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Early View

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Dyspnea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact – a prospective observational study

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Dyspnea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact – a prospective observational study –

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ABSTRACT

Dyspnea is a frequent and intense symptom in intubated patients, but little attention has been paid to dyspnea during noninvasive mechanical ventilation (NIV) in the intensive care unit (ICU).

The objectives of this study were to quantify the prevalence, intensity and prognostic impact of dyspnea in patients receiving NIV for acute respiratory failure (ARF) based on secondary analysis of a prospective observational cohort study in patients who received ventilatory support for ARF in 54 ICUs in France and Belgium. Dyspnea was measured by a modified Borg scale.

Among the 426 patients included, the median dyspnea score was 4 [3–5] on admission and 3 [2– 4] after the first NIV session (p=0.001). Dyspnea intensity ≥4 after the first NIV session was associated with SOFA (OR, 1.12; p=0.001), respiratory rate (OR, 1.03; p=0.032), anxiety (OR, 1.92; p=0.006), leaks (OR 2.5; p=0.002) and $PaCO_2$ (OR, 0.98; p=0.025). Dyspnea intensity ≥4 was independently associated with NIV failure (OR, 2.41, p=0.001) and mortality (OR, 2.11; p=0.009), but not with higher post-ICU burden and altered quality of life.

Dyspnea is frequent and intense in patients receiving NIV for ARF and is associated with a higher risk of NIV failure and poorer outcome.

INTRODUCTION

Dyspnea is a threatening sensation that shares common neural networks and clinical features with pain [1, 2]. In contrast with pain, which has received major attention in the intensive care unit (ICU) [3, 4], little attention has been paid to dyspnea [5]. However, almost one-half of intubated patients experience dyspnea, which they describe as intense and as one of the worst experiences of their ICU stay [6, 7]. Dyspnea is also associated with delayed extubation [6]. Finally, there is a body of literature suggesting that negative respiratory-related experiences could play an important role in the pathogenesis of ICU-related post-traumatic stress syndromes, thereby altering quality of life [8].

Most data concerning dyspnea in the ICU are derived from studies conducted in intubated patients [5, 6]. However, a growing number of patients admitted for ARF are now managed without being intubated due to the increasing use of noninvasive ventilation (NIV) [9] and the potential benefit of high-flow oxygen [10].

Although dyspnea is a warning sign of a critical threat to homeostasis [1], its prevalence, intensity and impact on outcome have not been systematically assessed in patients receiving NIV as first-line treatment for ARF. In these patients, dyspnea is one of the key symptoms of ARF that may also be modulated by NIV. Some data indirectly suggest that dyspnea may be frequent and severe in patients receiving NIV and could be improved in response to NIV [11-15].

The primary objective of this secondary analysis of a prospective cohort on mechanical ventilation in 54 ICUs in France and Belgium was to quantify the prevalence and intensity of dyspnea in patients receiving NIV for ARF, on admission to the ICU and after the first NIV session. We also examined factors associated with dyspnea. Finally, we investigated the impact of dyspnea on NIV success or failure, on outcome and on quality of life and post-ICU burden.

PATIENTS AND METHODS

The population of this study was selected from patients included in a prospective observational study conducted in 54 French and Belgian ICUs, members of the REVA (Research Network in Mechanical Ventilation) or FAMIREA (to improve the effectiveness of communication with the relatives of ICU patients) networks, which was initially designed to evaluate NIV use in terms of both frequency and indications and to assess the effects of NIV on ICU survival. Participating centers and collaborators are listed in the online supplement. The study was approved by the institutional review board of the French-language Society for Respiratory Medicine (*Société de Pneumologie de Langue Française*) and was registered on a publically available database (clinicaltrial.govNCT01449331). Written informed consent was obtained from all patients or relatives. Two other studies based on this cohort have been published elsewhere [9, 16].

Study population

Each participating ICU included consecutive adults requiring ventilatory assistance, either invasive mechanical ventilation or NIV for acute respiratory failure (ARF, defined by respiratory rate >30/min, or signs of respiratory distress, or SpO_2 < 90% on room air) in the prospective cohort over a 2-month enrolment period between November 2010 and April 2011. For the purposes of the present *post hoc* study, only patients who received NIV as first-line treatment for acute respiratory failure were included. Patients receiving NIV for comfort care only and patients with missing data or incomplete data on dyspnea were excluded.

Data collection

Patients were followed daily in the ICU, at hospital discharge and 90 days after ICU discharge (day-90). At each of these timepoints, the study investigators completed a standardized electronic case report form. Demographic data and medical history collected consisted of: age, gender, Simplified Acute Physiologic Score (SAPS) II [17], Sepsis-related

Organ Failure Assessment score (SOFA) [18], underlying diseases such as chronic respiratory disease (chronic obstructive or restrictive pulmonary disease, obesity, neuromuscular disease, etc.) and the need for home oxygen therapy, chronic heart failure (NYHA III or IV), immunosuppression (defined as neutrophil count less than 1,000/mm^3, malignancy treated by cancer chemotherapy, immunosuppressive therapy for solid organ transplantation, corticosteroid therapy at a daily dose of 20 mg or more for at least 3 weeks or AIDS). The cause of ARF was either acute on chronic respiratory failure defined as respiratory failure occurring in patients with preexisting respiratory disease, cardiogenic pulmonary edema or *de novo* ARF defined as respiratory failure not exacerbating chronic lung disease or heart failure (also called hypoxemic ARF).

Respiratory rate, intensity of dyspnea and arterial blood gas values were recorded 1) at ICU admission before initiation of ventilatory support and 2) after the first NIV session. To assess the intensity of dyspnea, patients were asked to rate their breathing discomfort (in French "*inconfort respiratoire*") on a modified Borg category-ratio (1-10) scale [19] that consists of verbal descriptors linked to specific numbers, in which the spacing of the numbers and corresponding descriptors essentially provides a category scale with ratio properties. This scale ranges from 0, representing no dyspnea, to 10, representing maximal dyspnea. It was used to identify two groups of patients based on a dyspnea intensity of 4 qualified as “somewhat severe dyspnea”. This cut-off was based on the many similar features shared by dyspnea and pain (noxious sensations, common pathways, similar cortical areas involved and affective dimension). A pain score ≥4 is considered to be a clear indication for analgesia [20]. In the present study, dyspnea intensity <4 was defined as mild-or-no-dyspnea, while dyspnea intensity ≥4 was defined as moderate-to-severe dyspnea [19, 21]. The presence of air leaks and anxiety and the prescription of analgesics including opioids were also recorded.

The need for invasive mechanical ventilation, ICU and in-hospital length of stay, ICU mortality, in-hospital mortality and day-90 mortality were recorded. NIV success or failure was defined as follows. Patients requiring endotracheal intubation or who died during the 24 hours following NIV discontinuation were classified as NIV failures. Patients treated with NIV until they no longer required ventilatory support were classified as NIV successes. Ninety days after ICU discharge, trained social workers coached by psychologists and sociologists of the FAMIREA study group interviewed survivors by telephone. Patients were asked to complete the SF-36 questionnaire to assess health-related quality of life (HRQOL), Impact of Event Scale Revised (IES-R) to assess PTSD-related symptoms [22, 23] and Hospital Anxiety and Depression Scale (HADS) to quantify symptoms of anxiety and depression [24] in that order. Lower HADS and IES scores indicate less post-ICU burden, but lower SF-36 scores indicate poorer HRQOL.

Data quality

An ICU physician not involved in the study resolved inconsistencies in the data entered by the investigators, based on comparison of the study case report forms with the medical charts. The database was audited by an independent check of all ICU variables on a random sample of 10% of patients.

Statistical analysis

Quantitative variables were described as median (interquartile range [IQR]) and were compared between groups using the non-parametric Wilcoxon rank-sum test or a paired Wilcoxon rank-sum test for matched data. Qualitative variables were described as frequency (percentages) and were compared between groups using Fisher's exact test. Median intensive care unit (ICU) and hospital length of stays (LOS) were estimated using a Kaplan-Meier estimator, with discharge alive as the event of interest and death as the censoring event.

Factors associated with moderate-to-severe dyspnea on ICU admission or after the first NIV session, and factors associated with NIV failure and hospital mortality were studied by multivariate logistic regression analysis. The multivariate model was built with variables that yielded p values less than 0.05 on univariate analysis and/or that were considered to be clinically relevant. A backward stepwise selection procedure was performed with an elimination process based on p values less than 0.05. Adjusted odds ratios (OR) of variables present in the final model are presented with their 95% confidence intervals. Log-linearity was checked for continuous variables and non-log-linear variables were categorized. Hosmer-Lemeshow goodness-of-fit tests were computed on final models. Finally, the impact of dyspnea on ICU mortality, health-related quality of life (SF-36), PTSD-related symptoms (IES-R) and symptoms of anxiety and depression (HADS) was evaluated in univariate analysis (using Fisher's exact test or a Wilcoxon test, as appropriate). Median hospital or ICU length of stay was compared using a log-rank test.

All tests were two-sided and p values less than 0.05 were considered statistically significant. All statistical analyses were performed with R statistical software, version 3.2.0 (available online at http://www.r-project.org/).

RESULTS

Study population and prevalence of dyspnea

Figure 1 displays the study flow chart. During the study period, 2,367 patients requiring ventilatory support were admitted to the ICU: 1,799 of them received invasive ventilatory support, 1,203 for a non-respiratory condition and 596 as first-line treatment for acute respiratory failure. The remaining 568 patients received NIV as first-line treatment for acute respiratory failure: 61 patients who received comfort care-only NIV and 81 patients with missing data on dyspnea were excluded from this study. A total of 426 patients were finally

assessed for dyspnea on admission and after the first NIV session and were included in the present study. Table 1 indicates the patient characteristics at the time of ICU admission. NIV interfaces and ventilator mode and settings are described elsewhere [9].

On admission to the ICU, before initiation of NIV, the median dyspnea score was 4 [3–5] on the modified Borg scale and with a score ≥ 4 (moderate-to-severe dyspnea) in 234 patients (55%). After the first NIV session, the median dyspnea score decreased to 3 [2–4] ($p<0.001$) with a score ≥ 4 in 166 patients (39%). The median absolute variation of dyspnea was 1 [0–2] and ≥ 1 point in 219 (51%) patients.

Factors associated with moderate-to-severe dyspnea on ICU admission and after the first NIV session

Table 1 displays the factors associated with moderate-to-severe dyspnea on ICU admission. On multivariate logistic regression analysis, respiratory rate ($cycles.min^{-1}$) was the only factor independently associated with moderate-to-severe dyspnea on ICU admission.

Table 2 shows the factors associated with moderate-to-severe dyspnea after the first NIV session. On multivariate logistic regression analysis, five of these factors were independently associated with dyspnea after the first NIV session. Four factors were associated with moderate-to-severe dyspnea after the first NIV session: SOFA, respiratory rate on ICU admission, anxiety and leaks. Patients with a high $PaCO_2$ were less likely to experience moderate-to-severe dyspnea.

Association between dyspnea and NIV failure

NIV failure rate was 31% (n=133). Table 3 displays the factors associated with NIV failure. On multivariate logistic regression analysis and after the selection process, three factors were independently associated with NIV failure or success. A high SOFA score and moderate-to-severe dyspnea after the first NIV session were associated with NIV failure, while acute-on-chronic respiratory failure as precipitating factor was associated with NIV

success. Patients with acute-on-chronic respiratory failure were less likely to experience NIV failure compared to patients with *de novo* acute respiratory failure (OR=0.40 (95% CI: 0.23-0.70)), p=0.001). Patients with moderate-to-severe dyspnea after the first NIV session were more likely to experience NIV failure (OR=2.41 (95% CI: 1.49 -3.91), p <0.0001).

Associations between dyspnea and outcome, quality of life and post-ICU burden

Table 4 displays mortality, length of stay, quality of life and post-ICU burden. Moderate-to-severe dyspnea on ICU admission was not associated with any alteration of outcome. SF-36, HADS anxiety and depression subscores and IES-R did not indicate greater burden in patients with moderate-to-severe dyspnea on ICU admission or after the first NIV session. In contrast, on univariate analysis, moderate-to-severe dyspnea after the first NIV session was associated with higher ICU, hospital and 90-day mortality and was also associated with longer hospital length of stay.

Table 5 displays the factors associated with in-hospital mortality. On multivariate logistic regression analysis, three of these factors were independently predictive of in-hospital mortality. Two factors were positively associated with in-hospital mortality: moderate-to-severe dyspnea after the first NIV session and SOFA score at admission. One factor, $PaCO_2$ on ICU admission, was negatively associated with in-hospital mortality.

DISCUSSION

The main and major findings of this study can be summarized as follows. In a population of patients admitted to the ICU for ARF requiring NIV: 1) the level of dyspnea was high and moderate-to-severe dyspnea after the first NIV session was associated with anxiety; 2) moderate-to-severe dyspnea after the first NIV session was independently associated with NIV failure and subsequent intubation; 3) persistence of moderate-to-severe dyspnea after the first NIV session was associated with longer length of stay and hospital

mortality, but was not associated with post-ICU burden or impaired quality of life. To the best of our knowledge, this is the largest study to investigate dyspnea in a population of non-intubated patients admitted for ARF and treated with NIV. Dyspnea has been measured as a secondary outcome in many trials evaluating the benefit of NIV in acute-on-chronic respiratory failure and acute cardiogenic pulmonary edema [11-14] and as a primary outcome in a trial on NIV in end-of-life patients [15], but the prevalence of dyspnea and its risk factors and prognostic impact have not been previously studied in such a large population.

Prevalence and intensity of dyspnea

The prevalence of moderate-to-severe dyspnea was 55% at the time of ICU admission prior to initiation of NIV and 39% after the first NIV session. This prevalence is similar to that reported in previous studies. Fifty percent of intubated patients complained of dyspnea as soon as they were able to answer symptom-related questions and the median dyspnea score on a visual analog scale was 5 [6]. In trials on the efficacy of NIV in ARF that included scoring of dyspnea, dyspnea scores ranged from 3 to 6 on a visual analog scale [11-14] with high levels of dyspnea in all studies. Similar pain scores would require immediate treatment and constitute a clear indication for analgesia [20]. Previous reports have suggested that the minimal clinically important difference (MCID) for the modified Borg scale is one point [25-27]. It is noteworthy that the first NIV session had a moderate impact on dyspnea, as the dyspnea score decreased by one point or more in only one-half of patients.

Although it is not surprising to observe dyspnea before initiation of NIV in patients admitted for ARF, as dyspnea is one of the major clinical features of ARF, we were surprised by the marked severity of dyspnea observed in this population, even after the first NIV session. These findings suggest that dyspnea should be actively investigated in ICU patients admitted for ARF, in the same way as pain. It must be stressed that relief of dyspnea is an

essential clinical mission that, as in the case of pain, is currently considered by some authors to be a basic human right [28, 29].

Theoretically, NIV can either alleviate dyspnea due to respiratory muscle unloading [30] or exacerbate dyspnea because of poor patient-ventilator interaction. In the present study, we observed that the median dyspnea score decreased in response to NIV.

Factors associated with dyspnea

Anxiety was independently associated with dyspnea after the first NIV session, as previously reported in mechanically ventilated patients [6]. The interplay between anxiety and dyspnea is complex with causal relationships in both directions. Anxiety, like pain, can increase dyspnea by stimulating ventilatory drive and consequently ventilation [31]. Reciprocally, dyspnea generates anxiety and it has been clearly demonstrated that relief of dyspnea decreases anxiety [32]. There is now a growing body of evidence to support the concept of overlap between anxiety and dyspnea and that relief of one should improve the other [31, 33].

Leaks were also independently associated with dyspnea. In NIV patients, leaks are a clearly demonstrated cause of alterations of breathing pattern and patient-ventilator asynchronies [34, 35]. In stable COPD patients receiving home NIV, adjustment of ventilator setting decreased asynchronies and leaks and improved morning dyspnea [36]. Adjustment of ventilator settings may therefore help to relieve patients with significant dyspnea. Similar observations have been reported in intubated patients [6].

Of note, although patients with moderate-to-severe dyspnea were more likely to receive analgesics, including opioids, only a small proportion (16%) of patients received such agents, which could be related to a fear of respiratory depression. However, some patients may have been deprived of a dyspnea-relieving treatment. The benefit-risk balance of these medications in patients with ARF remains unknown.

NIV failure

One of the major findings of this study is that dyspnea, a key symptom of ARF, was associated with NIV failure. More specifically, dyspnea after the first NIV session, but not dyspnea on ICU admission or the absolute variation of dyspnea, was associated with NIV failure, suggesting that improvement of dyspnea after the first NIV session designed to treat ARF may constitute a useful marker of the quality of response to NIV. Absence of improvement of dyspnea is also associated with treatment failure during acute exacerbations of COPD [37].

Clinical outcomes

Dyspnea was shown to be associated with higher short-term and long-term mortality. Previous studies have established a similar link in non-critically ill patients, in whom dyspnea is predictive of mortality and constitutes a proxy for underlying diseases, particularly heart and lung disease [38]. For instance, dyspnea alone is a predictor of survival in patients with stable COPD [39] and in patients referred for cardiac stress testing [40, 41]. In a more acute setting, dyspnea is a predictor of in-hospital mortality in patients admitted for acute exacerbations of COPD [42] and patients with suspected [43] or confirmed [44] acute myocardial infarction. Finally, even in patients without previously diagnosed cardiopulmonary diseases, dyspnea is independently associated with a higher risk of atrial fibrillation and myocardial infarction [45] and is a predictor of all-cause mortality [45, 46]. To the best of our knowledge, this is the first study to report an association between dyspnea after the first NIV session and a higher mortality rate in ICU patients.

In contrast, no correlation was observed between dyspnea and post-ICU burden and quality of life. This negative result was all the more surprising in that dyspnea is known to be an ICU stressor in the same way as pain and thirst [3, 7] and recent data suggest that negative

respiratory-related experiences can play an important role in the pathogenesis of ICU-related post-traumatic stress syndromes [47, 48].

Limitations

This study presents a number of limitations that need to be acknowledged. First, we chose to quantify dyspnea by means of a Borg scale rather than a visual analog scale. These two scales are the two instruments most commonly used to measure dyspnea in the ICU [49, 50], with strong correlations between the two scales their validity and reliability have been validated in critically ill patients [51, 52]. Unfortunately, the use of these tools requires patients to be alert and oriented and each instrument is only one-dimensional, only measuring intensity of dyspnea. Second, we quantified dyspnea on only two occasions, on admission to the ICU and after the first NIV session. A longitudinal analysis based on multiple repeated measurements would provide additional results [37]. Third, patients were not systematically assessed for delirium, although delirium may have an impact on assessment of dyspnea. However, patients who were unable to provide clear and coherent answers were not included in the study (incomplete or missing data in Figure 1). Finally, this study was an additional analysis of a prospective cohort in which the first objective was not the study of dyspnea in patients receiving noninvasive ventilation.

Conclusion

In conclusion, the results of this study show that dyspnea is frequent and often intense in patients receiving NIV. Given the impact of dyspnea on negative respiratory-related sensations and its close association with anxiety, taking the patient's perception of dyspnea into account could help to improve the patient's immediate comfort and the quality of care provided to these patients [5, 53]. Because dyspnea can be easily identified at the bedside, we propose that dyspnea should be monitored on a regular basis in these patients, both for human reasons, but also because our study suggests that dyspnea is a threatening signal, as moderate-

to-severe dyspnea after the first NIV session was independently associated with NIV failure, indicating that dyspnea could be a marker of response to NIV. Future studies should evaluate the benefit of systematic monitoring of dyspnea in patients receiving NIV. These studies should also evaluate the benefit of treatments designed to relieve dyspnea on patient comfort and outcome.

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Tables

Table 1. Univariate analysis: factors associated with moderate-to-severe dyspnea on admission to the intensive care unit.

	All patients (n=426)	**Mild or no dyspnea (n=192)** Borg scale <4	**Moderate-to-severe dyspnea (n=234)** Borg scale ≥4	**P value**
Patient characteristics				
Age, *years, median (IQR)*	69 (60 – 78)	71 (61 –79)	68 (59 – 77)	0.019
Male gender, *n (%)*	270 (63)	118 (61)	152 (65)	0.48
BMI, $kg.m^{-2}$	26 (22 – 32)	27 (23 – 33)	26 (22 – 31)	0.21
Chronic respiratory disease, *n (%)*	267 (63)	118 (61)	149 (64)	0.69
Chronic cardiac disease, *n (%)*	87 (20)	41 (21)	46 (20)	0.72
Immunosuppression, *n (%)*	112 (26)	47 (24)	65 (28)	0.51
Home oxygen therapy, *n (%)*	88 (21)	33 (17)	55 (23)	0.12
SAPSII, *median (IQR)*	35 (27 – 44)	37 (28 – 45)	35 (27 – 43)	0.16
SOFA, *median (IQR)*	3 (2 – 5)	3 (2 – 6)	3 (2 – 5)	0.93
Cause of ARF				
Acute-on-chronic, *n (%)*	251 (59)	110 (58)	141 (60)	0.62
Acute cardiogenic pulmonary edema, *n (%)*	58 (14)	26 (14)	32 (14)	1
De novo ARF, *n (%)*	116 (27)	55 (29)	61 (26)	0.58
On ICU admission, prior to NIV				
Respiratory rate, min^{-1}, *median (IQR)*	32 (27 – 36)	30 (25 – 35)	32 (28 –38)	0.0002
Blood gases				
PaO_2/FiO_2, *mmHg, median (IQR)*	219 (159 – 280)	210 (158 – 261)	223 (160 –294)	0.23
$PaCO_2$, *mmHg, median (IQR)*	53 (40 – 71)	55 (40 –71)	52 (40 –70)	0.57
pH, *mmHg, median (IQR)*	7.34 (7.27–7.40)	7.33 (7.27–7.40)	7.34 (7.27–7.41)	0.45

BMI, body mass index; SAPS 2, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment score; ARF, acute respiratory failure; NIV, noninvasive ventilation; PaO2/FiO2, ratio of arterial oxygen tension to inspired oxygen fraction; IQR interquartile range.

Table 2. Univariate analysis: factors associated with moderate to severe dyspnea after the first noninvasive ventilation session.

	All patients (n=426)	Mild or no dyspnea (n=260) Borg scale <4	Moderate-to-severe dyspnea (n=166) Borg scale ≥4	P value	Adjusted OR (95% CI) Final Multivariate selected model*	p value
Patient characteristics						
Age, *years, median (IQR)*	69 (60 – 78)	70 (61 – 79)	67 (59 – 77)	0.1		
Male gender, *n (%)*	270 (63)	173 (66)	97 (58)	0.099		
BMI, *kg.m^{-2}, median (IQR)*	26 (22 – 32)	26 (23 – 32)	25 (22 – 30)	0.22		
Chronic respiratory disease, *n (%)*	267 (63)	176 (68)	91 (55)	0.008		
Chronic cardiac disease, *n (%)*	87 (20)	54 (21)	33 (20)	0.90		
Immunosuppression, *n (%)*	112 (26)	63 (24)	49 (29)	0.26		
Home oxygen therapy, *n (%)*	88 (21)	61 (24)	27 (16)	0.086		
SAPSII, *median (IQR)*	35 (27 – 44)	35 (27 – 43)	37 (28 – 46)	0.080		
SOFA, *median (IQR)*	3 (2 – 5)	3 (2 – 5)	4 (2 – 6)	0.002	1.12 (1.04 - 1.2)	0.001
NIV episode						
Cause of ARF				0.004		
Acute-on-chronic, *n (%)*	251 (59)	169 (65)	82 (49)			
Acute cardiogenic pulmonary edema, n (%)	58 (14)	28 (11)	30 (18)			
De novo ARF, *n (%)*	116 (27)	62 (24)	54 (32)			
On ICU admission, prior to NIV						
Respiratory rate, *min^{-1}, median (IQR)*	32 (27 – 36)	31 (26 – 35)	32 (28 – 39)	0.004	1.03 (1.00 -1.06)	0.0325
Blood gases						
PaO_2/FiO_2, *mmHg, median (IQR)*	219 (159 – 280)	220 (167 – 274)	210 (144 – 282)	0.48		
$PaCO_2$, *mmHg, median (IQR)*	53 (40 – 71)	58 (43 – 72)	48 (38 – 66)	0.002	0.98 (0.97-0.99)	0.025
pH, *mmHg, median (IQR)*	7.34 (7.27–7.40)	7.33 [7.27–7.40]	7.35 [7.27–7.41]	0.16		
After the first NIV session						
Leaks, *n (%)*	276 (67)	155 (60)	121 (78)	0.0002	2.5 (1.52 - 4.12)	0.0002
Decrease in dyspnea ≥ 1 point, *n (%)*	219 (51)	175 (67)	44 (26.5)	<0.0001		
Anxiety, *n (%)*	260 (62)	142 (55)	118 (73)	0.0002	1.91 (1.18- 3.10)	0.006
Respiratory rate, *min^{-1}, median (IQR)*	27 (23 – 33)	25 (22 – 30)	30 (25 – 35)	<0.0001		
Blood gases						
PaO_2/FiO_2, *mmHg, median (IQR)*	213 (162 – 259)	220 (178 – 260)	190 (146 – 254)	0.051		
$PaCO_2$, *mmHg, median (IQR)*	53 (41 – 66)	55 (44 – 68)	48 (40 – 65)	0.12		
pH, *mmHg, median (IQR)*	7.36 (7.29–7.40)	7.36 (7.31–7.40)	7.35 (7.27–7.41)	0.53		
Analgesic consumption						
All analgesics, *n (%)*	70 (16)	34 (13)	36 (22)	0.023		
Opioid, *n (%)*	25 (6)	11 (4)	14 (8)	0.090		

BMI, body mass index; SAPS 2, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment score; NIV, non invasive ventilation; ARF, acute respiratory failure; PaO2/FiO2, ratio of arterial oxygen tension to inspired oxygen fraction; IQR interquartile range.

The following variables were included in the initial complete model: gender, age, cause of acute respiratory failure, SOFA, respiratory rate on ICU admission, $PaCO_2$ on ICU admission, anxiety and leaks

Goodness-of-fit (Hosmer-Lemeshow) P value, 0.70

Table 3. Univariate analysis: factors associated with failure of noninvasive ventilation

	NIV failure (n=133)	NIV success (n=293)	P value	Adjusted OR Final Multivariate selected model*	p value
Patient characteristics					
Age, *years, median (IQR)*	69 (59 –78)	69 (60 – 78)	0.79		
Male gender, *n (%)*	92 (69)	178 (61)	0.10		
BMI, *kg.m^{-2}, median (IQR)*	26 (23 – 30)	26 (22 – 33)	0.70		
Chronic respiratory disease, *n (%)*	64 (48)	203 (69)	<0.0001		
Chronic cardiac disease, *n (%)*	25 (19)	62 (21)	0.61		
Immunosuppression, *n (%)*	45 (34)	67 (23)	0.024		
Home oxygen therapy, *n (%)*	19 (14)	69 (24)	0.029		
NIV episode					
Cause of ARF					
Acute-on-chronic, *n (%)*	50 (38)	201 (69)	<0.0001	0.40 (0.23 – 0.70)	<0.01
Acute cardiogenic pulmonary edema, *n (%)*	22 (16)	36 (12)		0.52 (0.25 – 1.07)	
De novo ARF, *n (%)*	61 (46)	55 (19)		1	
SAPSII, *median (IQR)*	43 (35 – 56)	32 (26 – 40)	<0.0001		
SOFA, *median (IQR)*	6 (3 – 9)	3 (2 – 4)	<0.0001	1.35 (1.24 – 1.48)	<0.0001
On ICU admission, prior to NIV					
Moderate-to-severe dyspnea, *n (%)*	78 (59)	156 (53)	0.34		
Respiratory rate, *min^{-1}, median (IQR)*	32 (28 – 38)	31 (27 – 36)	0.11		
Blood gases prior to NIV					
PaO_2/FiO_2, *mmHg, median (IQR)*	184 (120 – 258)	228 (181 – 290)	<0.0001		
$PaCO_2 \geq 80$ mmHg, *n (%)*	9 (7)	52 (18)	0.003		
pH ,*median (IQR)*	7.35 (7.27–7.44)	7.33 (7.27–7.39)	0.12		
After the first NIV session					
Moderate-to-severe dyspnea, *n (%)*	75 (56)	91 (31)	<0.0001	2.41 (1.49 – 3.91)	<0.0001
Absolute variation of dyspnea	0 (-1 - 1)	-1 (-2 - 0)	0.002		
Respiratory rate, *min^{-1}, median (IQR)*	30 (25 – 35)	26 (22 – 31)	<0.0001		
Leaks, *n (%)*	88 (68)	188 (66)	0.82		
Blood gases					
PaO_2/FiO_2, *mmHg, median (IQR)*	190 (145 – 220)	229 (183 – 287)	0.001		
$PaCO_2$, *mmHg, median (IQR)*	45 (35 – 60)	57 (46 – 69)	<0.0001		
pH, *median (IQR)*	7.35 (7.26–7.43)	7.36 (7.30–7.40)	0.79		

NIV, noninvasive ventilation; BMI, body mass index; ARF, acute respiratory failure; SAPS 2, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment score; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction; IQR interquartile range.

The following variables were included in the initial complete model: immunosuppression, home oxygen therapy, cause of ARF, SOFA, $PaCO_2$ on ICU admission prior to NIV, dyspnea after the first NIV session, absolute variation of dyspnea, respiratory rate after the first NIV session, leaks.

Goodness-of-fit (Hosmer-Lemeshow): p=0.61

Table 4. Outcome, quality of life and post-ICU burden according to the severity of dyspnea on intensive care unit admission and after the first noninvasive ventilation session

	All patients (n=426)	Dyspnea on ICU admission			Dyspnea after the first NIV session		
		Light or no dyspnea (n=192)	Moderate to severe dyspnea (n=234)	P value	Light or no dyspnea (n=260)	Moderate to severe dyspnea (n=166)	P value
ICU discharge							
ICU LOS, *days, median (IQR)*	6 (3 – 10)	5 (3–9)	6 (3 – 12)	0.74	5 (3 – 8)	6 (3 – 15)	0.001
ICU mortality[a], *n (%)*	47 (11)	25 (13)	22 (10)	0.28	18 (7)	29 (18)	0.0008
Hospital discharge							
Hospital LOS, days, *median (IQR)*	8 (4 – 19)	7 (4–15)	8 (4–21)	0.43	7 (4–13)	12 (4 – 35)	<0.001
Hospital mortality[b], *n (%)*	77 (20)	34 (19)	43 (20)	0.90	33 (14)	44 (29)	0.0002
90-day mortality[c], n (%)	95 (41)	46(45)	49(38)	0.28	45 (32)	50 (54)	0.004
90-day assessment in surviving patients (n=136)							
SF-36 Physical health[d], *median (IQR)*	42 (39 – 48)	42 (40 – 48)	42 (39 – 48)	0.81	42 (39 – 48)	42 (40 – 47)	0.82
SF-36 Mental health[e], *median (IQR)*	47 (44 – 52)	49 (45 – 52)	47 (44 – 51)	0.44	47 (43 – 51)	47 (46 – 52)	0.61
HADS anxiety[f], day-90, *n (%)*	3 (2 – 8)	3 (1 – 7)	4 (2 – 8)	0.39	3 (1 – 7)	4 (2 – 8)	0.60
HADS depression[g], day-90, *n (%)*	4 (1 – 7)	5 (1 – 8)	4 (1 – 7)	0.97	4 (1 – 7)	4 (1 – 7)	0.93
IES – R[h], day 90, *n(%)*	3 (0 – 8)	3 (0 –10)	2 (0 – 7)	0.80	3 (0 – 9)	2 (0 – 7)	0.75

ICU, intensive care unit; NIV, noninvasive ventilation; LOS, length of stay; SF-36, 36-item short form, a questionnaire that assesses health-related quality of life by means of 36 short questions; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Event Scale revised, a questionnaire that assesses PTSD-related symptoms; IQR, interquartile range.

[a]Data available for 416 cases, [b]Data available for 390 cases, [c]Data available for 231 cases, [d]Data available for 99 cases, [e]Data available for 103 cases, [f]Data available for 104 cases, [g]Data available for 101 cases, [h]Data available for 101 cases.

Table 5. Factors associated with in-hospital mortality (n=390)

	Survivors (n=313)	Non-survivors (n=77)	P value	Adjusted OR (95% CI) Final Multivariate selected model*	P value
Patient characteristics					
Age, *years, median (IQR)*	69 (59 – 78)	73 (61 – 80)	0.14		
Male gender, *n (%)*	191 (61)	54 (70)	0.15		
Chronic respiratory disease, *n (%)*	208 (66)	35 (45)	0.001		
Chronic cardiac disease, *n (%)*	64 (20)	17 (22)	0.76		
Immunosuppression, *n (%)*	69 (22)	33 (43)	0.0004		
Home oxygen therapy, *n (%)*	71 (23)	12 (16)	0.21		
Cause of ARF			<0.001		
Acute-on-chronic, *n (%)*	201 (64)	31 (40)			
Acute cardiogenic pulmonary edema, *n (%)*	39 (12)	14 (18)			
De novo ARF, *n (%)*	72 (23)	32 (42)			
SAPSII, *median (IQR)*	33 (27 – 42)	46 (36 – 58)	<0.0001		
SOFA, *median (IQR)*	3 (2 – 4)	6 (3 – 9)	<0.0001	1.25 (1.15 – 1.36)	<0.001
On ICU admission, prior to NIV					
Moderate-to-severe dyspnea, *n (%)*	172 (55)	43 (56)	0.90		
Respiratory rate, *min^{-1}, median (IQR)*	31 (27 – 36)	32 (28 – 38)	0.26		
Blood gases					
PaO_2/FiO_2, *mmHg, median (IQR)*	228 (174– 295)	175 (120 – 248)	0.0003		
$PaCO_2$, *mmHg, median (IQR)*	58 (42 – 73)	44 (35 – 59)	<0.0001	0.98 (0.97 – 1)	0.014
After the first NIV session					
Moderate-to-severe dyspnea, *n (%)*	106 (34)	44 (57)	0.0002	2.11 (1.21 – 3.69)	0.009
Blood gases					
PaO_2/FiO_2, *mmHg, median (IQR)*	213 (174 – 254)	178 (137 – 236)	0.084		
$PaCO_2$, *mmHg, median (IQR)*	57 (45 – 68)	46 (39 – 56)	0.0007		

ARF, acute respiratory failure; SAPS 2, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment score; NIV, noninvasive ventilation; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction; IQR, interquartile range.

The following variables were included in the initial complete model: age, gender, cause of acute respiratory failure, SOFA, $PaCO_2$ on ICU admission prior to NIV, dyspnea after the first NIV session. Goodness-of-fit (Hosmer-Lemeshow): p=0.59

Figure Legend

Figure 1. Study flow chart

MV, mechanical ventilation; NIV, noninvasive ventilation.