Predictors of Non-Invasive Ventilation Failure in Severe Respiratory Failure Due to Community Acquired Pneumonia

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Background: Non-invasive ventilation (NIV) has been used for acute respiratory failure to avoid endotracheal intubation and intensive care admission. Few studies have assessed the usefulness of NIV in patients with severe community acquired pneumonia (CAP). The use of NIV in severe CAP is controversial because there is a greater variability in success compared to other pulmonary conditions.

Materials and Methods: We retrospectively followed 130 patients with CAP and severe acute respiratory failure (PaO2/FiO2 < 250) admitted to a Respiratory Monitoring Unit (RMU) and underwent NIV. We assessed predictors of NIV failure and hospital mortality using univariate and multivariate analyses.

Results: NIV failed in 26 patients (20.0%). Higher chest X-ray score at admission, higher heart rate after 1 hour of NIV, and a higher alveolar-arteriolar gradient (A-aDO2) after 24 hours of NIV each independently predicted NIV failure.

Higher chest X-ray score, higher LDH at admission, higher heart rate after 24 hours of NIV and higher A-aDO2 after 24 hours of NIV were directly related to hospital mortality.

Conclusion: NIV treatment had high rate of success. Successful treatment is related to less lung involvement and to early good response to NIV and continuous improvement in clinical response.

Key words: Community-acquired pneumonia, Severe respiratory failure, Non-invasive ventilation, Hospital mortality
the droplets generated during NIV are > 10 µm; these are unlikely to be airborne (6).

Over time, NIV success increased (7,8). The success rate was as high as 76% with avoidance of intubation and fewer associated infection complications (e.g., sepsis, septic shock and/or catheter-related infections (6). However, despite good outcomes in H1N1 patients and more recent randomized studies on the use of helmet continuous positive airway pressure (CPAP) versus oxygen therapy in severe hypoxemic respiratory failure due to pneumonia, in which the technique reduced the intubation rate (9,10), the efficacy of NIV in pneumonia has not been definitively established (11). Predictors of NIV failure have not been well defined (12). From our long experience with NIV, we learned that appropriate patient selection is the key to success (13).

The aim of this study was to evaluate the efficacy of NIV and factors related to its failure and mortality in patients with CAP and severe acute respiratory failure (ARF).

MATERIALS AND METHODS

We retrospectively followed 130 consecutive patients with severe ARF due to CAP defined as the ratio of arterial oxygen tension to inspired oxygen fraction (PaO₂/FiO₂) <250 receiving NIV treatment in the RMU of Sestri Levante Hospital, from June 2005 to July 2014. The RMU has four non-invasive monitored beds and admits patients with severe respiratory failure who need non-invasive ventilation. The RMU has both ventilators specifically designed for NIV and invasive ventilation (IMV). Our units can switch to invasive measures e.g., intubation and intensive care unit (ICU) admission quickly.

This study received the approval of Ethics Committee of ASL4 Chiavarese, Italy (n°302) and was carried out in accordance with the Helsinki Declaration. All the patients gave informed consent for NIV treatment and for the study.

Pneumonia was defined as a new pulmonary infiltrate on the admission chest radiograph with symptoms and signs of lower respiratory tract infection according to the American Thoracic Society and Infectious Disease Society of America (IDSA/ATS) guidelines (2,7).

Patients’ degree of disease severity and organ failure were estimated using Simplified Acute Physiology Score (SAPS)-II and Confusion, Elevated Blood Urea Nitrogen, Respiratory Rate and Blood pressure plus Age ≥65 years (CURB65) score (2). The exclusion criteria were any degree of immunosuppression, lack of spontaneous breathing, gasping, anatomical evidence of functional airway obstruction and gastrointestinal bleeding, or ileus, massive agitation, severe hypoxemia or acidosis (pH<7.10) (2,14,15). Upon admission, all patients received empirical antimicrobial therapy according to the IDSA/ATS guidelines (16).

Upon admission, specific urinary tests for Streptococcus pneumonia and Legionella pneumophila as well as blood culture were performed for all patients.

The indication for NIV use followed an established protocol: moderate to severe dyspnea accompanied by respiratory rate ≥ 30 breaths/m, signs of respiratory distress (e.g. use of accessory respiratory muscles), (PaO₂/FiO₂) < 250 (2,13-15).

The inability of patient to adapt himself/herself to the device or unwillingness to undergo NIV was considered a contraindication for NIV.

Patients were ventilated using pressure support ventilation (PSV) or bi-level-ST ventilation (BIPAP).

The following parameters were recorded upon admission: age, sex, co-morbidities, number of lobes involved on chest x-ray or on chest computed tomography (CT), Opravil radiological score (17), PaO₂ on room air, PaCO₂, pH, PaO₂/FiO₂ ratio, alveolar-arterial gradient (A-aDO₂), Simplified Acute Physiology Score (SAPS) II, Kelly-Matthay scale, ventilation mode, setting of mechanical ventilator and PaO₂/FiO₂ after 1 hour of non-invasive
ventilation. If a patient who underwent NIV did not experience an improvement of PaO2/FiO2 ratio of more than 175 after 1 hour of continued NIV, and/or if one or more complications occurred (neurological impairment, persistence of dyspnea and tachypnea, hemodynamic instability and intolerance of the interface, the patient was considered to have failed NIV and IMV was initiated. EPAP or PEEP (positive end expiratory pressure) was set initially at 5 cm H2O and the level was raised by 1-2 cm H2O if needed to achieve PaO2 > 60 mmHg or SpO2 of > 90%. Inspiratory pressure ventilation was increased, starting from 10 cmH2O, in increments of 2-3 cmH2O to obtain a tidal volume (VT) of 6-8 ml/Kg and a respiratory rate < 30 breaths/m'. Conversely, NIV was deemed successful when respiratory failure improved and the patient did not feel the need for more than 48 hours of ventilator treatment having a PaO2/FiO2 ratio > 250 with spontaneous breathing (3,13).

**Primary outcomes:**

NIV failure and hospital mortality were the primary outcomes.

**Secondary outcomes:**

Changes in arterial blood gases (ABG) analysis at admission and after 1 hour of NIV, NIV duration and the length of hospital stay were the secondary outcomes.

**Statistical analysis:**

Continuous variables expressed as mean ± standard deviation were compared with the regression analysis corrected for age. Categorical variables expressed as number and percentages were compared using chi-square test. A P-value ≤0.05 was considered significant. The predictors identified as predictors of NIV failure and hospital mortality were analyzed initially with univariate regression analysis and therefore, were also included in a multivariate logistic regression analysis. Adjusted odds ratios (OR) and 95% confidence interval (CI) were computed for variables independently associated with NIV failure or hospital mortality. The predictive capacity for NIV failure or hospital mortality of quantitative variables was assessed with receiver-operating characteristic (ROC) curves; the area under the curve (AUC), optimal cut-off values, sensitivity, specificity and positive and negative predictive values were calculated. Data analysis was made with statistical software R-Project version 2.13.2.

**RESULTS**

One hundred and thirty patients admitted with CAP received NIV (76 males and 54 females aged 59.74±16.17 years) for 90±96 hours, i.e., 3.7±3.3 days (mean ± SD). During NIV treatment, the pressure support ventilation (PSV) was 11±5 cm H2O and PEEP was 8±4 cmH2O. NIV was successfully used in 104 patients (80.0 %). Twenty-six patients experienced NIV failure; 18 were intubated and admitted to ICU. Eight other patients had previously stated that they did not want to be intubated and died. The main reasons for intubation were worsening of respiratory insufficiency (10 patients), cardio-respiratory arrest (four patients), and multi-organ failure (four patients).

Eight patients who were not intubated died because of multi-organ failure (three patients) and worsening of respiratory failure (five patients).

**Acute respiratory failure de novo:**

Acute respiratory failure de novo was considered as a separate entity (2) in which CAP occurred in patients with no previous cardio-respiratory co-morbidities. Patients in the de novo group who failed NIV had more severe scores (CURB 65 and SAPS II), more extensive radiological findings (Opravil score), and more severe respiratory impairment at admission (lower PaO2/FiO2 ratio and higher A-aDO2). They also presented with worse oxygenation and gas exchange, along with a higher respiratory rate after 1 h of NIV and after 24 hours. Moreover, at admission they presented with higher values of LDH and C-reactive protein. Patients who demonstrated NIV success had a SAPS II ≤ 34 and PaO2/FiO2 after 1 hour of NIV > 175, previously indicated marker of NIV success (P≤0.001) (4) as well as lower A-aDO2 after 1 hour of NIV and after 24 hours.
Patients with previous cardiac or respiratory disease were older and had higher PaCO₂ and bicarbonate, lower arterial pH and decreased consciousness at admission. But the only significant difference with the de novo respiratory failure group was in age (73±15 versus 47±16 years, P≤0.001) (Table 1).

Table 1. Clinical and ventilatory characteristics of the two groups

|                       | De novo ARF | Previous CR ARF | P-value |
|-----------------------|-------------|-----------------|---------|
| **age**               | Mean        | 47              | 73      | 0.001   |
|                       | Sd.         | 16              | 15      |          |
| **Male**              |             | 38              | 41      | 0.33     |
| **Female**            |             | 18              | 33      | 0.21     |
| **SAPS II**           |             | 21              | 10      | 0.31     |
| **Lobes (number)**    |             | 3               | 3       | 0.93     |
| **Chest X ray score** |             | 8               | 3       | 0.99     |
| **RMU STAY ( hours)** |             | 162             | 119     | 0.74     |
|                       |             | 116             | 136     |          |
| **CURB65**            |             | 1               | 2       | 0.33     |
|                       |             | 1               | 2       |          |
| **HCO3**              |             | 23              | 1       | 0.33     |
|                       |             | 27              | 7       |          |
| **C-R Prot**          |             | 22              | 9       | 0.25     |
| **LDH**               |             | 439             | 211     | 0.07     |
|                       |             | 576             | 522     |          |
| **Respiratory rate**  |             | 32              | 4       | 0.14     |
| **Heart rate**        |             | 103             | 11      | 0.07     |
|                       |             | 105             | 14      |          |
| **PaO₂**              |             | 48,50           | 12      | 0.13     |
|                       |             | 55              | 15      |          |
| **PaCO₂**             |             | 44              | 27      | 0.47     |
|                       |             | 60              | 40      |          |
| **pH**                |             | 7,40            | 0,10    | 0.27     |
|                       |             | 7,35            | 0,11    |          |
| **PaO₂/FiO₂**         |             | 162             | 48      | 0.99     |
|                       |             | 162             | 45      |          |
| **A-aDO₂**            |             | 121             | 92      | 0.80     |
|                       |             | 127             | 102     |          |
| **KMS**               |             | 1               | 1       | 0.12     |
|                       |             | 2               | 2       |          |

ARF Acute respiratory failure; CR cardiac-respiratory disease; *Opravil chest X-ray score SAPS II = Simplified acute physiology score; CURB 65 = confusion, elevated blood urea, respiratory rate, blood pressure plus age≥65 years; A-aDO₂ = Alveolar-arteriolar gradient; RMU STAY = Length of stay in High-dependency Respiratory Unit; KMS = Kelly-Matthay Scale

Patients in the ARF group did not have significant differences at admission and showed only a drop in respiratory rate and heart rate after 1 hour of NIV in patients with NIV success. In those who failed NIV there was a significant increase of A-aDO₂ after 24 hours in patients (P≤0.02) (Table 2). In multivariate analysis of predictors associated with NIV failure in the two groups, a higher heart rate after 1 hour, a higher A-aDO₂ after 24 hours, and a higher X-ray score (Opravil score) at admission predicted failure (Table 3).

**Survival:**

Hospital survivors had less pulmonary involvement as assessed by X ray (Opravil) score, a lower LDH at admission, a greater improvement of respiratory and heart rate after 24 hours of NIV and a better PaO₂/FiO₂ and A-aDO₂ after 24 hours compared with those who died. In patients with de novo ARF survival was also related to A-aDO₂ at admission and after 1 hour of NIV as well as initial C-reactive protein. In patients with previous cardiac and respiratory disease, ARF survival was also associated with a lower severity score at admission (CURB 65 and SAPS II), lower PaCO₂ and higher pH after 24 hours of NIV along with a lower respiratory rate after 1 hour of NIV. There was no significant difference between NIV duration or length of stay in the RMU among patients with NIV success or NIV failure (Table 4). In total population, the multivariate analysis identified a higher LDH at admission, a higher X-ray score (Opravil) at admission, higher heart rate after 24 hours and higher A-aDO₂ after 24 hours as independent predictors of hospital mortality (Table 5). Figure 1 shows the predictors of hospital mortality using ROC curves.
Table 2. Variables associated with failure of non-invasive ventilation in the two groups

| Variables | T | Label | Adj.OR | 95% CI | P-value | AUC | Optimal cut-off | Sensitivity (%) | Specificity (%) | Likelihood ratio | Predictive value |
|-----------|---|-------|--------|--------|---------|-----|----------------|----------------|----------------|----------------|-----------------|
| A-aDO2    | 2 | NIV fail | 214    | 19.4   | 12051   | 2001 | 0.885          | 131            | 88.90          | 92.90          | 12.44           | 0.12            | 66.7            | 98.1            |
| Heart rate| 1 | NIV fail | 12.75  | 2.6    | 69.4    | 0.002| 0.862          | 108            | 55.60          | 91.11          | 6.22            | 0.49            | 50.0            | 92.7            |
| X-ray score| 0 | NIV fail | 14.13  | 2.5    | 92.1    | 0.003| 0.821          | 11             | 44.40          | 96.40          | 8.30            | 0.59            | 57.1            | 91.4            |

NIV fail = Non invasive ventilation failure
A-aDO2 = Alveolar-arteriolar gradient
X-ray score = Chest X-ray score (Opravil)
T 0 at admission
T1 after 1 hour of NIV
T2 after 24 hours of NIV
Adj OR = Adjusted odds ratio
CI = confidence interval
AUC = area under the curve

Table 3. Multivariate analysis of variables independently associated with non invasive ventilation failure in the total population

| Variables | T | Label | Adj.OR | 95% CI | P-value | AUC | Optimal cut-off | Sensitivity (%) | Specificity (%) | Likelihood ratio | Predictive value |
|-----------|---|-------|--------|--------|---------|-----|----------------|----------------|----------------|----------------|-----------------|
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T 0 at admission
T1 after 1 hour of NIV
T2 after 24 hours of NIV
Adj OR = Adjusted odds ratio
CI = confidence interval
AUC = area under the curve
### Table 4. Variables associated with hospital mortality in the two groups

| Variables               | T0 | T1 | T2 | P value | AUC | Optimal cutoff | Sensitivity (%) | Specificity (%) | Likelihood ratio | Predictive value |
|-------------------------|----|----|----|---------|-----|----------------|-----------------|-----------------|-----------------|-------------------|
| **De novo ARF**          |    |    |    |         |     |                |                 |                 |                 |                   |
| Alive (52)              |    |    |    |         |     |                |                 |                 |                 |                   |
| Alive (58)              |    |    |    |         |     |                |                 |                 |                 |                   |
| Dead (4)                |    |    |    |         |     |                |                 |                 |                 |                   |
| Dead (16)               |    |    |    |         |     |                |                 |                 |                 |                   |
| A-aDO2                  |    |    |    | 0.03    | 0.92 | 247            | 30.00           | 98.20           | 16.50           | 75.0              |
| Heart rate              |    |    |    | 0.01    | 0.95 | 728            | 60.00           | 94.50           | 13.40           | 68.4              |
| LDH                     |    |    |    | 0.03    | 0.90 | 108            | 80.00           | 92.70           | 11.00           | 66.7              |
| Chest X-ray score       |    |    |    | 0.04    | 0.80 | 11             | 40.00           | 94.50           | 7.33            | 57.1              |

* Variable entered into a multivariate logistic regression analysis

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### Table 5. Multivariate analysis of variables independently associated with hospital mortality in the total population

| Variables               | T Label | Adj OR | 95% CI | P value | AUC | Optimal cutoff | Sensitivity (%) | Specificity (%) | Likelihood ratio | Predictive value |
|-------------------------|---------|--------|--------|---------|-----|----------------|-----------------|-----------------|-----------------|-------------------|
| A-aDO2                  | H mort  | 1.107  | 1.000  | 1.210  | 0.03| 0.902          | 30.00           | 98.20           | 16.50           | 75.0              |
| Heart rate              | H mort  | 1.681  | 1.420  | 1.970  | 0.03| 0.908          | 80.00           | 92.70           | 11.00           | 66.7              |
| LDH                     | H mort  | 3.17   | 3.01   | 3.35   | 0.01| 0.956          | 60.00           | 94.50           | 13.40           | 68.4              |
| X-ray score             | H mort  | 1.26   | 1.09   | 1.44   | 0.04| 0.803          | 40.00           | 94.50           | 7.33            | 57.1              |

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SAPS II = Simplified acute physiology score
CURB 65 = confusion, elevated blood urea, respiratory rate, blood pressure plus age ≥ 65 years
A-aDO2 = Alveolar-arteriolar gradient
RMU STAY = Length of stay in Respiratory Monitoring Unit
C-R prot = C reactive protein

A-aDO2 = Alveolar-arteriolar gradient
T0 at admission
T1 after 1 h NIV
T2 after 24 h NIV

T0 at admission
T2 after 24 hours of non-invasive ventilation
Adj OR = Adjusted odds ratio
CI = Confidence interval
AUC = Area under the curve

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DISCUSSION

Patients with severe respiratory failure due to CAP and previous cardiac or respiratory disease usually have a better response to NIV than patients with de novo acute respiratory failure (as demonstrated in previous studies) (2,18,19). Few studies have investigated the benefits of NIV in patients with severe CAP: the oldest showed good results principally in patients with chronic obstructive pulmonary disease (COPD) and hypercapnic respiratory failure (18). Subsequent researches demonstrated that NIV was effective in decreasing the rates of intubation and mortality compared with high concentration oxygen therapy (9,10,20). Another recent investigation examined patients with ARF de novo and ARF due to cardiac or respiratory disease; this study showed that NIV is a safe and effective modality. In patients with ARF de novo, NIV failure was associated with a high mortality (2).

Three recent studies (21-23) support the effectiveness of NIV in severe CAP. The first evaluated 151 COPD patients requiring ICU admission, who underwent NIV and reported a failure rate of 31.1%. Nearly 70% of patients has success with NIV. Non-invasive ventilation, hypertension and corticosteroid treatment were associated with decreased mortality; whereas bilateral infiltration, length of ICU stay and duration of IMV were associated with increased mortality (21). The second study included a cohort of 1,946 elderly immunocompromised patients. Unexpectedly, patients who underwent NIV had decreased mortality at 90 days when compared to those treated with invasive mechanical ventilation. The authors concluded that data obtained suggest that physicians should consider the use of NIV for the elderly immunocompromised patients hospitalized with pneumonia. It seemed that patients receiving NIV fared no worse than similar patients receiving IMV (22). The third study reported a similar NIV success rate (75%) related to early use of NIV and to strict patient selection protocol (23). Only a few studies evaluated the interrelations of radiographic findings and the need for mechanical ventilation in patients admitted with pneumonia (24,25). Erdem et al. demonstrated that patients with bilateral pulmonary involvement most often needed NIV while those with multi-lobar involvement more frequently required IMV (25). A final consideration concerning a high rate of NIV success (80%): the success begins in the emergency department where a strict selection protocol is followed. For example, a patient with PaO2/FIO2 ratio < 150 was not considered for NIV (13, 26). Our center has strict and continuous monitoring at admission and during the stay at the RMU. Another point worth considering is our long use of NIV. Success could be the result of the expertise of our team (physicians and nurses) who have been using NIV for more than 10 years (27).

We are aware that this real-life study has important limitations: 1. It is a single center study and reflects the skills of a single group. Therefore, these data may not be generalized to other settings (28). 2. The effectiveness of any treatment is established by a randomized controlled trial. In the absence of a control group, definitive conclusions cannot be drawn. 3. Microbiological data were available only for a minority of our patients; therefore, different pathogens may have affected patient outcomes. 4. The criteria for intubation were not standardized “a priori” but followed our institutional guidelines. This reflects the “real life” scenario of the study.

CONCLUSIONS

In conclusion, in this observational study, successful treatment was strongly related to less pulmonary involvement and to a prompt and continued response to medical and NIV treatment. Continuous and strict monitoring in an appropriate environment is of paramount importance.

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