48%) patients were classified into the ARDSp group, and 160 (52%) patients were classified into the ARDSexp group. ARDSp patients were more likely to be male (69% vs. 56%; p = 0.02), and had a lower PaO$_2$/FiO$_2$ at study entry (137 ± 44 vs. 170 ± 48 mmHg; p < 0.01) than ARDSexp patients (Table 1). They also had a lower non-pulmonary SOFA score (median: 1 vs. 2; p < 0.01), a lower proportion of septic shock (9% vs. 18%; p = 0.03), and a lower heart rate (111 ± 23 vs. 126 ± 22 beats/min; p < 0.01). After propensity matching, we enrolled 62 patients in each group. The variables at baseline were comparable between the two groups.
Table 1
Baseline data between patients with pulmonary and extrapulmonary ARDS

|                      | Overall cohort | Propensity-matched cohort | p     | Overall cohort | Propensity-matched cohort | p     |
|----------------------|---------------|---------------------------|-------|---------------|---------------------------|-------|
|                      | ARDSp         | ARDSexp                   |       | ARDSp         | ARDSexp                   |       |
|                      | N = 146       | N = 160                   |       | N = 62        | N = 62                    |       |
| Age, years           | 55 ± 16       | 52 ± 16                   | 0.13  | 56 ± 17       | 55 ± 18                   | 0.78  |
| Male                 | 101 (69%)     | 89 (56%)                  | 0.02  | 40 (65%)      | 40 (65%)                  | > 0.99|
| SOFA score           | 4 (3–6)       | 5 (4–7)                   | < 0.01| 4 (4–7)       | 5 (3–7)                   | 0.72  |
| Non-pulmonary SOFA score | 1 (0–2)       | 2 (1–4)                   | < 0.01| 1 (1–4)       | 2 (1–4)                   | 0.53  |
| Septic shock         | 13 (9%)       | 28 (18%)                  | 0.03  | 6 (10%)       | 7 (11%)                   | > 0.99|
| Chronic heart disease| 13 (9%)       | 7 (4%)                    | 0.16  | 3 (5%)        | 4 (7%)                    | > 0.99|
| Chronic respiratory disease | 9 (6%)       | 3 (2%)                    | 0.08  | 3 (5%)        | 3 (5%)                    | > 0.99|
| Etiology of ARDS     |               |                           |       |               |                           |       |
| Pneumonia            | 142 (97%)     | -                         |       | 59 (95%)      | -                         |       |
| Pulmonary contusion  | 3 (2%)        | -                         |       | 2 (3%)        | -                         |       |
| Drowning             | 1 (1%)        | -                         |       | 1 (2%)        | -                         |       |
| Pancreatitis         | -             | 100 (63%)                 |       | -             | 38 (61%)                  |       |
| Intra-abdominal infection | -            | 23 (14%)                 |       | -             | 9 (15%)                   |       |
| Urinary infection    | -             | 11 (7%)                   |       | -             | 3 (5%)                    |       |
| Trauma               | -             | 5 (3%)                    |       | -             | 4 (7%)                    |       |
| Skin or soft tissue infection | -        | 4 (3%)                   |       | -             | 3 (5%)                    |       |
| Others               | -             | 17 (11%)                  |       | -             | 5 (8%)                    |       |

NIV = noninvasive ventilation, ARDS = acute respiratory distress syndrome, ARDSp = pulmonary ARDS, ARDSexp = extrapulmonary ARDS, SOFA = sequential organ failure assessment, MAP = mean arterial pressure, PEEP = positive end expiratory pressure
|                      | Overall cohort | Propensity-matched cohort |
|----------------------|----------------|--------------------------|
|                      |                |                          |                           |
| Heart rate, bpm      | 111 ± 23       | 126 ± 22                 | < 0.01                    |
|                      |                | 119 ± 22                 | 119 ± 20                  | 0.83                      |
| Respiratory rate, bpm| 32 ± 8         | 32 ± 8                   | 0.71                      |
|                      |                | 32 ± 8                   | 32 ± 7                    | 0.83                      |
| MAP, mmHg            | 94 ± 15        | 96 ± 18                  | 0.24                      |
|                      |                | 96 ± 18                  | 95 ± 17                   | 0.73                      |
| pH                   | 7.44 ± 0.08    | 7.42 ± 0.09              | < 0.01                    |
|                      |                | 7.43 ± 0.10              | 7.43 ± 0.08               | 0.82                      |
| PaCO₂, mmHg          | 32 ± 7         | 32 ± 7                   | 0.78                      |
|                      |                | 32 ± 8                   | 32 ± 7                    | 0.89                      |
| PaO₂/FiO₂, mmHg      | 137 ± 44       | 170 ± 48                 | < 0.01                    |
|                      |                | 153 ± 46                 | 160 ± 46                  | 0.38                      |

ARDS severity

|       |                |                          |                           |                           |
|-------|----------------|--------------------------|--------------------------|
|       | Mild           | 18 (12%)                 | 34 (21%)                 | < 0.01                    |
|       |                | 12 (19%)                 | 12 (19%)                 | 0.41                      |
|       | Moderate       | 98 (67%)                 | 119 (74%)                |                           |
|       |                | 43 (69%)                 | 47 (76%)                 |                           |
|       | Severe         | 20 (21%)                 | 7 (4%)                   |                           |
|       |                | 7 (11%)                  | 3 (5%)                   |                           |

Ventilator parameters

|                      |                |                          |                           |
|----------------------|----------------|--------------------------|--------------------------|
|                      |                |                          |                           |
| VT at 1–2 h of NIV, mL| 532 ± 181     | 495 ± 174                | 0.06                      |
|                      |                | 525 ± 199                | 525 ± 181                | 0.98                      |
| PEEP at 1–2 h of NIV | 6 (5–7)        | 6 (6–8)                  | < 0.01                    |
|                      |                | 6 (5–8)                  | 6 (6–7)                  | 0.99                      |
| VT at 12 h of NIV, mL| 507 ± 160      | 465 ± 155                | 0.04                      |
|                      |                | 487 ± 142                | 491 ± 162                | 0.91                      |
| PEEP at 12 h of NIV  | 6 (5–8)        | 6 (6–8)                  | 0.03                      |
|                      |                | 6 (5–8)                  | 6 (6–8)                  | 0.81                      |
| VT at 24 h of NIV, mL| 497 ± 192      | 465 ± 147                | 0.17                      |
|                      |                | 470 ± 145                | 509 ± 166                | 0.28                      |
| PEEP at 24 h of NIV  | 6 (5–8)        | 6 (6–8)                  | 0.16                      |
|                      |                | 7 (5–8)                  | 6 (6–8)                  | 0.55                      |

NIV = noninvasive ventilation, ARDS = acute respiratory distress syndrome, ARDSp = pulmonary ARDS, ARDSexp = extrapulmonary ARDS, SOFA = sequential organ failure assessment, MAP = mean arterial pressure, PEEP = positive end expiratory pressure

NIV improved PaO₂/FiO₂ both ARDSp and ARDSexp patients (Fig. 2). However, it improved more slowly in patients with ARDSp than in those with ARDSexp (interaction effect: p < 0.01). And ARDSp patients experienced more NIV failure (52% vs. 28%; p < 0.01) and higher 28-day mortality (47% vs. 14%; p < 0.01; Fig. 3). Similar results were confirmed in the propensity-matched cohort (NIV failure: 58% vs. 31%; 28-day mortality: 44% vs. 15%).

In the overall cohort, ARDSp was independently associated with NIV failure (hazard ratio [HR] = 2.81, 95% confidence interval [CI]: 1.89–4.18) and 28-day mortality (HR = 7.49, 95% CI: 4.32–13.01; Table 2). In
propensity-matched cohort, ARDSp was still independently associated with NIV failure and 28-day mortality (HR = 2.62, 95%CI: 1.49–4.61 and 5.70, 2.59–12.55, respectively). Sensitivity analysis was summarized in Fig. 4. ARDSp was also associated with NIV failure and 28-day mortality in different subgroups.

| Table 2 | Multivariate Cox regression analysis to determine the factor associated with NIV failure and 28-day mortality |
|---------|----------------------------------------------------------------------------------------------------------|
|         | Overall cohort                                                                                         | Propensity-matched cohort |
|         | HR (95%CI)                                                                                             | p                      | HR (95%CI)                                                                 | p                      |
| NIV failure |                                                                                                |                        |                                                                                          |                        |
| ARDSp         | 2.81 (1.89–4.18)                                                                                  | < 0.01                | 2.62 (1.49–4.61)                                                                 | < 0.01                |
| VT, mL       | 1.001 (1.001–1.002)                                                                                 | < 0.01                | 1.002 (1.002–1.003)                                                                 | < 0.01                |
| Non-pulmonary SOFA | 1.20 (1.12–1.28)                                                                                  | < 0.01                | 1.14 (1.03–1.27)                                                                 | 0.01                  |
| Respiratory rate, bpm | 1.04 (1.01–1.06)                                                                                  | < 0.01                | -                                                                                     | -                     |
| Age, years   | 1.01 (1.00–1.03)                                                                                    | 0.02                  | -                                                                                     | -                     |
| 28-day mortality |                                                                                                |                        |                                                                                          |                        |
| ARDSp         | 7.49 (4.32–13.01)                                                                                  | < 0.01                | 5.70 (2.59–12.55)                                                                 | < 0.01                |
| Age, years   | 1.02 (1.01–1.03)                                                                                    | < 0.01                | 1.03 (1.01–1.05)                                                                 | 0.02                  |
| Non-pulmonary SOFA | 1.26 (1.16–1.36)                                                                                  | < 0.01                | 1.40 (1.23–1.60)                                                                 | < 0.01                |
| VT, mL       | 1.001 (1.000–1.002)                                                                                 | 0.03                  | -                                                                                     | -                     |

We entered sex, age, septic shock, chronic heart disease, chronic respiratory disease, non-pulmonary SOFA score, ARDS severity, respiratory rate before NIV, heart rate before NIV, arterial blood gas tests before NIV (pH, PaCO2 and PaO2/FiO2), tidal volume at 1–2 h of NIV, and PEEP at 1–2 h of NIV into the Cox regression model.

HR = hazard ratio, CI = confidence interval, NIV = noninvasive ventilation, ARDS = acute respiratory distress syndrome, ARDSp = pulmonary ARDS, SOFA = sequential organ failure assessment, PEEP = positive end expiratory pressure

Discussion

This multicenter study shows that PaO2/FiO2 from initiation to 24 h of NIV improved slower in patients with ARDSp than in those with ARDSexp. More NIV failure and higher 28-day mortality were observed in ARDSp patients. And ARDSp was associated with NIV failure and 28-day mortality regardless of whether it was in overall cohort, propensity-matched cohort, or other subgroups.
Our study shows that ARDSexp patients respond better to NIV than ARDSp patients. The different pathophysiological mechanisms of the two types of ARDS contribute greatly to the different effects of NIV among patients. The main etiologies of ARDSp are pneumonia, aspiration, and drowning. These factors cause injury to the pulmonary epithelium and direct insult to the alveolus [12]. This direct insult is mainly represented by alveolar filling by edema, fibrin, collagen, neutrophilic aggregates, and/or blood. In contrast, the predominant etiologies of ARDSexp are non-pulmonary sepsis, pancreatitis, and trauma. These factors cause injury to pulmonary endothelial cells and lead to microvascular congestion and interstitial edema, with a relative sparing of the intra-alveolar spaces. In addition, consolidation on chest CT scan is greater and response to lung recruitment maneuver worse in ARDSp patients than in ARDSexp patients [22, 23]. These pathophysiological mechanisms can explain the better response to NIV in ARDSexp patients than in ARDSp patients.

Among NIV patients with de novo acute respiratory failure, delayed intubation is associated with increased hospital mortality [24]. As ARDS accounts for a large proportion of de novo acute respiratory failure, early identification of NIV failure in ARDS patients has the potential to reduce mortality. In our study, we innovatively explored the impact of ARDS etiology on NIV failure and found that ARDSp patients experience more NIV failure and higher 28-day mortality than ARDSexp patients. Therefore, this study provides new insight for clinical staff managing NIV in ARDS patients. More attention should be paid to ARDSp patients to avoid delayed intubation.

Organ dysfunction is associated with NIV failure [19, 25]. Higher SOFA scores are also associated with more NIV failure. However, the lung is one of six organs assessed for the SOFA score. The pulmonary SOFA score is collinear with PaO$_2$/FiO$_2$. Thus, we used the non-pulmonary SOFA score to assess the risk for NIV failure and found it was associated with NIV failure. In addition, we also found the tidal volume was associated with NIV failure, which was similar with previous studies [26, 27]. Therefore, assessment of NIV failure in ARDSexp patients should be considered other risk factors (e.g. non-pulmonary SOFA score and tidal volume).

This study was limited by its methodology. Although we predefined the criteria for intubation, the decision to intubate was made by the attending physicians. This may have led to bias in the incidence of NIV failure. Second, the expired tidal volume of predicted body weight is associated with NIV failure [26, 27]. However, the height was not recorded in our study. We were unable to calculate the tidal volume of predicted body weight. This may diminish the association between NIV failure and tidal volume. Third, missing data were present in 4.6% of cases. However, we used multiple imputations to deal with this problem, which may partly improve the accuracy of the results.

Conclusions

Nearly half of ARDS patients in this study who received NIV as a first-line therapy had an ARDS etiology that was pulmonary in origin. From initiation to 24 h of NIV, PaO$_2$/FiO$_2$ improved more slowly in ARDSp
patients than in ARDSexp patients. ARDSp patients experienced more NIV failure and higher 28-day mortality.

**Abbreviations**

NIV = noninvasive ventilation  
ARDS = acute respiratory distress syndrome  
ARDSp = pulmonary ARDS  
ARDSexp = extra-pulmonary ARDS  
SOFA = sequential organ failure assessment  
MAP = mean arterial pressure  
PEEP = positive end expiratory pressure  
HR = hazard ratio  
CI = confidence interval  
HFNC = high-flow nasal cannula

**Declarations**

Consent for publication

All authors have reviewed and approved the manuscript for publication.

Availability of data and material

The datasets analyzed during the current study available from the corresponding author on reasonable request.

Ethical approval and consent to participate

The Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University approved the study (No. 2016150). Informed consent was obtained from patients or their family members.

Competing interests

We declare that we have no competing interests.

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Authors’ contributions

WS, SG, FY, BL, ZZ, XL and JD participated in study conception, study design, and study supervision. WS, BL, ZZ and JD participated in data analysis and data interpretation. WS, SG, FY, ZZ, XL, BC, TH, LL, KW, DH, QC, BW, LC, MT, GY, MM, ZT, FD, WG, XH, RZ, LJ, LB and JD participated in patient recruitment. All authors revised the manuscript and approved the final manuscript.

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