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Non-invasive ventilation of patients with ARDS: Insights from the LUNG SAFE Study

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At a Glance Commentary

Scientific Knowledge on the Subject: Non-invasive ventilation (NIV) is used to treat patients with Acute Respiratory Distress Syndrome (ARDS). Current worldwide practice in the use of this technique, its implications for patients' management, and association with outcome are poorly understood. The Berlin definition of ARDS is unclear in regard to the severity classification of patients with NIV.

What This Study Adds to the Field: NIV is used in about 15% patients with ARDS, irrespective of the severity of hypoxemia. Classification of ARDS severity in NIV patients based on PaO_2/FiO_2 ratio had management and prognostic significance. Use of NIV, in comparison with invasive ventilation has important implications for patients' management. While mortality rate was low in patients successfully managed with NIV, patients who failed NIV had a high mortality. NIV may be

associated with a worse ICU outcome than invasive mechanical ventilation in moderate to severe ARDS.

This article has an online data supplement, which is accessible from this issue's table of content online at http://www.atsjournals.org

Author Contributions

Conception and Design: GB, JGL, TP, EF, LB, AE, LG, FV, AL, DFM, MR, GDR, BTT, HW, ASS, AP

Analysis and Interpretation: GB, JGL, TP, FM, EF, LB, MR, GDR, AS, BTT, AP

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Abstract

Background: Non-invasive ventilation (NIV) is increasingly used in patients with Acute Respiratory Distress Syndrome (ARDS). Whether, during NIV, the categorization of ARDS severity based on the PaO_2/FiO_2 Berlin criteria is useful is unknown. The evidence supporting NIV use in patients with ARDS remains relatively sparse.

Methods: The Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study described the management of patients with ARDS. This sub-study examines the current practice of NIV use in ARDS, the utility of the PaO_2/FiO_2 ratio in classifying patients receiving NIV and the impact of NIV on outcome.

Results: Of 2,813 patients with ARDS, 436 (15.5%) were managed with NIV on days 1 and 2, with a similar proportion in each severity category. Classification of ARDS severity based on PaO_2/FiO_2 ratio was associated with an increase in intensity of ventilatory support, NIV failure, and ICU mortality. NIV failure occurred in 37.5% of patients (22.2% in mild, 42.3% in moderate and 47.1% in severe ARDS). Hospital mortality in patients with NIV success and failure was 16.1 % and 45.4%, respectively. NIV use was independently associated with increased ICU (HR 1.446; [1.159-1.805]), but not hospital mortality. In a propensity matched analysis, ICU mortality was higher in NIV than invasively ventilated patients with a PaO_2/FiO_2 lower than 150 mmHg.

Conclusions: NIV was used in 15% of patients with ARDS, irrespective of severity category. NIV appears to be associated with higher ICU mortality in patients with a PaO_2/FiO_2 lower than 150 mmHg.

Trial Registration: ClinicalTrials.gov NCT02010073

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Introduction

Non-invasive ventilation (NIV) has become an established approach in the management of patients with acute respiratory failure, with strong evidence for its benefits in patients with acute exacerbations of chronic obstructive pulmonary disease (1-3) and cardiogenic pulmonary edema (4). NIV is not uncommonly used in the management of patients with Acute Respiratory Distress Syndrome (ARDS) {Antonelli, 2007 #5;Walkey, 2013 #49}, as evidenced by its formal recognition in the Berlin criteria for ARDS introduced in 2012 (6).

Potential advantages of NIV in the management of patients with ARDS are mainly related to the avoidance of complications linked to sedation, muscle paralysis, and ventilator-associated complications associated with endotracheal intubation and invasive mechanical ventilation (MV) (7). Initially, the use of NIV in patients with ARDS focused on immunocompromised patients such as those with hematologic malignancies (8-12). However, NIV has been used in a broader selection of ARDS patients (13). Of concern, the evidence supporting NIV use in patients with ARDS is based on relatively small samples (5, 14). Moreover, in most studies, patients treated with NIV were compared to patients treated with oxygen administration (15) or to historical cohorts (16).

A number of concerns exist regarding the use of NIV in patients with ARDS. The subgroup of ARDS most likely to benefit from NIV remains unclear. While some literature suggests that NIV may best be reserved for patients with mild ARDS (i.e. patients with a PaO_2/FiO_2 ratio of 200-300 mmHg) (5, 14, 17, 18), it is not always the case in practice (19). While some factors leading to NIV failure in patients with ARDS are better understood, relatively few patients have been studied to date (20, 21). The impact of NIV on outcome in ARDS is therefore not well understood. In particular, concerns have been raised regarding the impact of prolonged NIV in the absence of respiratory status improvement, potentially delaying tracheal intubation and invasive MV (19, 20, 22, 23). Finally, the recent Berlin definition of ARDS does not specify whether all patients with

ARDS managed with NIV should be classified as all having 'mild' ARDS or whether the PaO_2/FiO_2 ratio severity stratification is more appropriate (24).

For these reasons, a key pre-specified secondary aim of the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) (25) study was to describe the current practice of the use of NIV in ARDS and to determine its impact on patients' management, the incidence of and risk factors leading to NIV failure and the relationship between NIV and patient outcome.

The primary objective was to determine the proportion of ARDS patients managed with NIV on days 1 and 2. This period was chosen to avoid classifying patients as treated with NIV if this treatment was applied only for a very short period of time. Secondary objectives included: the utility of the PaO_2/FiO_2 ratio severity categories in the classification of NIV patients; characteristics of patients managed with NIV; ventilatory settings used in these patients; factors associated with NIV failure; and the association between NIV use and mortality in patients with ARDS.

METHODS (word count=535)

LUNG SAFE was a prospective, observational, international multi-centre cohort study. Detailed methods have been published elsewhere (25), and are also available in the online data supplement.

Patients, Study Design and Data Collection

Patients receiving were enrolled in the participating ICUs for four consecutive weeks. Exclusion criteria were: age<16 years or inability to obtain informed consent. Following enrollment, patients were evaluated daily for Acute Hypoxemic Respiratory Failure (AHRF), defined as: (1) $PaO_2/FiO_2 \leq 300$ mmHg while on invasive MV or NIV with end expiratory pressure ≥ 5 cmH_2O (2) new radiological pulmonary parenchymal abnormalities. For patients fulfilling AHRF criteria a

more detailed set of data was recorded, to determine whether the patient fulfilled the Berlin criteria for ARDS.

Data on arterial blood gases, type of ventilatory support/settings and Sequential Organ Failure Assessment (SOFA) score were collected on selected days during the ICU stay. Data were collected once per day, as close as possible to 10 AM. Data on ventilatory settings were recorded simultaneously with arterial blood gas analysis. Decisions to withhold or withdraw life sustaining treatments and their timing were recorded. ICU and hospital survival were collected at the time of discharge, censored at 90 days after enrollment.

We assessed clinician recognition of ARDS at two time points: on day 1 of study entry, and when patients exited the study. ARDS was deemed to have been clinician-recognized if either question was answered positively.

NIV Patient Cohort

We restricted analyses to the subset of patients (93%) fulfilling ARDS criteria on day 1 or 2 from onset of AHRF. Patients were classified as "NIV patients" if they received NIV on day 1 and 2 of ARDS. Patients were classified as "invasive-MV patients" if they received invasive-MV on day 1 and/or day 2 of ARDS (Table E1 in the online data supplement).

"NIV" definition encompassed all forms of patient interface and ventilatory modes. High flow oxygen therapy was not included. Since data were collected once per day and the duration of NIV session was not recorded, patients (n=81) switched from NIV to invasive-MV during the first 24 hours (i.e. before the day 2 data collection) were classified in the invasive-MV group as we considered that, in these patients, the NIV session may have been too short to be meaningful.

"NIV failure" was defined as the need to switch to invasive-MV after the first 24 hours (i.e. after the day 2 data collection). We limited the comparison of NIV "success" and "failure" groups to patients without treatment limitation (whose definition encompassed all forms of treatment

limitations, without further specification) unless this occurred after institution of invasive-MV (see also statistical analysis).

Statistical Analysis

For continuous variables, we reported median with interquartile range (IQR) or mean with standard deviation (SD), and for categorical variables we reported proportions. Student's t, ANOVA, Wilcoxon rank sum, Kruskal–Wallis, Chi-Square or Fisher tests were used when appropriate.

Multivariate Cox proportional hazard models were applied to investigate the relationship between potential covariates and outcomes (ICU and hospital mortality, NIV failure). Propensity score matching method was used to evaluate the possible different treatment effects (invasive-MV and NIV) on survival (Table E2, in the online data supplement). Patients were matched (1:1 match without replacement), using a caliper of 0.2 SD of the logit of the propensity score. For all tests, a two-sided α of 0.05 was considered significant. The analyses were performed using SAS and R software.

RESULTS

Incidence of NIV use

A total of 459 ICUs enrolled patients in the study and 422 enrolled patients with ARDS. In the ICUs enrolling ARDS, 207 (49.1 %) used NIV, on days 1 and 2, in at least one patient. Of a total of 2,813 patients with ARDS within two days from AHRF onset, 436 (15.5%) were managed with NIV on days 1 and 2 (Figure 1).

CPAP was used in 28.2% of patients in the NIV group (Table 1), while the remaining patients were managed with pressure cycled modes.

Classification of NIV Patients

Also in patients managed with NIV, classification of ARDS severity in mild moderate and severe according to the PaO_2/FiO_2 bands proposed by the Berlin definition, was associated with a step-wise increase in PEEP and FiO_2 (Table 1). Greater ARDS severity category was associated with an increase in clinician recognition of ARDS, and a worsening in outcomes, including ICU length of stay, ICU mortality, and non-significant increase in hospital mortality (Table 2). Increasing ARDS severity category was associated with a significant increase in NIV failure in patients without pre-intubation treatment limitations (from 22.2% to 42.3% to 47.1%, p=0.008).

Of interest, the use of NIV did not vary significantly among mild (14.3%), moderate (17.3%) and severe (13.2 %) ARDS (Table 1).

Baseline characteristics of NIV patients

NIV patients, in comparison with invasive-MV patients, were older with lower non-pulmonary SOFA scores, both in the whole population (3 ± 3 vs 7 ± 4; p<0.001) and across the different severity categories (Table 1).

NIV patients had a higher prevalence of chronic renal failure, congestive heart failure and COPD than invasive-MV patients (Table 1). The prevalence of immunosuppression and/or malignancies did not differ between the two groups. Clinician recognition of ARDS was significantly lower in NIV patients compared to invasive-MV patients (Table 2). The use of NIV was independently associated with a lower recognition of ARDS by clinicians (odds ratio 0.585, confidence interval 95%: 0.45-0.76) (Table E3 in the online data supplement). There were no differences in treatment limitation rates in NIV versus invasive-MV patients.

Effect of NIV versus invasive MV on ventilation and gas exchange

NIV patients had significantly lower levels of PEEP, and higher respiratory rates than invasive-MV patients. In NIV patients, measured tidal volumes and minute ventilation were greater than in invasive-MV patients, and did not significantly change with greater ARDS severity (Table 1).

At ARDS onset, PaO_2/FiO_2 ratio was not different between the NIV and invasive-MV patients (Table 1). PaO_2/FiO_2 ratios improved more rapidly in the patients treated with invasive-MV (Figure 2B and E1). Baseline $PaCO_2$ did not differ between the NIV and invasive-MV patients. However, while baseline $PaCO_2$ in mild ARDS was higher in NIV compared to invasive-MV patients (48±18 vs 41±10 mmHg, p=0.002), $PaCO_2$ in severe ARDS was lower in NIV (43±14 vs 52±18 mmHg, p<0.001) compared to invasive-MV. In contrast to patients managed with invasive-MV, where $PaCO_2$ significantly increased with greater ARDS severity ($p < 0.001$), the $PaCO_2$ in the NIV group did not change ($p = 0.134$) with severity category (Table 1 and Figure 2).

NIV Failure versus Success

Among the 349 NIV patients without pre-intubation treatment limitations, 131 (37.5%) failed NIV (Table 3), after a mean of … ± … days. A multivariate Cox model revealed that higher non-pulmonary SOFA score, lower PaO_2/FiO_2 and the percentage increase of $PaCO_2$ over the first two days of treatment were independently associated with NIV failure within 28 days from AHRF onset (Table E4 in the online data supplement).

Effect of Intubation on Physiological Variables

Table E5 in the online data supplement and figure 2C show the comparison, for physiological variables, between the last available recording of NIV and the first available recording during invasive-MV. After intubation, both PaO_2/FiO_2 (152±68 vs 182±95 mmHg, p<.001) and $PaCO_2$ significantly increased. After initiation of invasive-MV, patients were managed with a higher PEEP and had lower respiratory rates, received lower tidal and minute volumes, compared to pre-intubation values.

Outcomes in NIV patients

Crude ICU and hospital mortalities were not significantly different between the NIV and the invasive-MV patients (Table 2 and Figure E2 in the online data supplement).

Patients that failed NIV were more severely ill (Table 3) and had significantly worse ICU (42.7% vs 10.6%, p-value<0.001) and hospital mortality compared to those that were successfully managed with NIV (Table 3).

In a multivariate Cox regression model adjusting for covariates significantly associated with outcome (see Table E6 in the online data supplement, NIV use was independently associated with increased ICU (but not hospital) mortality rate (HR 1.446; [1.159-1.805]). Furthermore, we matched 353 NIV with invasive-MV patients using propensity score (Table E2 in the online data supplement). The two matched populations were homogeneous for demographic characteristics, comorbidities and severity of organ failures (Table E2 in the online data supplement). ICU and hospital mortality rates did not differ (Table 4). Kaplan-Meier survival estimates for invasive-MV and NIV patients of the matched samples were non significantly (p =0.093) different (Figure 3). In the subset of patients with a PaO_2/FiO_2 ratio<150, ICU mortality was 36.2 % with NIV compared to 24.7 % with invasive-MV (p =0.033) (Table 4). Figure 3 shows survival curves in NIV and invasive-MV groups for matched patients with a PaO_2/FiO_2 higher and lower than 150 mmHg.

Table E7 in the online data supplement, shows the comparison between survivors and non-survivors at hospital discharge, in NIV patients. Non-survivors were older, with a higher prevalence of immunosuppression or neoplastic disease and had a higher non-pulmonary SOFA score. Moreover, non-survivors had, on the day of ARDS diagnosis, a lower PaO_2/FiO_2 and higher respiratory rate than survivors. A multivariate Cox model performed on baseline characteristics in the NIV group showed that chronic heart failure, presence of hematologic or neoplastic disease, chronic liver failure, age, ARDS severity, percentage decrease of PaO_2/FiO_2 ratio between days 1 and 2, total respiratory rate and non-pulmonary SOFA score were each independently associated with risk of in-hospital death (Table E8).

DISCUSSION

Of the 2,813 patients that were diagnosed with ARDS criteria within two days of developing AHRF enrolled into the LUNG SAFE study, 436 (15.5%) were managed with NIV on days 1 and 2. NIV patients were older and had more comorbidities, but had lower non-pulmonary SOFA scores compared to invasive-MV patients. NIV failure occurred in 134 (30.7%) patients, necessitating change to invasive-MV. Classification of ARDS severity based on PaO_2/FiO_2 ratio categories was indicative of a higher intensity of treatment and worse outcome, as is seen in ARDS patients managed with invasive-MV. Of interest, NIV applications rates were similar across the ARDS severity categories. While crude mortality was not different, after adjustment for covariates NIV was associated with increased ICU (but not hospital mortality). This finding appeared confined, in the propensity matched analysis, to the more severe patients, i.e. those with a PF ratio < 150 mHg.

The finding that NIV use was similar across the ARDS severity categories was surprising given the fact that recommendations for NIV use in ARDS suggest that its use be confined to mild ARDS (18). While success rates of NIV in mild ARDS were 78%, this decreased to 58% in moderate and 53% in severe ARDS, consistent with previous findings (23). Although NIV has been shown to be beneficial in the subgroup of patients with immunosuppression/neoplastic diseases (8-12), the presence of these diseases were not associated with a greater use of NIV in our patients. NIV use appeared associated with other factors, such as pre-existing COPD, congestive heart failure and chronic renal failure.

While the Berlin definition clearly acknowledges that ARDS diagnosis can be fulfilled by patients undergoing NIV, the definition is less clear concerning how ARDS severity should be determined in these patients. While some authors used the PaO_2/FiO_2 severity bands also for NIV patients (26), others considered that NIV patients with PaO2/FiO2 <200 mmHg could not be classified according to Berlin definition and these patients were excluded from analysis (24). Our results support the use

of PaO_2/FiO_2 bands to classify NIV patients in mild, moderate and severe: worsening ARDS categories were associated with more prolonged and aggressive ventilator support, and worse patient outcomes.

The use of NIV was associated with important differences in the clinical management of patients with ARDS, which might be, in part, explained by the low recognition of ARDS in these patients. NIV patients received lower levels of PEEP (with a median value of 7 cmH_2O) in all the ARDS categories and a predominant use of FiO_2 to correct hypoxemia. This finding is clinically relevant, since application of higher levels of PEEP has been associated with improved outcomes in patients with moderate to severe ARDS (27). While the use of lower PEEP may be seen as "inherent" to the use of NIV, due to constraints in increasing airway pressure, our results also highlight the effects of the lack of control over respiratory drive. Minute ventilation was higher in NIV patients as a result of higher respiratory rate and tidal volumes. Tidal volumes were also higher than the 6-8 ml/kg of ideal body weight recommended for lung protective ventilation. This data should be interpreted cautiously, since it was measured only in a subset of NIV patients and limitations exist regarding the accuracy of measurement of tidal volume during NIV. In NIV patients, minute ventilation increased with greater ARDS severity during NIV with no significant difference in $PaCO_2$, suggesting that the increased patient respiratory drive compensated for the increased dead space. In patients failing NIV, institution of invasive-MV was associated with increased PEEP, decreased oxygen fraction, and improved PaO_2/FiO_2 ratios, as well as decreases in tidal volume and respiratory rate leading to a ≈30% drop of minute ventilation, resulting in an increased $PaCO_2$. Ventilator settings in patients transitioned to invasive-MV were closer to 'protective' settings than those seen prior to NIV failure, suggesting that institution of invasive-MV (which might have required increased sedation) facilitated better control of tidal volume and airway pressures, possibly decreasing the risk of lung injury.

NIV failure was associated with a substantial increase in the risk of death, with mortality higher than for severe ARDS managed with invasive-MV. While this finding may reflect the fact that these patients were sicker at commencement of NIV, and worsened over time, it underlines the need for careful patient selection when considering NIV use in ARDS. Factors independently associated with NIV failure included higher non-pulmonary SOFA score and higher respiratory rate. Evaluating the patient's response to NIV is also important, with the percentage increase of $PaCO_2$ over the first two days of treatment also associated with NIV failure. A decline of PaO_2/FiO_2 ratio between day 1 and 2 of treatment was independently associated with an increased mortality in NIV patients. These parameters could be used to stratify patients when deciding to treat patients with NIV or in deciding to terminate NIV and proceed to invasive-MV.

Of concern is the finding that NIV use appears to be associated with increased ICU mortality. After adjusting for potential confounders, a patient treated with NIV at ARDS onset appeared to have a 30% increased risk of dying in ICU compared to a similar patient treated with invasive-MV. This result should be interpreted cautiously, since it was not confirmed for the hospital mortality and is partly discrepant with the propensity matched analysis (affected by a lower power due to the smaller number of patients included). Finally, while the model did not highlight any effect of the interaction between NIV and PaO_2/FiO_2 ratio on mortality, in the propensity matched cohort, the ICU mortality was significantly higher for NIV than for invasive-MV in the cohort of patients with PaO_2/FiO_2 <150 mmHg. In this respect our data are consistent with previous reports showing an increase in NIV failure rates, in patients with a PaO_2/FiO_2 ratio $\leq$ 150 mmHg (28).

The LUNG SAFE study represents one of the largest prospective datasets of ARDS patients treated with NIV. Nonetheless, it does have limitations. To limit the burden on investigators, data were collected as often as once/day and we did not collect hours of duration of NIV treatment, a factor previously thought to be important in NIV success/failure (29). For this reason, we conservatively

considered “NIV patients” as only those undergoing this treatment on days 1 and 2. Patients treated with NIV for a shorter period and subsequently intubated were considered in the invasive MV group. This was done for consistency with our previous work and to avoid considering as “NIV patients” those receiving only a short NIV trial, or who entered the ICU under NIV, and were subsequently intubated quickly. Clearly, a drawback of this approach is the potential underestimation of NIV failure rate. We did not include patients undergoing high flow oxygen, as these patients did not fulfill the Berlin criteria for ARDS (30, 31). We did not collect data on the type of interface used for NIV, which may be a potentially important determinant of NIV success (32). Moreover we did not collect patients’ severity scores, such as APACHE and SAPS, but relied on the SOFA score to characterize the non –pulmonary severity of illness severity. Finally, although we collected data regarding the presence of treatment limitation decisions, we cannot completely exclude the possibility that clinicians may have been reluctant to use invasive-MV in patients at higher risk of dying due to pre-existing medical conditions (as suggested, for example, by older age of the NIV patients).

In conclusion, in a large cohort of ARDS patients, NIV was used in 15% of cases, and was used to a similar extent across the severity categories. Use of NIV was independently associated with an under-recognition of ARDS by clinicians. NIV failure occurred in more than one-third of ARDS patients and in almost half of patients with moderate and severe ARDS. Mortality rates in patients that failed NIV were high. Of concern, NIV was associated with a worse adjusted ICU mortality than invasive-MV in patients in patients with a PaO_2/FiO_2 lower than 150 mmHg. These findings raise further concerns regarding NIV use in this patient group.

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A complete list of LUNG SAFE national coordinators, site investigators and national societies endorsing the study can be found in the On Line supplement

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Figure legends:

Figure 1: Flowchart of the study population

* Treatment limitation before AHRF onset or within 28 day; † Failure of non-invasively ventilation was evaluated within 28 days from AHRF onset; ‡ We reported vital status at hospital discharge censored at day 90 after AHRF onset. Vital status was unknown for 9 patients: 8 invasively ventilated and 1 non-invasively ventilated within 48 hours from AHRF onset.

Figure 2: Differences in physiological variables for patients treated with invasive and non-invasive ventilation. Panel A: While for mild ARDS $PaCO_2$ was significantly higher in patients managed with non-invasive ventilation, the opposite was true for severe ARDS, where $PaCO_2$ was lower in patients treated with non-invasive ventilation. * p-value < 0.05, comparison between Invasive-MV and NIV group. Panel B: While PaO_2/FiO_2 was not different over the first two days in patients managed with non-invasive and invasive ventilation, this improved more rapidly in the patients managed with invasive ventilation (for NIV n=422, 421, 382, 293, 228, 149, 94, 50, 18, from day 1 to 28). * p-value < 0.05, comparison between Invasive-MV and NIV group. Panel C: relative differences (increase of decrease) of selected physiological variables between the last day of non-invasive ventilation and the first day of invasive ventilation, in the subset of patients with non-invasive ventilation failure. † p-value < 0.05, no change in the variable.

Figure 3: Kaplan-Meier survival curves in the propensity score matched samples of patients managed with non-invasive and invasive ventilation. Panels A, B, C report respectively the survival over time in the entire sample (N=706), in matched sample with PaO_2/FiO_2 ratio < 150 mmHg (N=184) and in matched sample for PaO_2/FiO_2 ratio ≥ 150 mmHg (N=194). Note: vital status was evaluated at hospital discharge. Patients were censored on day 28 from AHRF onset. Patients discharged alive from hospital before the day 28 from AHRF onset were considered alive at day 28.

Table 1. Demographic and clinic characteristics of study population (stratified by ARDS severity and ventilation) at baseline (ARDS onset).

	ARDS – Mild		ARDS – Moderate		ARDS - Severe		ARDS		*p-value within NIV*	*p-value within invasive-MV*
	NIV	**Invasive -MV**	**NIV**	**Invasive -MV**	**NIV**	**Invasive -MV**	**NIV**	**Invasive -MV**		
N	119	714	232	1,106	85	557	436	2,377	-	-
% within ARDS severity	14.3	85.7	17.3	82.7	13.2	86.8	15.50	84.50	-	-
Male, n (%)	58 (48.7)	439 (61.5)*	150 (64.7)	683 (61.8)	49 (57.6)	350 (62.8)	257 (58.9)	1,472 (61.9)	*0.016*	*0.875*
Age (years), median [IQR]	71 [59 - 77]	64 [51 - 75]*	68 [56 - 79]	64 [52 - 74]*	64 [49 - 76]	58 [44 - 70]*	68 [54 - 78]	63[50 - 73]*	*0.110*	*<.001*
Risk factors for ARDS, n (%)									*0.4775*	*<.0001*
None	19 (16.0)	69 (9.7)*	30 (12.9)	85 (7.7)*	13 (15.3)	36 (6.5)*	62 (14.2)	190 (8.0)*		
Non-pulmonary	15 (12.6)	180 (25.2)*	28 (12.1)	219 (19.8)*	5 (5.9)	81 (14.5)*	48 (11.0)	480 (20.2)*		
Pulmonary	85 (71.4)	465 (65.1)	174 (75.0)	802 (72.5)	67 (78.8)	440 (79.0)	326 (74.8)	1,707 (71.8)		
Comorbities, n (%)										
Diabetes	28 (23.5)	153 (21.4)	52 (22.4)	253 (22.9)	18 (21.2)	109 (19.6)	98 (22.5)	515 (21.7)	*0.924*	*0.298*
Chronic renal failure	19 (16.0)	77 (10.8)	31 (13.4)	111 (10.0)	12 (14.1)	36 (6.5)*	62 (14.2)	224 (9.4)*	*0.803*	*0.021*
Heart failure	22 (18.5)	74 (10.4)*	34 (14.7)	105 (9.5)*	10 (11.8)	45 (8.1)	66 (15.1)	224 (9.4)*	*0.400*	*0.382*
Chronic liver failure	4 (3.4)	31 (4.3)	2 (0.9)	45 (4.1)*	3 (3.5)	27 (4.8)	9 (2.1)	103 (4.3)*	*0.109*	*0.763*
Neoplasm or immunosuppression	20 (16.8)	147 (20.6)	62 (26.7)	209 (18.9)*	17 (20.0)	129 (23.2)	99 (22.7)	485 (20.4)	*0.089*	*0.125*
COPD	46 (38.7)	132 (18.5)*	70 (30.2)	239 (21.6)*	19 (22.4)	101 (18.1)	135 (31.0)	472 (19.9)*	*0.043*	*0.134*
Home ventilation	8 (6.7)	13 (1.8)*	10 (4.3)	20 (1.8)*	3 (3.5)	5 (0.9)	21 (4.8)	38 (1.6)*	*0.502*	*0.321*
Parameters at day of ARDS onset, mean ± SD										
PaO_2 (mmHg)	109.4 ± 42.1	118.2 ± 46.6	80.7 ± 21.7	90.7 ± 28.3*	67.7 ± 14.0	66.3 ± 15.2	86.0 ± 31.6	93.2 ± 37.9*	*<.001*	*<.001*
FiO_2	0.45 ± 0.18	0.48 ± 0.19*	0.57 ± 0.16	0.62 ± 0.19*	0.88 ± 0.13	0.90 ± 0.15*	0.60 ± 0.22	0.65 ± 0.24*	*<.001*	*<.001*
PaO_2/FiO_2 (mmHg)	243 ± 29	246 ± 28	146 ± 29	149 ± 28	79 ± 17	75 ± 17	160 ± 63	161 ± 68	*<.001*	*<.001*
pH	7.37 ± 0.09	7.36 ± 0.10	7.37 ± 0.10	7.33 ± 0.12*	7.41 ± 0.09	7.27 ± 0.14*	7.38 ± 0.10	7.33 ± 0.12*	*0.007*	*<.001*
$PaCO_2$ (mmHg)	48 ± 18	41 ± 10*	47 ± 18	46 ± 15	43 ± 14	52 ± 18*	46 ± 17	46 ± 15	*0.134*	*<.001*
Base Excess (mmol/L)	1.49 ± 7.50	-1.93 ± 6.23*	0.42 ± 6.53	-2.23 ± 6.85*	1.18 ± 5.99	-2.74 ± 8.11*	0.86 ± 6.72	-2.26 ± 6.99*	*0.181*	*0.009*
PEEP (cmH_2O)	7 ± 2	7 ± 3	7 ± 2	8 ± 3*	7 ± 2	10 ± 4*	7 ± 2	8 ± 3*	*0.042*	*<.001*
Total Respiratory rate (breaths/min)	24 ± 7	19 ± 6*	27 ± 7	21 ± 6*	27 ± 6	23 ± 14*	26 ± 7	21 ± 9*	*<0.001*	*<.001*
Minute ventilation (L/min)	12.19 ± 5.24	9.13 ± 2.93*	13.63 ± 5.74	9.50 ± 3.10*	13.29 ± 4.90	9.91 ±3.15*	13.18 ± 5.47	9.49 ± 3.07*	*0.057*	*<.001*
Tidal Volume (ml/kg PBW)	8.73 ± 2.85	7.76 ± 1.77*	8.37 ± 2.84	7.60 ± 1.92*	7.98 ± 2.62	7.46 ± 1.93*	8.39 ± 2.81	7.61 ± 1.88*	*0.348*	*0.007*
Non-pulmonary SOFA score adj.	3 ± 3	7 ± 4*	3 ± 3	7 ± 4*	3 ± 3	7 ± 4*	3 ± 3	7 ± 4*	*0.548*	*0.370*

Use of vasopressors, n (%)	16 (14.4)	342 (51.8)*	37 (17.6)	575 (55.2)*	9 (11.8)	325 (61.2)*	62 (15.6)	1,242 (55.6)*	*0.453*	*0.005*
Use of CPAP, n (%)	35 (29.4)	-	65 (28.0)	-	23 (27.0)	-	123 (28.2)	-	*0.930*	-

Abbreviations: IQR: interquartile range; MV: mechanical ventilation; NIV: Non-invasive ventilation; SD: standard deviation; COPD: Chronic Obstructive Pulmonary Disease; PBW: *predicted body weight; PEEP: Positive end-expiratory pressure; SOFA: Sequential Organ Failure Assessment; CPAP: continuous positive airway pressure.*

** p-value < 0.05, comparison vs NIV group with same ARDS severity.*

Table 2. Events occurred during follow-up in study population (stratified by ARDS severity and ventilation).

	ARDS - Mild		ARDS – Moderate		ARDS - Severe		ARDS		*p-value*	*p-value*
	NIV	**Invasive-MV**	**NIV**	**Invasive-MV**	**NIV**	**Invasive-MV**	**NIV**	**Invasive-MV**	*within NIV*	*within invasive-MV*
N	119	714	232	1.106	85	557	436	2.377	-	-
Clinical recognition of ARDS, n (%)										
At study entry										
At any time	41 (34.5)	366 (51.3)*	122 (52.3)	722 (65.3)*	47 (55.3)	437 (78.5)*	210 (48.2)	1,525 (64.2)*	*0.002*	*<.001*
Patients with treatment limitation, n (%)	27 (22.7)	171 (23.9)	68 (29.3)	272 (24.6)	29 (34.1)	135 (24.2)	124 (28.4)	578 (24.3)	*0.186*	*0.951*
Length of stay (from ARDS onset) in ICU (days), median [IQR]										
all patients	6 [3 -10]	8 [4 - 16]*	8 [4 - 13.5]	10 [5 - 19]*	7 [4 - 12]	10 [4 - 18]*	7 [4 - 12]	9 [5 - 18]*	*0.032*	*0.019*
alive patients at ICU discharge	5 [3 -8]	9 [5 - 18]*	8 [4 - 13]	11 [6 - 20]*	7 [4 - 13]	13 [7 - 23]*	7 [4 -12]	11 [6 - 20]*	*0.002*	*<.001*
ICU mortality, n (%)	26 (21.8)	191 (26.8)	64 (27.8)	351 (31.7)	34 (40.0)	221 (39.7)	124 (28.4)	763 (32.1)	*0.017*	*<.001*
Hospital mortality, n (%)	36 (30.3)	249 (34.9)	83 (35.8)	446 (40.3)	37 (43.5)	257 (46.4)	156 (35.8)	952 (40.1)	*0.130*	*<.001*

Abbreviations: ARDS: Acute respiratory Distress Syndrome; MV: mechanical ventilation; NIV: Non-invasive ventilation; IQR: interquartile range; ICU: Intensive Care Unit;

** p-value < 0.05, comparison vs NIV group with same ARDS severity.*

Note: vital status was evaluated at ICU / hospital discharge. Patients who were still in ICU / hospital were censored on day 90 from AHRF onset.

Table 3. Demographic and clinical characteristics of ARDS NIV patients at baseline (ARDS onset). Population was stratified according the NIV treatment outcome (success-failure) occurred in ICU during 28 days from AHRF onset.

	ARDS - NIV (without treatment limitations)		*p-value*
	Success	**Failure***	
Patients, n (%)			*0.001*
All	218 (62.5)	131 (37.5)	
Mild ARDS	77 (77.8)	22 (22.2)	
Moderate ARDS	105 (57.7)	77 (42.3)	
Severe ARDS	36 (52.9)	32 (47.1)	
Male, n (%)	129 (59.2)	80 (61.1)	*0.727*
Age, median [IQR]	66.5 [52 - 78]	63.0 [53 - 74]	*0.081*
ICU mortality, n (%)	23 (10.6)	56 (42.7)	*<.001*
Hospital mortality, n (%)	35 (16.1)	59 (45.4)	*<.001*
Clinical recognition of ARDS, n (%)			
At study entry			
At any time			
Risk factors for ARDS, n (%)			*0.2114*
None	33 (15.1)	12 (9.2)	
Non-pulmonary	27 (12.4)	14 (10.7)	
Pulmonary	158 (72.5)	105 (80.1)	
Comorbidities, n (%)			
Diabetes	56 (25.7)	21 (16.0)	*0.035*
Chronic renal failure	36 (16.5)	11 (8.4)	*0.032*
Heart failure (NYHA III-IV)	28 (12.8)	18 (13.7)	*0.811*
Chronic liver failure	4 (1.8)	2 (1.5)	*1.000*
Active neoplasm or immunosuppression or hematologic neoplasm	42 (19.3)	34 (26.0)	*0.143*
COPD	74 (33.9)	33 (25.2)	*0.086*
Home ventilation	13 (6.0)	5 (3.8)	*0.380*
Parameters at day of ARDS onset, mean ± SD			
PaO_2 (mmHg)	88.6 ± 31.6	83.1 ± 30.5	*0.097*
FiO_2	0.58 ± 0.22	0.63 ± 0.21	*0.007*
PaO_2/FiO_2 ratio (mmHg)	171 ± 65	145 ± 60	*<.001*
pH	7.38 ± 0.09	7.38 ± 0.09	*0.967*
$PaCO_2$ (mmHg)	48 ± 17	44 ± 17	*0.009*
Base Excess (mmol/L)	1.91 ± 6.73	-0.02 ± 6.83	*0.002*
PEEP (cmH_2O)	7 ± 2	7 ± 2	*0.478*
Total Respiratory rate (breaths/min)	25 ± 6	27 ± 8	*0.012*
Minute ventilation (L/min)	12.71 ± 5.07	14.03 ± 6.25	*0.107*
Tidal Volume (ml/kg PBW)	8.38 ± 2.60	8.65 ± 3.11	*0.795*
Non-pulmonary SOFA score adjusted	2 ± 3	3 ± 3	*0.019*
Patients under pressors agents, n (%)	23 (11.7)	18 (15.1)	*0.376*
Use of CPAP, n (%)	59 (27.1)	35 (26.7)	*0.907*

Abbreviations: ARDS: Acute respiratory Distress Syndrome; NIV: Non-invasive ventilation; IQR: interquartile range; SD: standard deviation; COPD: Chronic Obstructive Pulmonary Disease; PBW: *predicted body weight; PEEP:*

Positive end-expiratory pressure; SOFA: Sequential Organ Failure Assessment; CPAP: continuous positive airway pressure.

Note 1: patients with pre-intubation treatment limitations were excluded from this analysis.

Note 2: vital status was evaluated at ICU / hospital discharge. Patients who were still in ICU / hospital were censored on day 90 from AHRF onset.

Table 4. Effect of treatment and clinical parameters at ARDS onset for invasive-MV and NIV patients in the propensity score matched sample.

	Invasive-MV patients (n=353)	**NIV patients (n=353)**	*p-value*
ARDS severity at onset, n (%)			
Mild	100 (28.33)	101 (28.61)	*1.000*
Moderate	184 (52.12)	165 (46.74)	*0.195*
Severe	69 (19.55)	87 (24.65)	*0.127*
Patients with PaO_2/FiO_2 ratio < 150 mmHg at ARDS onset, n (%)	174 (49.29)	174 (49.29)	*1.0000*
Parameters at ARDS onset, mean±SD			
pH	7.35 ± 0.11	7.38 ± 0.09	*0.001*
FiO_2	0.66 ± 0.24	0.60 ± 0.22	*0.001*
SPO_2 (%)	94.53 ± 5.51	94.99 ± 3.85	*0.660*
Total Respiratory Rate (breaths/min)	20.66 ± 6.46	25.63 ± 7.01	*<.001*
PEEP (cmH_2O)	8.09 ± 3.1	7.02 ± 1.95	*<.001*
Peak Inspiratory Pressure (cmH_2O)	26.77 ± 7.66	17.43 ± 7.22	*<.001*
PaO_2 (mmHg)	94.64 ± 40.32	87.96 ± 32.55	*0.031*
$PaCO_2$ (mmHg)	46.5 ± 14.41	45.8 ± 17.36	*0.320*
PaO_2/FiO_2 (mmHg)	157.62 ± 65.58	160.94 ± 64.29	*0.492*
Tidal Volume (ml/Kg PBW)	7.53 ± 1.75	8.46 ± 2.77	*0.001*
Minute ventilation (L/min)	9.31 ± 2.90	13.26 ± 5.60	*<.001*
Base excess (mmol/L)	-0.74 ± 5.93	0.60 ± 6.55	*0.002*
HCO_3 (mmol/L)	24.39 ± 5.65	25.4 ± 6.95	*0.086*
Non-pulmonary SOFA adjusted	3.26 ± 2.82	3.19 ± 2.84	*0.423*
Δ (%)* PaO_2/FiO_2 ratio	36.31 ± 76.76	28.17 ± 76.77	*0.063*
Δ (%)* $PaCO_2$	-0.3 ± 29.86	3.37 ± 25.92	*0.025*
Use of vaso pressors, n (%)	80 (24.32)	49 (15.03)	*0.005*
Duration of mechanical ventilation (days)			
all patients			
ICU survivors			
Length of ICU stay (days)			
all patients			
ICU survivors			
All-cause in-ICU mortality, n (%)			
all patients	92 (26.06)	99 (28.05)	*0.608*
matched patients with PaO_2/FiO_2 ratio<150 mmHg	43 (24.71)	63 (36.21)	*0.033*
All-cause in-hospital mortality, n (%)			
all patients	115 (32.76)	117 (33.24)	*0.871*
matched patients with PaO_2/FiO_2 ratio<150 mmHg	55 (31.61)	66 (38.15)	*0.224*

Abbreviations: ARDS: Acute respiratory Distress Syndrome; MV: mechanical ventilation; NIV: Non-invasive ventilation; IQR: interquartile range; SD: standard deviation; PBW: *predicted body weight; PEEP: Positive end-expiratory pressure; SOFA: Sequential Organ Failure Assessment.*

** Delta (Δ) was evaluated as difference between the value measured at the second day from ARDS onset and those measured at the ARDS onset day. Percentage was evaluated as rate between Δ and value measured at the ARDS onset day.*

Note 1: statistical tests accounted for the matched nature of the sample (paired t-test or Wilcoxon Signed Ranks test for continuous variables, McNemar's test for dichotomous variables).

Note 2: for 3 patients (2 Invasive-MV *and 1 NIV) vital status at hospital discharge were missing.*

Note 3: vital status was evaluated at ICU / hospital discharge. Patients who were still in ICU / hospital were censored on day 90 from AHRF onset.