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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

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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 following fulfillment of diagnostic criteria. Classification of ARDS severity based on PaO_2/FiO_2 ratio was associated with an increase in intensity of ventilatory support, NIV failure, and Intensive Care Unit (ICU) mortality. NIV failure occurred in 22.2% of mild, 42.3% of moderate and 47.1% of patients with 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.

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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) (5-7), as evidenced by its formal recognition in the Berlin criteria for ARDS introduced in 2012 (8).

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) (9). Initially, the use of NIV in patients with ARDS focused on immunocompromised patients such as those with hematologic malignancies (10-14). However, NIV has been used in a broader selection of ARDS patients (7). Of concern, the evidence supporting NIV use in patients with ARDS is based on relatively small samples (5, 15). Moreover, in most studies, patients treated with NIV were compared to patients treated with oxygen administration (16) or to historical cohorts (17).

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, 15, 18, 19), it is not always the case in practice (20). While some factors leading to NIV failure in patients with ARDS are better understood, relatively few patients have been studied to date (21, 22). 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 (20, 21, 23, 24). Finally, the recent Berlin definition of ARDS does not specify whether patients with ARDS

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managed with NIV should be all classified as having 'mild' ARDS or whether the PaO_2/FiO_2 ratio severity stratification is more appropriate (25).

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) (26) study was to describe the current practice of the use of NIV in ARDS. Our primary objective was to determine the proportion of patients managed with NIV on days 1 and 2 following fulfillment of diagnostic criteria for ARDS. Secondary objectives included determining: 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=559)

LUNG SAFE was a prospective, observational, international multi-centre cohort study. Detailed methods have been published elsewhere (26), and are also available in the online data supplement.

Patients, Study Design and Data Collection

Patients receiving invasive MV or NIV 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 simultaneously receiving invasive MV or NIV (depending on the patient group) 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 and Definitions

We restricted analyses to the subset of patients (93%) fulfilling ARDS criteria on day 1 or 2 following the onset of AHRF. Patients were classified as "NIV patients" if they received NIV on day 1 and 2 following fulfillment of ARDS criteria. In all "NIV patients", arterial blood gas measurements were taken while the patient was receiving NIV. 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 sessions was not recorded, patients that were switched from NIV to invasive-MV prior to the day 2 data collection (n=75) were classified in the invasive-MV group. 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 day 1 and 2 of NIV. We limited the comparison of NIV "success" and "failure" groups to patients without treatment limitation (whose definition encompassed all forms of treatment limitation) unless this occurred after institution of invasive-MV (see also statistical analysis).

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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 patients, 207 (49.1 %) used NIV on days 1 and 2 of ARDS, in at least one patient. Of the 2,813 patients that developed ARDS within two days of AHRF onset, 507 patients received NIV on Day 1 (18%). Of these, 436 (15.5%) were managed with NIV on days 1 and 2, and constitute the study population (Figure 1), while 75 patients were managed with NIV on day 1 and on invasive MV on day 2 (Table E3).

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

In ARDS patients managed with NIV, classification of severity into mild, moderate, and severe categories according to the PaO_2/FiO_2 bands in 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 with mild (14.3%), moderate (17.3%) and severe (13.2 %) ARDS severity category (Table 1).

Baseline characteristics of NIV patients

NIV patients were older and had lower non-pulmonary SOFA scores, both in the whole population and across the different severity categories, compared to invasive-MV patients (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 E4, online data supplement). ARDS recognition was increased in patients that failed NIV (Table 3). 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

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invasive-MV patients (Table 1). In contrast to patients managed with invasive-MV, tidal and minute ventilation did not change significantly 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 invasive-MV patients, where $PaCO_2$ increased, the $PaCO_2$ in the NIV group did not change (p = 0.134) with greater ARDS severity (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). A multivariate Cox model revealed that higher non-pulmonary SOFA score, lowerPaO_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 E5, online data supplement).

Effect of Intubation on Physiological Variables

Table E6 (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 (Table E7, 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, online data supplement). The two matched populations were homogeneous for demographic characteristics, comorbidities and severity of organ failures (Table E2). 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 not significantly 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 E8 (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

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respiratory rate and non-pulmonary SOFA score were each independently associated with risk of in-hospital death (Table E9).

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 of ARDS. 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 PaO_2/FiO_2 ratio < 150 mmHg.

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 restricted to mild ARDS (19). 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 (24). Although NIV has been shown to be beneficial in the subgroup of patients with immunosuppression/neoplastic diseases (10-14), 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 (27), others considered that NIV patients with PaO2/FiO2 <200 mmHg could not be classified according

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to Berlin definition and these patients were excluded from analysis (25). 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 fact that use of NIV was independently associated with an under-recognition of ARDS by clinicians both at study entry and any time. Interestingly, clinicians recognized ARDS much more frequently in patients that failed NIV, as shown by the very high rate of "delayed" recognition 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 (28). 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 ≤ 150 mmHg (29).

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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 (30). 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 to avoid considering as "NIV patients" those receiving only a short NIV trial, or who entered the ICU while receiving NIV, and were subsequently intubated quickly. In these patients, it seems likely that the impact of invasive MV would likely have the predominant effect on patient outcome. 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 (31, 32). We did not collect data on the type of interface used for NIV, which may be a potentially important determinant of NIV success (33). 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. 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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References

1. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 817-822.

2. Keenan SP, Sinuff T, Cook DJ, Hill NS. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med* 2003; 138: 861-870.

3. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003; 326: 185.

4. Masip J, Roque M, Sanchez B, Fernandez R, Subirana M, Exposito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JAMA* 2005; 294: 3124-3130.

5. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, Rocco M, Maviglia R, Pennisi MA, Gonzalez-Diaz G, Meduri GU. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med* 2007; 35: 18-25.

6. Walkey AJ, Wiener RS. Use of noninvasive ventilation in patients with acute respiratory failure, 2000-2009: a population-based study. *Annals of the American Thoracic Society* 2013; 10: 10-17.

7. Demoule A, Chevret S, Carlucci A, Kouatchet A, Jaber S, Meziani F, Schmidt M, Schnell D, Clergue C, Aboab J, Rabbat A, Eon B, Guerin C, Georges H, Zuber B, Dellamonica J, Das V, Cousson J, Perez D, Brochard L, Azoulay E. Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries. *Intensive care medicine* 2016; 42: 82-92.

8. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; 307: 2526-2533.

9. Rittayamai N, Brochard L. Recent advances in mechanical ventilation in patients with acute respiratory distress syndrome. *European respiratory review : an official journal of the European Respiratory Society* 2015; 24: 132-140.

10. Lemiale V, Resche-Rigon M, Mokart D, Pene F, Rabbat A, Kouatchet A, Vincent F, Bruneel F, Nyunga M, Lebert C, Perez P, Meert AP, Benoit D, Chevret S, Azoulay E. Acute respiratory failure in patients with hematological malignancies: outcomes according to initial ventilation strategy. A groupe de recherche respiratoire en reanimation onco-hematologique (Grrr-OH) study. *Ann Intensive Care* 2015; 5: 28.

11. Azoulay E, Mokart D, Pene F, Lambert J, Kouatchet A, Mayaux J, Vincent F, Nyunga M, Bruneel F, Laisne LM, Rabbat A, Lebert C, Perez P, Chaize M, Renault A, Meert AP, Benoit D, Hamidfar R, Jourdain M, Darmon M, Schlemmer B, Chevret S, Lemiale V. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en reanimation onco-hematologique study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; 31: 2810-2818.

12. Gristina GR, Antonelli M, Conti G, Ciarlone A, Rogante S, Rossi C, Bertolini G. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. *Crit Care Med* 2011; 39: 2232-2239.

13. Conti G, Marino P, Cogliati A, Dell'Utri D, Lappa A, Rosa G, Gasparetto A. Noninvasive ventilation for the treatment of acute respiratory failure in patients with hematologic malignancies: a pilot study. *Intensive care medicine* 1998; 24: 1283-1288.

AJRCCM Articles in Press. Published on 18-October-2016 as 10.1164/rccm.201606-1306OC

14. Depuydt PO, Benoit DD, Roosens CD, Offner FC, Noens LA, Decruyenaere JM. The impact of the initial ventilatory strategy on survival in hematological patients with acute hypoxemic respiratory failure. *J Crit Care* 2010; 25: 30-36.

15. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. *Crit Care* 2006; 10: R79.

16. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168: 1438-1444.

17. Wang S, Singh B, Tian L, Biehl M, Krastev IL, Kojicic M, Li G. Epidemiology of noninvasive mechanical ventilation in acute respiratory failure--a retrospective population-based study. *BMC Emerg Med* 2013; 13: 6.

18. Agarwal R, Aggarwal AN, Gupta D. Role of noninvasive ventilation in acute lung injury/acute respiratory distress syndrome: a proportion meta-analysis. *Respir Care* 2010; 55: 1653-1660.

19. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Esteban A, Gattinoni L, Rhodes A, Slutsky AS, Vincent JL, Rubenfeld GD, Thompson BT, Ranieri VM. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive care medicine* 2012; 38: 1573-1582.

20. Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, Calfee CS. Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016; 44: 120-129.

21. Chawla R, Mansuriya J, Modi N, Pandey A, Juneja D, Chawla A, Kansal S. Acute respiratory distress syndrome: Predictors of noninvasive ventilation failure and intensive care unit mortality in clinical practice. *J Crit Care* 2016; 31: 26-30.

22. Carteaux G, Millan-Guilarte T, De Prost N, Razazi K, Abid S, Thille AW, Schortgen F, Brochard L, Brun-Buisson C, Mekontso Dessap A. Failure of Noninvasive Ventilation for

De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume. *Crit Care Med* 2016; 44: 282-290.

23. Mosier JM, Sakles JC, Whitmore SP, Hypes CD, Hallett DK, Hawbaker KE, Snyder LS, Bloom JW. Failed noninvasive positive-pressure ventilation is associated with an increased risk of intubation-related complications. *Ann Intensive Care* 2015; 5: 4.

24. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, Pelaia P, Principi T, Gregoretti C, Beltrame F, Pennisi MA, Arcangeli A, Proietti R, Passariello M, Meduri GU. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive care medicine* 2001; 27: 1718-1728.

25. Hernu R, Wallet F, Thiolliere F, Martin O, Richard JC, Schmitt Z, Wallon G, Delannoy B, Rimmele T, Demaret C, Magnin C, Vallin H, Lepape A, Baboi L, Argaud L, Piriou V, Allaouchiche B, Aubrun F, Bastien O, Lehot JJ, Ayzac L, Guerin C. An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. *Intensive care medicine* 2013; 39: 2161-2170.

26. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016; 315: 788-800.

27. Zhao X, Huang W, Li J, Liu Y, Wan M, Xue G, Zhu S, Guo H, Xia Q, Tang W. Noninvasive Positive-Pressure Ventilation in Acute Respiratory Distress Syndrome in Patients With Acute Pancreatitis: A Retrospective Cohort Study. *Pancreas* 2016; 45: 58-63.

28. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt

AJRCCM Articles in Press. Published on 18-October-2016 as 10.1164/rccm.201606-1306OC

G. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *Jama* 2010; 303: 865-873.

29. Thille AW, Contou D, Fragnoli C, Cordoba-Izquierdo A, Boissier F, Brun-Buisson C. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. *Crit Care* 2013; 17: R269.
30. Principi T, Pantanetti S, Catani F, Elisei D, Gabbanelli V, Pelaia P, Leoni P. Noninvasive continuous positive airway pressure delivered by helmet in hematological malignancy patients with hypoxemic acute respiratory failure. *Intensive care medicine* 2004; 30: 147-150.
31. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. *Chest* 2015; 148: 253-261.
32. Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. *Respir Care* 2011; 56: 1151-1155.
33. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *Jama* 2016; 315: 2435-2441.

Figure legends:

Figure 1: Flowchart of the study population

* 75 patients received NIV on day 1 and invasive ventilation at day 2

† Limitation of care 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

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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)		
Comorbidities, 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*

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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	21 (17.6)	178 (24.9)	63 (27.2)	372 (33.6)	17 (20.0)	236 (42.4)*	101 (23.2)*	786 (33.1)	*0.101*	*<.001*
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.

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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 (%)			
All	23 (10.6)	56 (42.7)	*<.001*
Patients with PaO_2/FiO_2 ratio < 150 mmHg	13 (14.6)	36 (45.0)	*<.001*
Patients with PaO_2/FiO_2 ratio ≥ 150 mmHg	10 (7.8)	20 (39.2)	*<.001*
Hospital mortality, n (%)	35 (16.1)	59 (45.4)	*<.001*
Clinical recognition of ARDS, n (%)			
At study entry	43 (19.7)	42 (32.1)	*0.009*
At any time	73 (34.1)	88 (68.2)	*<.001*
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.

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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 vasopressors, n (%)	80 (24.32)	49 (15.03)	*0.005*
Duration of mechanical ventilation (days) , median [IQR]			
all patients	8 [4 - 15]	9 [5 - 13]	*0.293*
ICU survivors	7 [4 - 14]	10 [7 - 13]	*0.744*
Length of ICU stay (days), median [IQR]			
all patients	10 [6 - 18]	7 [4 - 12]	*<.001*
ICU survivors	10 [6 - 19]	7 [4 - 12]	*<.001*
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*

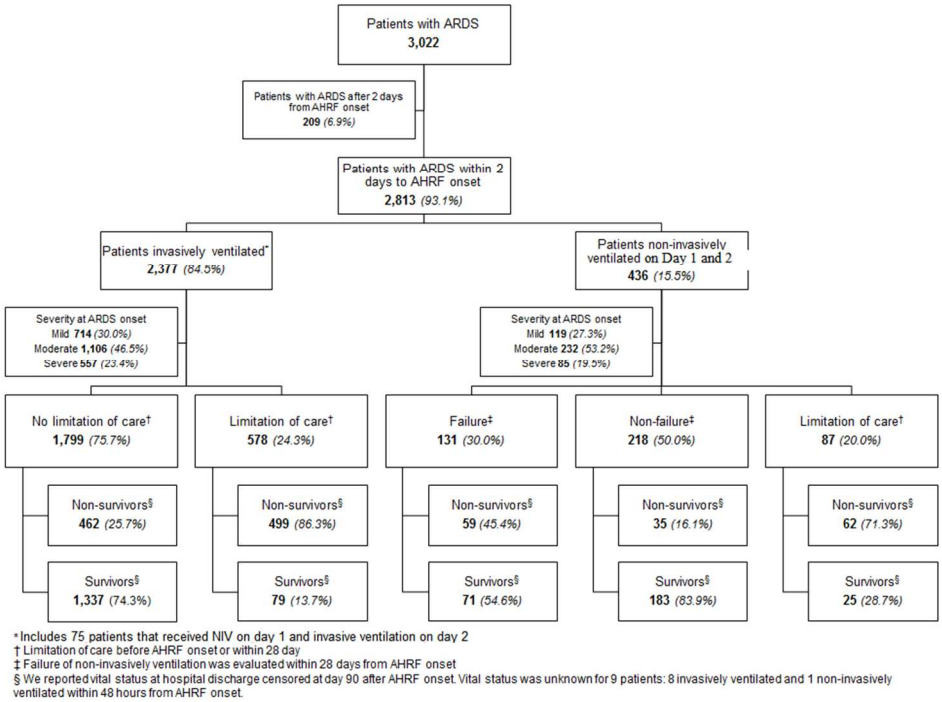
Abbreviations: ARDS: Acute respiratory Distress Syndrome; MV: mechanical ventilation; NIV: Non-invasive ventilation; IQR: interquartile range; SD: standard deviation; PBW: *predicted body weight; PEEP: Positive end-expiratory pressure; SOFA: Sequential Organ Failure Assessment.*

** 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.



* Includes 75 patients that received NIV on day 1 and invasive ventilation on day 2
† Limitation of care 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 1

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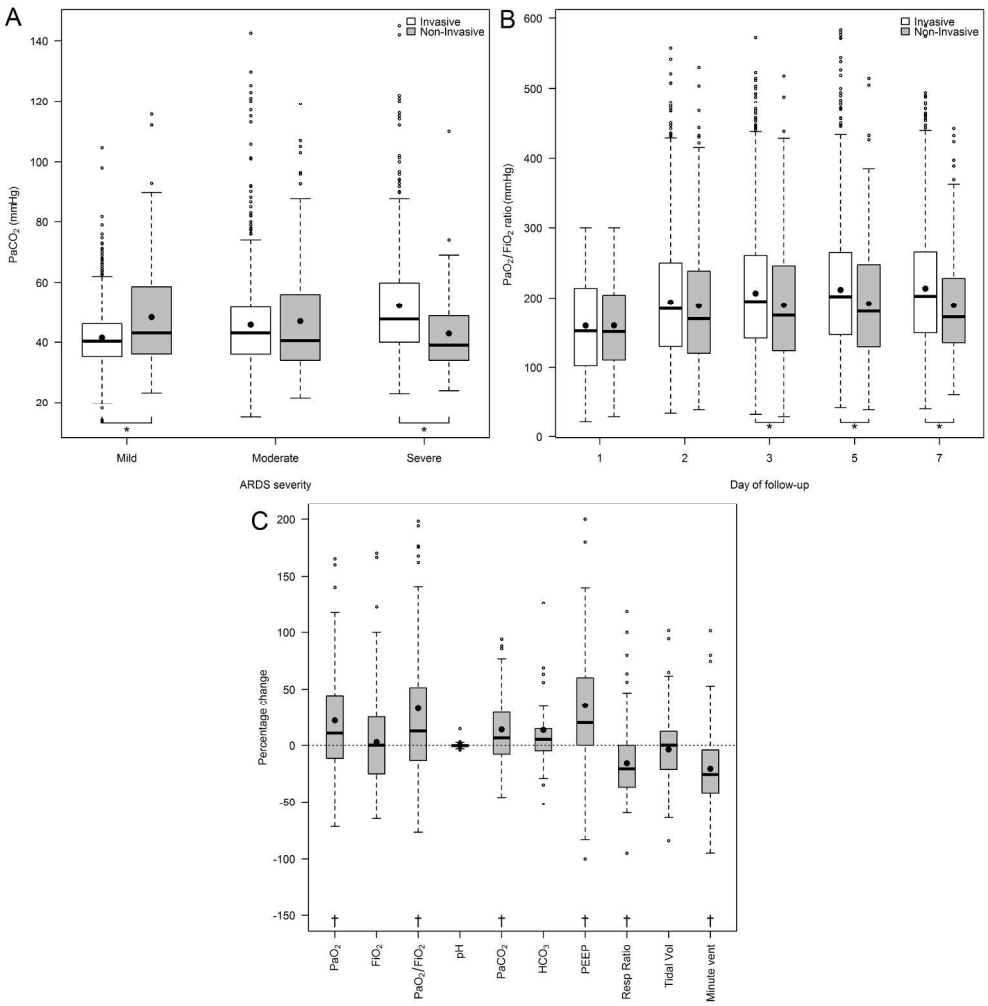

Figure 2

254x254mm (300 x 300 DPI)

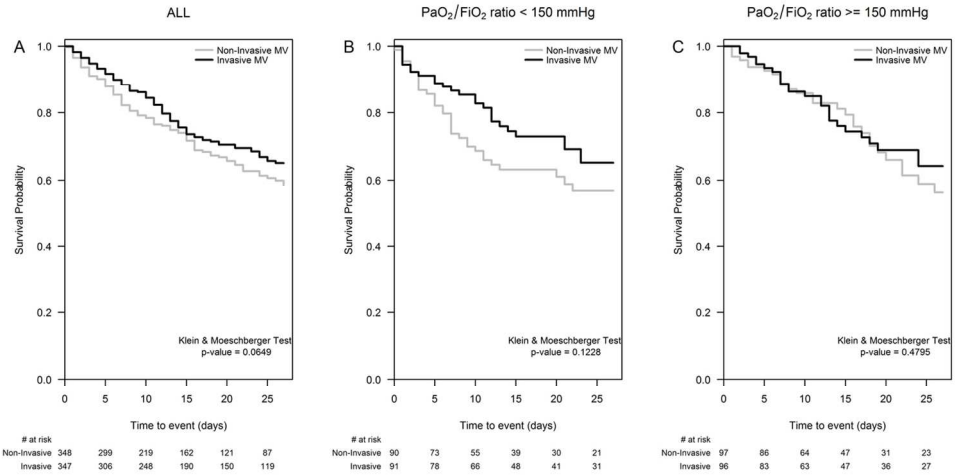

Figure 3

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

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ONLINE DATA SUPPLEMENT

Table of contents:

Expanded Methods

LUNG SAFE (ClinicalTrials.gov NCT02010073) was a prospective, observational, international multi-centre cohort study. Enrollment took place over four consecutive winter weeks (February-March in the northern hemisphere and June-August 2014 in the southern hemisphere), as selected by each participating site. National coordinators and/or site investigators (see below*)* were responsible for obtaining ethics' approval where required, data integrity and validity. Data were collected by means of an electronic case report form (eCRF, Clinfile®, Paris, France). Data quality was subsequently verified on the database and investigators were queried in regard to outlier or inconsistent data. Full methods are described in detail in the primary study paper (1), in which patients undergoing non invasive ventilation (NIV) had not been considered in most of the analyses.

Patients, Study Design and Data Collection

Investigators were requested to enroll all patients admitted to their Intensive Care Unit (ICU) within the 4-week enrollment window and receiving invasive mechanical ventilation (MV) or NIV. As previously described (1), exclusion criteria were: age<16 years or inability to obtain informed consent, where required. Following enrollment, patients were evaluated daily for Acute Hypoxemic Respiratory Failure (AHRF), defined as the concurrent presence of: (1) $PaO_2/FiO_2 \leq 300$ mmHg; (2) new pulmonary parenchymal abnormalities on chest X-Ray or computed tomography; and (3) ventilatory support with continuous positive airway pressure (CPAP) or expiratory positive airway pressure (EPAP) or positive end expiratory pressure (PEEP) ≥ 5 cmH_2O. At this stage, for patients fulfilling criteria for AHRF a more detailed set of data was recorded, which allowed us to determine whether or not the patient fulfilled the Berlin criteria for ARDS.

Data on arterial blood gases, type of ventilatory support with relative settings and Sequential Organ Failure Assessment (SOFA) score were collected on selected days during the ICU stay. Data were collected once per day: if more than one value was available during the day, investigator were asked

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to record data collected as close as possible to 10 AM. Data on ventilatory settings were recorded simultaneously with arterial blood gas. Decisions to withhold or withdraw life sustaining treatments during the ICU stay and the time at which this decision was taken were recorded (all-time treatment limitations). The subset of treatment limitation not occurring after intubation [NOTE: which is different than "before" as it includes patients who were never intubated] were defined as "pre-intubation treatment limitations". We did not collect data on which specific intervention was withdrawn or withheld (e.g. intubation, dialysis, use of vasopressors and so forth). Patients with treatment limitation decisions were excluded only from the analyses concerning NIV failure and success (see also statistical analysis). ICU and hospital survival were collected at the time of discharge, censored at 90 days after enrollment (whichever occurred earlier). Hence, in the manuscript, ICU- and hospital survival indicate the respective values censored at 90 days.
From the variables originally collected we also derived the following variables: bicarbonate (HCO_3), Base excess (BE), percent change of PaO_2/FiO_2 ratio and $PaCO_2$ over the first two days of ARDS.

NIV Patient Cohort and Definitions

Consistent with our previous report, we restricted subsequent analyses to the large 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. In all "NIV patients", arterial blood gas measurements were taken while the patient was receiving NIV. Patients were classified as "INVASIVE-MV patients" if they received INVASIVE-MV on day 1 and/or day 2 of ARDS. If data for day 2 was not available (e.g. if patient died or was transferred from the ICU) patients were classified only based on their status at day 1. Since "day 1" is the day of ARDS diagnosis, patients classified in the NIV group did not receive INVASIVE-MV for at least the first 24 hours since diagnosis of ARDS (interval between day 1 and day 2 recording).

Our "NIV" definition encompassed all forms of patient interface and ventilatory modes (bilevel ventilation or CPAP) where PEEP/EPAP was ≥5 cm H_2O. Since, as stated, data on ventilatory settings were recorded simultaneously with arterial blood gas, it follows that also in NIV patients PaO_2/FiO_2 was measured with a PEEP of at least 5 cmH_2O. Patients undergoing high flow oxygen therapy did not fulfill AHRF criteria, since this device delivers a PEEP < 5 cmH_2O (2, 3).

"NIV failure" was defined as the need to switch to INVASIVE-MV at any time point of ICU stay after day 2. Since we reasoned that in some patients intubation and INVASIVE-MV might have been deliberately avoided, due to treatment limitations (hence appearing as "false NIV success"), we limited the comparison of NIV "success" and "failure" groups to patients that did not have treatment limitation (unless these were decided after institution of INVASIVE-MV).

Primary and Secondary objectives

The primary objective was to determine the proportion of patients with ARDS managed with NIV for at least the first 24 hours of ARDS. Secondary outcomes included: the utility of the PAO2/FIO2 ratio severity categories in the classification of NIV patients; characteristics of patients managed with NIV; the ventilatory settings used in these patients; the factors associated with NIV success and failure; and the impact of management of patients with NIV on ICU and hospital mortality in patients with ARDS.

Statistical Analysis

We evaluated demographic and clinical characteristics of the study population at ARDS diagnosis. For continuous variables, we reported median with interquartile range (IQR) or mean with standard deviation (SD), and for categorical variables we reported proportions. The Student's t-test or ANOVA were used to detect the differences among groups when the continuous variable was normally distributed. The normality of data was assessed with the Shapiro-Wilks test. In case of

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non-normal distribution, we used Wilcoxon rank sum test or Kruskal–Wallis test. Categorical data were compared using the Chi-Square test or Fisher exact test.

In patients with NIV failure, we compared the clinical characteristics observed in the last day in which NIV was used and in the first day in which INVASIVE-MV was used, by paired t-test or Wilcoxon signed-rank test when assumption of normality was not met.

Differences between examined variables were evaluated: (a) between the NIV and INVASIVE-MV groups in each ARDS severity; and (b) among ARDS severity groups in each treatment.

Multivariate Cox proportional hazard models were applied to investigate the relationship between potential covariates (demographic and baseline clinical characteristics) and outcomes: ICU and hospital mortality in all ARDS patients and failure of NIV treatment within 28 days from AHRF onset in "NIV group". In the analysis of NIV failure, we excluded patients with pre-intubation treatment limitations. To avoid overfitting, we included in the multivariate models covariates significantly associated with outcome in the stepwise Cox analysis. Results are presented as model coefficients with standard error (SE), tests of significance and hazard ratios (HRs) with 95% confidence intervals (CIs). The validity of the proportional hazards assumption in the Cox regression models was assessed with the test proposed by Harrel and Lee based on Schoenfeld residuals.

Propensity score

To assess the effect of mechanical ventilation on ICU and hospital mortality and to avoid potential confounding by selection bias and other factors, we identified the comparison groups with the propensity score matching approach. Logistic regression was used to estimate propensity scores able to predict the probability of undergoing invasive-MV or NIV treatment. The predictors, (chosen a-priori as possibly influencing the choice between invasive-MV or NIV and/or influencing mortality) included: patients' age and gender, comorbidities, risk factors for ARDS (pulmonary, non-pulmonary, none), number of ICU beds, treatment limitation before intubation, PaO2/FiO2 and SOFA scores (cardiovascular, liver, coagulation, renal, central nervous system) measured at date of

ARDS onset or at date of intubation for patients treated with INVASIVE-MV. Patients with similar propensity score in the two treatment groups were matched (1:1 match without replacement), using a caliper of 0.2 standard deviation of the logit of the propensity score. We assessed the similarity of the matched treatment groups through the standardized differences of each predictor. Since previous reports showed that NIV success and failure is different for PaO_2/FiO_2 greater or lower than 150 mmHg, we also subdivided our propensity-matched population according to this cut off (4). Statistical significance of the difference in means was evaluated with paired t-test or Wilcoxon signed-rank test, while for difference in proportions we applied McNemar's test.

For all statistical tests, a pre-specified two-sided α of 0.05 was regarded as significant. The analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA) and R, version 3.0.2 (R Project for Statistical Computing, http://www.R-project.org).

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Supplemental Tables

Table E1: Approach to classification of Ventilatory mode

Ventilatory mode		Group
Day 1	**Day 2**	
Invasive MV	Invasive MV	Invasive MV
Invasive MV	Non-invasive	Invasive MV
Non-invasive	Invasive	Invasive MV
Non-invasive	Non-invasive	NIV
Invasive MV	None*	Invasive MV
Non-invasive	None*	NIV

Abbreviations: NIV: Non-invasive ventilation; MV: mechanical ventilation.

** Examples of this situation include oxygen therapy, ICU discharge, hospital discharge and death.*

Table E2: Characteristics of invasive-MV and NIV patients in the propensity score matched sample.

Covariates	**Invasive-MV patients (n=353)**	**NIV patients (n=353)**	**ARDS (n=706)**	***Standardized difference of the mean***
Age (years), mean ± SD	63.86 ± 15.92	64.20 ± 15.99	64.03 ± 15.95	*0.02*
Gender, n (%)				
Male	208 (58.92)	215 (60.91)	423 (59.92)	*0.04*
Risk factors for ARDS, n (%)				
None	47 (13.31)	42 (11.90)	89 (12.61)	*0.04*
Non-pulmonary	40 (11.33)	44 (12.46)	84 (11.90)	*0.04*
Pulmonary	266 (75.35)	267 (75.64)	533 (75.50)	*0.01*
Diabetes mellitus, n (%)	81 (22.95)	81 (22.95)	162 (22.95)	*0.00*
Chronic renal failure, n (%)	56 (15.86)	48 (13.60)	104 (14.73)	*0.06*
Chronic liver failure, n (%)	5 (1.42)	7 (1.98)	12 (1.70)	*0.04*
Chronic Heart failure, n (%)	42 (11.90)	46 (13.03)	88 (12.46)	*0.03*
Active neoplasm or immunosuppression or hematologic neoplasm, n (%)	87 (24.65)	78 (22.10)	165 (23.37)	*0.06*
COPD or home ventilation, n (%)	95 (26.91)	108 (30.59)	203 (28.75)	*0.08*
Non-pulmonary SOFA score adjusted, mean ± SD	3.26 ± 2.82	3.19 ± 2.94	3.22 ± 2.88	*0.02*
PaO_2/FiO_2 (mmHg), mean ± SD	164.11 ± 84.58	160.94 ± 64.29	162.52 ± 75.08	*0.04*
Treatment limitation, n (%)	4 (1.13)	4 (1.13)	8 (1.13)	*0.00*
ICU beds, mean ± SD	21.86 ± 16.31	21.62 ± 18.08	21.74 ± 17.20	*0.01*

Abbreviations. ARDS: Acute respiratory Distress Syndrome; MV: mechanical ventilation; NIV: Non-invasive ventilation.; SD: standard deviation; COPD: Chronic Obstructive Pulmonary Disease; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit.

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Table E3 Comparison between patients receiving NIV on day 1 and invasive MV on day 2, NIV failure after day 2 and Invasive MV from day 1

	NIV in day 1 and invasive MV on day 2	**NIV failure after day 2**	**Invasive MV at day 1**	***p-value column 1 vs column 2***	***p-value column 1 vs column 3***
N	71	131	2,252		
ARDS severity, n (%)				*0.114*	*0.048*
Mild ARDS	15 (21.1)	22 (16.8)	679 (30.2)		
Moderate ARDS	31 (43.7)	77 (58.8)	1,047 (46.5)		
Severe ARDS	25 (35.2)	32 (24.4)	526 (23.4)		
Male, n (%)	43 (60.6)	80 (61.1)	1,397 (61.9)	*0.944*	*0.819*
Age, median [IQR]	62.0 [49 - 70]	63.0 [53 - 74]	63.0 [49 - 73]	*0.304*	*0.558*
ICU mortality, n (%)	27 (38.0)	56 (42.7)	774 (34.4)	*0.515*	*0.523*
Hospital mortality, n (%)	29 (40.8)	59 (45.4)	886 (39.5)	*0.535*	*0.817*
Clinical recognition of ARDS, n (%)					
At study entry	20 (28.2)	42 (32.1)	754 (33.5)	*0.567*	*0.350*
At any time	56 (80.0)	88 (68.2)	1,331 (61.1)	*0.076*	*0.001*
Risk factors for ARDS, n (%)				*0.582*	*0.014*
None	5 (7.0)	12 (9.2)	178 (7.9)		
Non-pulmonary	5 (7.0)	14 (10.7)	469 (20.8)		
Pulmonary	61 (85.9)	105 (80.1)	1,605 (71.3)		
Comorbidities, n (%)					
Diabetes	12 (16.9)	21 (16.0)	491 (21.8)	*0.873*	*0.324*
Chronic renal failure	4 (5.6)	11 (8.4)	213 (9.5)	*0.475*	*0.276*
Heart failure (NYHA III-IV)	3 (4.2)	18 (13.7)	211 (9.4)	*0.034*	*0.140*
Chronic liver failure	4 (5.6)	2 (1.5)	95 (4.2)	*0.187*	*0.543*
Active neoplasm or immunosuppression or hematologic neoplasm	27 (38.0)	34 (26.0)	445 (19.8)	*0.074*	*0.002*
COPD	10 (14.1)	33 (25.2)	455 (20.2)	*0.066*	*0.205*
Home ventilation	3 (4.2)	5 (3.8)	35 (1.6)	*1.000*	*0.108*
Parameters at day of ARDS onset, mean ± SD					
PaO_2 (mmHg)	88.4 ± 27.6	83.1 ± 30.5	93.5 ± 38.5	*0.069*	*0.775*
FiO_2	0.69 ± 0.22	0.63 ± 0.21	0.65 ± 0.24	*0.064*	*0.059*
PaO_2/FiO_2 ratio (mmHg)	144 ± 67	145 ± 60	161 ± 68	*0.549*	*0.027*
pH	7.33 ± 0.11	7.38 ± 0.09	7.32 ± 0.12	*0.003*	*0.787*
$PaCO_2$ (mmHg)	47 ± 11	44 ± 17	46 ± 15	*0.003*	*0.113*
Base Excess (mmol/L)	-1.18 ± 6.49	-0.02 ± 6.83	-2.27 ± 7.01	*0.540*	*0.113*
PEEP (cmH_2O)	9 ± 3	7 ± 2	8 ± 3	*<.001*	*0.001*
Total Respiratory rate (breaths/min)	22 ± 6	27 ± 8	21 ± 9	*<.001*	*0.206*
Minute ventilation (L/min)	9.65 ± 3.41	14.03 ± 6.25	9.48 ± 3.05	*<.001*	*0.983*
Tidal Volume (ml/kg PBW)	7.33 ± 1.55	8.65 ± 3.11	7.62 ± 1.88	*0.007*	*0.286*
Non-pulmonary SOFA score adjusted	7 ± 4	3 ± 3	7 ± 4	*<.001*	*0.499*
Use of CPAP, n (%)	2 (2.8)	35 (26.7)	48 (2.1)	*<.001*	*0.664*

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 before IOT 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.

Note 3: statistical significance level is 0.025, due to the Bonferroni correction for multiple comparisons.

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Table E4. Factors associated with clinician recognition of ARDS

	ARDS recognized N / Total No. (%)	Absolute difference (95% CI)	Bivariate model		Multivariate model	
			OR (95% CI)	p-value	OR (95% CI)	p-value
No. of patients/staff physician (for each additional patient)		-1.17 (-1.59 - -0.77)	0.959 (0.944 - 0.974)	<0.001	0.957 (0.940 - 0.982)	<0.001
No. of patients/nurse (for each additional patient)		-0.263 (-0.44 - -0.08)	0.934 (0.891 - 0.974)	0.002	0.940 (0.896 - 0.982)	0.007
Age (years)		-4.43 (65.69 - -3.18)	0.984 (0.979 - 0.989)	<0.001	0.986 (0.980 to 0.992)	<0.001
Predicted body weight (kg)		-0.83 (-1.66 - -0.02)	0.992 (0.985 - 1.000)	0.044	0.987 (0.978 - 0.995)	0.003
Non-pulmonary SOFA score adj.		0.99 (0.69 - 1.29)	1.064 (1.044 - 1.085)	<0.001	1.049 (1.024 - 1.076)	<0.001
PaO_2/FiO_2 (mmHg)		-29.97 (-35.53 - -24.42)	0.993 (0.992 - 0.995)	<0.001	0.994 (0.992 - 0.995)	<0.001
Medical or surgical admission with trauma						
No	1685/2704 (62.3)	Reference	Reference	-	Reference	-
Yes	50/109 (45.9)	-16.4 (-26.0 - -6.9)	0.512 (0.348 - 0.752)	<0.001	0.602 (0.376 - 0.960)	0.033
Active neoplasm or immunosuppression or hematologic neoplasm						
Absence	1325/2229 (59.4)	Reference	Reference	-	Reference	-
Presence	410/584 (70.2)	10.7 (6.5 - 15.0)	1.608 (1.323 - 1.960)	<0.001	1.353 (1.073 - 1.713)	0.011
Pneumonia						
Absence	616/1143 (53.9)	Reference	Reference	-	Reference	-
Presence	1119/1670 (67.0)	13.1 (9.4 - 16.8)	1.737 (1.489 - 2.028)	<0.001	1.520 (1.227 - 1.884)	<0.001
Extra-pulmonary sepsis						
Absence	1427/2360 (60.5)	Reference	Reference	-	Reference	-
Presence	308/453 (68.0)	7.5 (2.7 - 12.2)	1.389 (1.123 - 1.724)	0.003	1.654 (1.260 - 2.182)	<0.001
Pancreatitis						
Absence	1687/2755 (61.2)	Reference	Reference	-	Reference	-
Presence	48/58 (82.8)	21.5 (11.6 - 31.4)	3.039 (1.598 - 6.393)	0.001	4.612 (2.012 - 12.598)	<0.001
Risk factors for ARDS						
Absence	1638/2532 (64.7)	Reference	Reference	-	Reference	-

Presence	97/281 (34.5)	-30.1 (-36.0 - -24.3)	0.288 (0.221 - 0.372)	<0.001	0.423 (0.305 - 0.584)	<0.001
NIV without intubation in the first 48hs						
Absence	1525/2377 (64.2)	Reference	Reference	-	Reference	-
Presence	210/436 (48.2)	-16.0 (-21.1 - -10.9)	0.519 (0.422 - 0.638)	<0.001	0.585 (0.450 - 0.760)	<0.001
Chronic Heart failure						
Absence	1532/2376 (64.5)	Reference	Reference	-	Reference	-
Presence	203/437 (46.5)	-18.0 (-23.1 - -13.0)	0.478 (0.389 - 0.587)	<0.001	0.469 (0.366 - 0.601)	<0.001

Abbreviations. ARDS: Acute respiratory Distress Syndrome; NIV: Non-invasive ventilation; SOFA: Sequential Organ Failure Assessment; OR: odds ratio; CI: confidence interval.

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Table E5. Effect of baseline characteristics on NIV treatment failure occurred in ICU during 28 days from AHRF onset. Cox's regression model (n=369).

Parameters	Beta	SE	p-value	Hazard Ratio (95% CI)
Non-pulmonary SOFA score adjusted	0.067	0.032	0.038	1.070 (1.004 - 1.139)
PaO_2/FiO_2 (mmHg)	- 0.004	0.002	0.023	0.996 (0.993 – 1.000)
Δ (%)* $PaCO_2$	0.007	0.003	0.015	1.007 (1.002 - 1.013)

Abbreviations: SOFA: Sequential Organ Failure Assessment; CI: confidence interval.

** 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. Δ (%) was evaluated as rate between Δ and value measured at the ARDS onset day.*

Table E6. Comparison of clinical characteristics observed in the last day of NIV and in the first day of Invasive-MV (N=131).

	Last NIV day	**First IOT day**	**First - Last**	***p-value***
Parameters at day of ARDS onset, mean ± sd				
PaO_2 (mmHg)	83.9 ± 31.0	96.3 ± 50.9	13.6 ± 55.1	*0.0020*
FiO_2	0.63 ± 0.22	0.60 ± 0.22	-0.03 ± 0.25	*0.2621*
PaO_2/FiO_2 ratio (mmHg)	151 ± 68	181 ± 95	32 ± 98	*0.0003*
pH	7.38 ± 0.12	7.4 ± 0.09	-0.01 ± 0.14	*0.0190*
$PaCO_2$ (mmHg)	45 ± 16	49 ± 14	4 ± 14	*0.0015*
HCO_3 (mmol/L)	25.66 ± 7.78	26.66 ± 7.07	1.07 ± 5.28	*0.0056*
Base Excess (mmol/L)	0.84 ± 7.80	1.58 ± 7.01	0.80 ± 5.85	*0.1012*
PEEP (cmH_2O)	7 ± 2	9 ± 4	2 ± 4	*<.0001*
Total Respiratory rate (breaths/min)	28 ± 8	22 ± 7	-5 ± 8	*<.0001*
Tidal Volume (ml/Kg PBW)	8.7 ± 2.9	7.8 ± 2.4	-1.0 ± 3.0	*0.0093*
Minute ventilation (L/min)	14.55 ± 6.84	9.99 ± 3.51	-4.50 ± 6.49	*<.0001*
Non-pulmonary SOFA score adjusted	4 ± 3	7 ± 4	2 ± 4	*0.0039*
ARDS category at first day post invasive MV in comparison with those in the last NIV day, n (%)				
Better	-	40 (30.5)	-	-
Same	-	55 (42.0)	-	-
Worse	-	18 (13.7)	-	-
Unknown	-	18 (13.7)	-	-
ARDS category at first day post invasive MV in comparison with those in the day of ARDS onset, n (%)				
Better	-	58 (44.3)	-	-
Same	-	49 (37.4)	-	-
Worse	-	13 (9.9)	-	-
Unknown	-	11 (8.4)	-	-

Abbreviations: ARDS: Acute respiratory Distress Syndrome; NIV: Non-invasive ventilation; PBW: predicted body weight; PEEP: Positive end-expiratory pressure; SOFA: Sequential Organ Failure Assessment.

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Table E7. Effect of baseline characteristics on mortality in the entire cohort of ARDS patients.

Parameters		Beta	SE	p-value	Hazard Ratio (95% CI)
Outcome: all-cause in-ICU mortality (n=2,501)					
Age		0.0138	0.0024	<.0001	1.014 (1.009 - 1.019)
Chronic liver failure (reference. absence)		0.7780	0.1377	<.0001	2.177 (1.662 - 2.851)
Heart failure (reference. absence)		0.1887	0.1057	0.0743	1.208 (0.982 - 1.486)
Active neoplasm or immunosuppression or hematologic neoplasm (reference. absence)		0.4324	0.0775	<.0001	1.541 (1.324 - 1.794)
Non-pulmonary SOFA score adjusted		0.0773	0.0094	<.0001	1.080 (1.061 - 1.100)
Invasive-MV treatment (reference: presence)		0.3690	0.1131	0.0011	1.446; (1.159-1.805)
ARDS severity (reference: Mild)	Moderate	0.1813	0.0880	0.0395	1.199 (1.009 - 1.424)
	Severe	0.6003	0.1077	<.0001	1.823 (1.476 - 2.251)
Δ (%)* PaO_2/FiO_2		-0.0035	0.0006	<.0001	0.996 (0.995 - 0.998)
Δ (%)* $PaCO_2$		0.0023	0.0010	0.0198	1.002 (1.000 - 1.004)
pH		-2.5639	0.3031	<.0001	0.077 (0.043 - 0.139)
Total respiratory rate (breaths/min)		0.0148	0.0028	<.0001	1.015 (1.009 - 1.020)
PEEP (cmH_2O)		-0.0503	0.0114	<.0001	0.951 (0.930 - 0.972)
Outcome: all-cause in-hospital mortality (n=2,506)					
Age		0.0153	0.0022	<.0001	1.015 (1.011 - 1.020)
Chronic liver failure (reference: absence)		0.7376	0.1312	<.0001	2.091 (1.617 - 2.704)
Heart failure (reference. absence)		0.2449	0.0997	0.0141	1.277 (1.051 - 1.553)
Active neoplasm or immunosuppression or hematologic neoplasm (reference. absence)		0.4526	0.0722	<.0001	1.572 (1.365 - 1.811)
Non-pulmonary SOFA score adjusted		0.0639	0.0086	<.0001	1.066 (1.048 - 1.084)
ARDS severity (reference: Mild)	Moderate	0.2576	0.0806	0.0014	1.294 (1.105 - 1.515)
	Severe	0.6936	0.1021	<.0001	2.001 (1.638 - 2.444)
Δ (%)* PaO_2/FiO_2		-0.0042	0.0006	<.0001	0.996 (0.995 - 0.997)
$PaCO_2$ (cmH_2O)		-0.0075	0.0026	0.0036	0.993 (0.988 - 0.998)
pH		-2.7664	0.3204	<.0001	0.063 (0.034 - 0.118)
Total respiratory rate (breaths/min)		0.0161	0.0024	<.0001	1.016 (1.011 - 1.021)
PEEP (cmH_2O)		-0.0482	0.0108	<.0001	0.953 (0.933 - 0.973)

Abbreviations: ARDS: Acute respiratory Distress Syndrome; MV: mechanical ventilation; PEEP: Positive end-expiratory pressure; SOFA: Sequential Organ Failure Assessment; CI confidence interval.

** 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. Δ (%) was evaluated as rate between Δ and value measured at the ARDS onset day.*

Note 1: vital status was evaluated at ICU / hospital discharge. If the date of hospital discharge was missing, patient was censored at the date of ICU discharge. Patients who were still in ICU / hospital were censored on day 90 from AHRF onset.

Note 2: in the first model (all-cause in-ICU mortality), the interaction term between INVASIVE-MV treatment and ARDS severity was tested but did not result statistically significant (p-value=0.4530). In the second model (all-cause in-hospital mortality), the variable "invasive-MV treatment" was forced and p-value associated to this parameter was 0.1632. We also forced the variable "invasive-MV treatment" and the interaction term between treatment and ARDS severity: p-values associated were 0.4728 and 0.4951 respectively.

Table E8. Demographic and clinic characteristics of ARDS NIV patients at ARDS onset. Population were stratified according the vital status at hospital discharge.

	ARDS - NIV		*p-value*
	Survivors	**Non-survivors**	
N (%)	279 (64.1)	156 (35.9)	-
Male, n (%)	161 (57.7)	96 (61.5)	*0.4356*
Age (years), median [IQR]	65 [53 - 77]	71 [59 - 79]	*0.0046*
NIV failure, n (%)	73 (26.2)	60 (38.5)	*0.0076*
Days between AHRF onset and invasive intubation, median [IQR]	2 [1 - 4]	2 [1 - 4]	*0.7260*
Patients with treatment limitation, n (%)	30 (10.8)	94 (60.3)	*<.0001*
Risk factors for ARDS, n (%)			*0.1691*
None	42 (15.1)	20 (12.8)	
Non-pulmonary	36 (12.9)	12 (7.7)	
Pulmonary	201 (72.0)	124 (79.5)	
Comorbities, n (%)			
Diabetes	64 (22.9)	34 (21.8)	*0.7841*
Chronic renal failure	34 (12.2)	28 (17.9)	*0.0992*
Heart failure (NYHA III-IV)	34 (12.2)	32 (20.5)	*0.0203*
Chronic liver failure	1 (0.4)	8 (5.1)	*0.0015*
Active neoplasm or immunosuppression or hematologic neoplasm	50 (17.9)	49 (31.4)	*0.0013*
COPD	91 (32.6)	43 (27.6)	*0.2737*
Home ventilation	18 (6.5)	3 (1.9)	*0.0365*
Parameters at day of ARDS onset, mean±SD			
PaO_2 (mmHg)	85.72 ± 32.07	86.58 ± 31.00	*0.5218*
FiO_2	0.57 ± 0.21	0.64 ± 0.22	*0.0015*
PaO_2/FiO_2 ratio (mmHg)	165 ± 63	150 ± 64	*0.0075*
pH	7.38 ± 0.09	7.38 ± 0.10	*0.6676*
$PaCO_2$ (mmHg)	48 ± 18	44 ± 16	*0.1098*
HCO_3(mmol/L)	26.27 ± 7.19	24.66 ± 6.71	*0.0385*
Base Excess (mmol/L)	1.38 ± 6.75	-0.12 ± 6.55	*0.0576*
PEEP (cmH_2O)	7 ± 2	7 ± 2	*0.6613*
Total Respiratory rate (breaths/min)	25 ± 7	28 ± 7	*<.0001*
Minute ventilation (L/min)	12.58 ± 4.91	14.25 ± 6.28	*0.0261*
Tidal Volume (ml/Kg PBW)	8.3 ± 2.6	8.5 ± 3.1	*0.8926*
Non-pulmonary SOFA score adjusted	3 ± 3	4 ± 3	*0.0014*
Use of CPAP, n (%)	76 (27.2)	46 (29.5)	*0.6168*

Abbreviations: ARDS: Acute respiratory Distress Syndrome; MV: mechanical ventilation; 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: vital status was evaluated at hospital discharge. Patients who were still in hospital were censored on day 90 from AHRF onset.

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Table E9. ARDS-NIV patients - Effect of baseline characteristics on mortality. Cox's regression models.

Parameters	Beta	SE	p-value	Hazard Ratio (95% CI)
Outcome: all-cause in-ICU mortality (n=427)				
Age (years)	0.0166	0.0066	0.0117	1.017 (1.004 - 1.030)
Chronic Liver Failure (reference: absence)	1.2065	0.4331	0.0053	3.342 (1.430 - 7.809)
Heart failure (reference: absence)	0.7238	0.2459	0.0032	2.062 (1.274 - 3.339)
Active neoplasm or immunosuppression or hematologic neoplasm (reference: absence)	0.5029	0.2008	0.0123	1.653 (1.115 - 2.451)
Non-pulmonary SOFA adjusted	0.1028	0.0285	0.0003	1.108 (1.048 - 1.172)
PaO_2/FiO_2 (mmHg)	-0.0040	0.0016	0.0154	0.996 (0.993 - 0.999)
Total respiratory rate (breaths/min)	0.0451	0.0129	0.0004	1.046 (1.020 - 1.073)
Outcome: all-cause in-hospital mortality (n=361)				
Age (years)	0.0154	0.0064	0.0171	1.015 (1.003 - 1.028)
Chronic Liver Failure (reference: absence)	1.1093	0.3992	0.0055	3.032 (1.387 - 6.630)
Heart failure (ref. No)	0.6131	0.2390	0.0103	1.846 (1.156 - 2.950)
Hematologic neoplasm (reference: absence)	0.7635	0.2698	0.0047	2.146 (1.265 - 3.641)
Non-pulmonary SOFA adjusted	0.0969	0.0285	0.0007	1.102 (1.045 - 1.165)
PaO_2/FiO_2 (mmHg)	-0.0039	0.0016	0.0156	0.996 (0.993 - 0.999)
Δ* PaO_2/FiO_2 (mmHg)	-0.0036	0.0013	0.0064	0.996 (0.994 - 0.999)
Total respiratory rate (breaths/min)	0.0480	0.0121	<.0001	1.049 (1.025 - 1.074)

Abbreviations: ARDS: Acute respiratory Distress Syndrome; SOFA: Sequential Organ Failure Assessment; CI: confidence interval.

** 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.*

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

Supplemental Figures

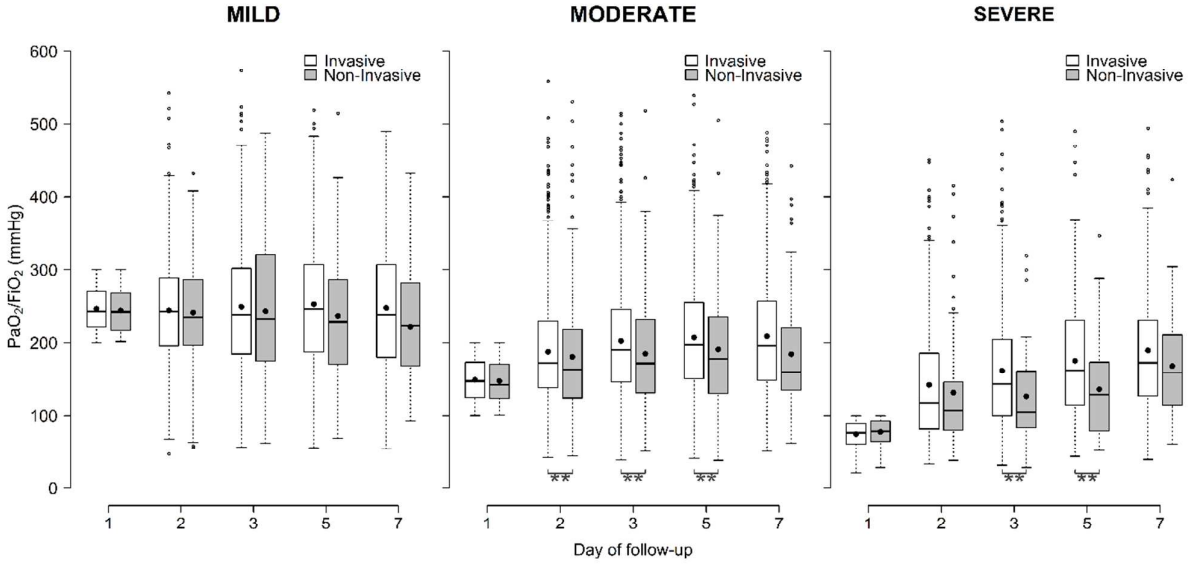

Figure E1: Evolution of PaO_2/FiO_2 over the days in patients treated with non-invasive and invasive mechanical ventilation (MV). While the time course was similar for patients with mild ARDS, in moderate and severe ARDS the improvement was more rapid for patients treated with invasive than for those treated with non-invasive MV * p-value < 0.05, comparison between non-invasive and invasive MV.

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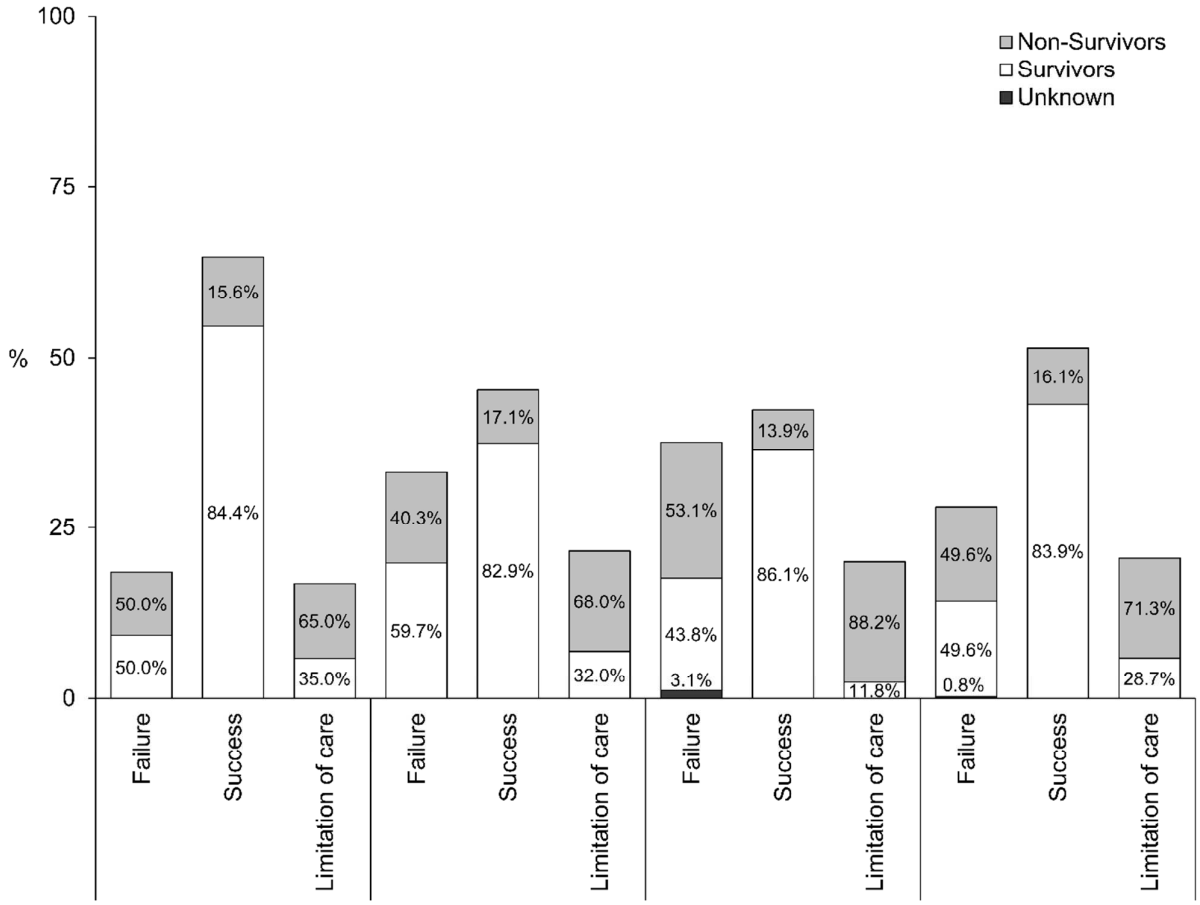

Figure E2: Proportion of non-invasive ventilation (NIV) failure/success and relative hospital outcomes in patients with mild, moderate, and severe ARDS and in the entire NIV population.

References

1. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016; 315: 788-800.
2. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. *Chest* 2015; 148: 253-261.
3. Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. *Respir Care* 2011; 56: 1151-1155.
4. Thille AW, Contou D, Fragnoli C, Cordoba-Izquierdo A, Boissier F, Brun-Buisson C. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. *Crit Care* 2013; 17: R269.

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