Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome
Insights from the LUNG SAFE Study

Giacomo Bellani1,2, John G. Laffey3,4,5,6,7,8, Tài Pham9,10,11, Fabiana Madotto12, Eddy Fan8,13,14,15, Laurent Brochard4,5,8,14,1, Andres Esteban16, Luciano Gattinoni17, Vesna Bumbasirevic18,19, Lise Piquilloud20,21, Frank van Haren22,23, Anders Larsson24, Daniel F. McAuley25,26, Philippe R. Bauer27, Yaseen M. Arabi28,29, Marco Ranieri30, Massimo Antonelli31, Gordon D. Rubenfeld8,14,32, B. Taylor Thompson33, Hermann Wrigge34, Arthur S. Slutsky8,14,11, and Antonio Pesenti35,36, on behalf of the LUNG SAFE Investigators and the ESICM Trials Group*

1Department of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy; 2Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy; 3Department of Anesthesia, 4Department of Critical Care Medicine, and 5Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Canada; 6Department of Anesthesia, 7Department of Physiology, 8Interdepartmental Division of Critical Care Medicine, 9Institute of Health Policy, Management and Evaluation, and 10Department of Medicine, University of Toronto, Toronto, Canada; 11Assistance Publique–Hôpitaux de Paris, Hôpital Tenon, Unité de Réanimation Médico-Chirurgicale, Pôle Thorax Vaès Aërennes, Groupe Hospitalier des Hôpitaux Universitaires de l’Est Parisien, Paris, France; 12Unité Mixte de Recherche 1153, Inserm, Sorbonne Paris Cité, Épidémiologie Clinique et Statistiques, pour la Recherche en Santé Team, Université Paris Diderot, Paris, France; 13Sorbonne Universités, Université Pierre et Marie Curie, Paris 06, France; 14Research Centre on Public Health, Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; 15Department of Medicine, University Health Network and Mount Sinai Hospital, Toronto, Canada; 16Hospital Universitario de Getafe, Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Madrid, Spain; 17Department of Anesthesiology, Emergency and Intensive Care Medicine, University Medical Center Göttingen, Göttingen, Germany; 18School of Medicine, University of Belgrade, Belgrade, Serbia; 19Department of Anesthesia and Intensive Care, Emergency Center, Clinical Center of Serbia, Belgrade, Serbia; 20Adult Intensive Care and Burn Unit, University Hospital of Lausanne, Lausanne, Switzerland; 21Department of Medical Intensive Care, University Hospital of Angers, Angers, France; 22Intensive Care Unit, The Canberra Hospital, Canberra, Australia; 23Australian National University, Canberra, Australia; 24Section of Anesthesiology and Intensive Care, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; 25Centre for Experimental Medicine, Queen’s University of Belfast, Wellcome-Wolfson Institute for Experimental Medicine, Belfast, United Kingdom; 26Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, United Kingdom; 27Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota; 28King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; 29King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; 30Dipartimento di Anestesia e Rianimazione, Policlinico Umberto I, Sapienza Università di Roma, Roma, Italy; 31Istituto di Anestesiologia e Rianimazione, Università Cattolica del Sacro Cuore-Fondazione Policlinico Universitario A. Gemelli, Roma, Italy; 32Sunnybrook Health Sciences Center, Toronto, Canada; 33Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; 34Department of Anesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany; 35Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione Istituto di ricovero e Cura a Carattere Scientifico Cà Granda-Ospedale Maggiore Policlinico, Milan, Italy; and 36Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

ORCID ID: 0000-0002-1246-9573 (J.G.L.).

Abstract
Rationale: Noninvasive ventilation (NIV) is increasingly used in patients with acute respiratory distress syndrome (ARDS). The evidence supporting NIV use in patients with ARDS remains relatively sparse.

Objectives: To determine whether, during NIV, the categorization of ARDS severity based on the PaO2/FiO2 Berlin criteria is useful.

Methods: The LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study described the management of patients with ARDS. This substudy examines the current practice of NIV use in ARDS, the utility of the PaO2/FiO2 ratio in classifying patients receiving NIV, and the impact of NIV on outcome.

Measurements and Main 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 PaO2/FiO2 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 (hazard ratio, 1.446 [95% confidence interval, 1.159–1.805]), but not hospital, mortality. In a propensity matched analysis, ICU mortality was higher in NIV than in ventilated patients with a PaO2/FiO2 lower than 150 mm Hg.

Conclusions: NIV was used in 15% of patients with ARDS, irrespective of severity category. NIV seems to be associated with higher ICU mortality in patients with a PaO2/FiO2 lower than 150 mm Hg.

Clinical trial registered with www.clinicaltrials.gov (NCT 02010073).

Keywords: noninvasive ventilation; acute respiratory distress syndrome

Bellani, Laffey, Pham, et al.: Noninvasive Ventilation of Patients with ARDS
Noninvasive 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 patients with ARDS (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 with patients treated with oxygen administration (16) or with historical cohorts (17).

Several concerns exist regarding the use of NIV in patients with ARDS. The subgroup of ARDS most likely to benefit from NIV remains unclear. Although some literature suggests that NIV may best be reserved for patients with mild ARDS (i.e., patients with a PaO2/FiO2 ratio of 200–300 mm Hg) (5, 15, 18, 19), it is not always the case in practice (20). Although 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 managed with NIV should be all classified as having “mild” ARDS or whether the PaO2/FiO2 ratio severity stratification is more appropriate (25).

For these reasons, a key prespecified secondary aim of the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) (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 fulfilment of diagnostic criteria for ARDS. Secondary objectives included determining the utility of the PaO2/FiO2 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

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

Patients, Study Design, and Data Collection

Patients receiving invasive MV or NIV were enrolled in the participating intensive care units (ICUs) for 4 consecutive weeks. Exclusion criteria were age less than 16 years or inability to obtain informed consent. Following enrollment, patients were evaluated daily for acute hypoxemic respiratory failure (AHRF), defined as PaO2/FiO2 less than or equal to 300 mm Hg while simultaneously receiving invasive MV or NIV (depending on the patient group) with end-expiratory pressure greater than or equal to 5 cm H2O, and new radiologic 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 10:00 A.M. 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 (see Table E1 in the online supplement).

NIV definition encompassed all forms of patient interface and ventilatory modes. High-flow oxygen therapy was not included. Because data were collected once per day and the duration of NIV sessions was not recorded, patients that were switched from NIV to invasive-MV before 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).

### Statistical Analysis

For continuous variables, we reported median with interquartile range or mean ± SD, and for categorical variables, we reported proportions. Student’s t test, analysis of variance, Wilcoxon rank sum test, or Kruskal-Wallis, chi-square, or Fisher tests were used when appropriate.

### 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 patients with ARDS, 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 2 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), whereas 75 patients were managed with NIV on Day 1 and on invasive MV on Day 2 (see Table E3).

Continuous positive airway pressure was used in 28.2% of patients in the NIV group (Table 1), whereas the remaining patients were managed with pressure cycled modes.

#### Classification of NIV Patients

In patients with ARDS managed with NIV, classification of severity into mild, moderate, and severe categories according to the PaO2/FiO2 bands in the Berlin definition was associated with a step-wise increase in positive end-expiratory pressure (PEEP) and FiO2 (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 nonsignificant increase in hospital mortality (Table 2). Increasing ARDS severity category was associated with a significant increase in NIV failure in patients without preintubation 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 nonpulmonary SOFA scores, both in the whole population and across the different severity categories, compared with invasive-MV patients (Table 1). NIV patients had a higher prevalence of chronic renal failure, congestive heart failure, and chronic obstructive pulmonary disease 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 with invasive-MV patients (Table 2). The use of NIV was independently associated with a lower recognition of ARDS by clinicians (odds ratio, 0.585; 95% confidence interval, 0.45–0.76) (see Table E4). ARDS recognition was increased in patients that failed NIV (Table 3). There were no differences in treatment limitation rates in NIV patients 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 (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, PaO2/FiO2 ratio was not different between the NIV and invasive-MV patients (Table 1). PaO2/FiO2 ratios improved more rapidly in the patients treated with invasive-MV (Figure 2B; see Figure E1). Baseline PaCO2 did not differ between the NIV and invasive-MV patients. However, although baseline PaCO2 in mild ARDS was higher in NIV compared with invasive-MV patients (48 ± 18 vs. 41 ± 10 mm Hg; P = 0.002), PaCO2 in severe ARDS was lower in NIV (43 ± 14 vs. 52 ± 18 mm Hg; P < 0.001) compared with invasive-MV. In contrast to invasive-MV patients, where PaCO2 increased, the PaCO2 in the NIV group did not change.
Patients with ARDS 3,022

Patients with ARDS after 2 days from AHRF onset 209 (6.9%)

Patients with ARDS within 2 days of AHRF onset 2,813 (83.1%)

Patients invasively ventilated 2,377 (84.5%)

Patients non-invasively ventilated on Day 1 and 2 436 (15.5%)

Severity at ARDS onset
- Mild 714 (24.3%)
- Moderate 1,106 (46.5%)
- Severe 557 (23.4%)

Severity at ARDS onset
- Mild 119 (27.3%)
- Moderate 222 (53.2%)
- Severe 85 (19.5%)

No limitation of care† 1,799 (75.7%)

Limitation of care† 578 (24.3%)

Failure‡ 131 (30.0%)

Non-failure‡ 218 (50.0%)

Limitation of care† 87 (20.0%)

Non-survivors§ 462 (25.7%)

Survivors§ 1,337 (74.3%)

Non-survivors§ 499 (86.3%)

Survivors§ 79 (13.7%)

Non-survivors§ 59 (45.4%)

Survivors§ 71 (54.6%)

Non-survivors§ 35 (16.1%)

Survivors§ 183 (83.9%)

Non-survivors§ 62 (71.3%)

Survivors§ 25 (28.7%)

Figure 1. Flowchart of the study population. *Seventy-five patients received noninvasive ventilation on Day 1 and invasive ventilation at Day 2. †Limitation of care before acute hypoxic respiratory failure (AHRF) onset or within 28 days. ‡Failure of noninvasive 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 nine patients: eight invasively ventilated and one noninvasively ventilated within 48 hours from AHRF onset. ARDS = acute respiratory distress syndrome.

NIV Failure versus Success

Among the 349 NIV patients without preintubation treatment limitations, 131 (37.5%) failed NIV (Table 3). A multivariate Cox model revealed that higher nonpulmonary SOFA score, lower PaCO2/FIO2, and the percentage increase of PaCO2 over the 2 days of treatment were independently associated with NIV failure within 28 days from AHRF onset (see Table E5).

Effect of Intubation on Physiologic Variables

Table E6 and Figure 2C show the comparison, for physiologic variables, between the last available recording of NIV and the first available recording during invasive-MV. After intubation, both PaO2/FIO2 (152 ± 68 vs. 182 ± 95 mm Hg; P < 0.001) and PaCO2 significantly increased. After initiation of invasive-MV, patients were managed with a higher PEEP and had lower respiratory rates, and received lower tidal and minute volumes compared with preintubation values.

Outcomes in NIV Patients

Crude ICU and hospital mortalities were not significantly different between the NIV and the invasive-MV patients (Table 2; see Figure E2).

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

In a multivariate Cox regression model adjusting for covariates significantly associated with outcome (see Table E7), NIV use was independently associated with increased ICU (but not hospital) mortality rate (hazard ratio, 1.446 [95% confidence interval, 1.159–1.805]). Furthermore, we matched 353 NIV patients with invasive-MV patients using propensity score (see Table E2). The two matched populations were homogeneous for demographic characteristics, comorbidities, and severity of organ failures (see 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 PaO2/FIO2 ratio less than 150, ICU mortality was 36.2% with NIV compared with 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 PaO2/FIO2 higher and lower than 150 mm Hg.

Table E8 shows the comparison between survivors and nonsurvivors at hospital discharge in NIV patients. Nonsurvivors were older, with a higher prevalence of immunosuppression or neoplastic disease, and had a higher nonpulmonary SOFA score. Moreover, nonsurvivors had, on the day of ARDS diagnosis, a lower PaO2/FIO2 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 PaO2/FIO2 ratio between Days 1 and 2, total respiratory rate, 

(P = 0.134) with greater ARDS severity (Table 1, Figure 2).
Table 1. Demographic and Clinic Characteristics of Study Population (Stratified by ARDS Severity and Ventilation) at Baseline (ARDS Onset)

<table>
<thead>
<tr>
<th></th>
<th>NIV</th>
<th>ARDS, Mild</th>
<th></th>
<th>NIV</th>
<th>ARDS, Moderate</th>
<th></th>
<th>NIV</th>
<th>ARDS, Severe</th>
<th></th>
<th>NIV</th>
<th>ARDS</th>
<th>P Value within NIV</th>
<th>P Value within Invasive-MV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>119</td>
<td>714</td>
<td>232</td>
<td>1,106</td>
<td>85</td>
<td>557</td>
<td>436</td>
<td>2,377</td>
<td></td>
<td>14.3</td>
<td>85.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>% within ARDS severity</td>
<td>14.3</td>
<td>85.7</td>
<td>17.3</td>
<td>82.7</td>
<td>13.2</td>
<td>86.8</td>
<td>15.0</td>
<td>84.50</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>58 (48.7)</td>
<td>439 (61.5)*</td>
<td>150 (64.7)</td>
<td>683 (61.8)</td>
<td>49 (57.6)</td>
<td>350 (62.8)</td>
<td>257 (58.9)</td>
<td>1,472 (61.9)</td>
<td>0.016</td>
<td>0.875</td>
<td>—</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yr, median (IQR)</td>
<td>71 (59 to 77)</td>
<td>64 (51 to 75)*</td>
<td>68 (56 to 79)</td>
<td>64 (52 to 74)*</td>
<td>64 (49 to 76)</td>
<td>58 (44 to 70)*</td>
<td>68 (54 to 78)</td>
<td>63 (50 to 73)*</td>
<td>0.110</td>
<td>&lt;0.001</td>
<td>0.478</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td><strong>Risk factors for ARDS, n (%)</strong></td>
<td>19 (16.0)</td>
<td>69 (9.7)*</td>
<td>30 (12.9)</td>
<td>85 (7.7)*</td>
<td>13 (15.3)</td>
<td>36 (6.5)*</td>
<td>62 (14.2)</td>
<td>190 (8.0)*</td>
<td>0.016</td>
<td>0.875</td>
<td>—</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td>15 (12.6)</td>
<td>180 (25.2)*</td>
<td>28 (12.1)</td>
<td>219 (19.8)*</td>
<td>5 (5.9)</td>
<td>81 (14.5)*</td>
<td>48 (11.0)</td>
<td>480 (20.2)*</td>
<td>0.016</td>
<td>0.875</td>
<td>—</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Parameters at day of ARDS onset, mean ± SD</strong></td>
<td>85 (71.4)</td>
<td>465 (65.1)</td>
<td>174 (75.0)</td>
<td>802 (72.5)</td>
<td>67 (78.8)</td>
<td>440 (79.0)</td>
<td>326 (74.8)</td>
<td>1,707 (71.8)</td>
<td>0.016</td>
<td>0.875</td>
<td>—</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| **Definition of abbreviations:** ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; IQR = interquartile range; MV = mechanical ventilation; NIV = noninvasive ventilation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; SOFA = Sequential Organ Failure Assessment.

*P < 0.05, comparison versus NIV group with same ARDS severity.
Table 2. Events Occurring during Follow-up in Study Population (Stratified by ARDS Severity and Ventilation)

<table>
<thead>
<tr>
<th>ARDS</th>
<th>NIV</th>
<th>Invasive-MV</th>
<th>NIV</th>
<th>Invasive-MV</th>
<th>NIV</th>
<th>Invasive-MV</th>
<th>NIV</th>
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<tr>
<td>N</td>
<td>119</td>
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<td>1,106</td>
<td>85</td>
<td>557</td>
<td>436</td>
<td>2,377</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clinical recognition of ARDS, n (%)</td>
<td>21 (17.6)</td>
<td>178 (24.9)</td>
<td>63 (27.2)</td>
<td>372 (33.6)</td>
<td>17 (20.0)</td>
<td>236 (42.4)</td>
<td>101 (23.2)</td>
<td>786 (33.1)</td>
<td>0.101</td>
<td>0.05, comparison versus NIV group with same ARDS severity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At study entry</td>
<td>26 (21.8)</td>
<td>191 (26.8)</td>
<td>64 (27.8)</td>
<td>351 (31.7)</td>
<td>34 (40.0)</td>
<td>221 (39.7)</td>
<td>124 (28.4)</td>
<td>763 (32.1)</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At any time</td>
<td>27 (22.7)</td>
<td>171 (23.9)</td>
<td>68 (29.3)</td>
<td>272 (24.6)</td>
<td>29 (34.1)</td>
<td>135 (24.2)</td>
<td>124 (28.4)</td>
<td>763 (32.1)</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with treatment limitation, n (%)</td>
<td>6 (3–10)</td>
<td>8 (4–16)*</td>
<td>8 (4–13.5)</td>
<td>10 (5–19)*</td>
<td>7 (4–12)</td>
<td>10 (4–18)*</td>
<td>7 (4–12)</td>
<td>9 (5–18)*</td>
<td>0.032</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay (from ARDS onset in ICU, median [IQR])</td>
<td>5 (3–8)</td>
<td>9 (5–18)*</td>
<td>8 (4–13)</td>
<td>11 (6–20)*</td>
<td>7 (4–13)</td>
<td>13 (7–23)*</td>
<td>7 (4–12)</td>
<td>11 (6–20)*</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
<td>26 (21.8)</td>
<td>191 (26.8)</td>
<td>64 (27.8)</td>
<td>351 (31.7)</td>
<td>34 (40.0)</td>
<td>221 (39.7)</td>
<td>124 (28.4)</td>
<td>763 (32.1)</td>
<td>0.017</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>36 (30.3)</td>
<td>249 (34.9)</td>
<td>83 (35.8)</td>
<td>446 (40.3)</td>
<td>37 (43.5)</td>
<td>257 (46.4)</td>
<td>156 (35.8)</td>
<td>952 (40.1)</td>
<td>0.130</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation; NIV = noninvasive ventilation.

and nonpulmonary SOFA score were each independently associated with risk of in-hospital death (see Table E9).

Discussion

Of the 2,813 patients that were diagnosed with ARDS criteria within 2 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 nonpulmonary SOFA scores compared with invasive-MV patients. NIV failure occurred in 134 (36.7%) patients, necessitating change to invasive-MV. Classification of ARDS severity based on PaO2/FIO2 ratio categories was indicative of a higher intensity of treatment and worse outcome, as is seen in patients with ARDS managed with invasive-MV. Of interest, NIV applications rates were similar across the ARDS severity categories. Although 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 PaO2/FIO2 ratio <150 mm Hg).

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). Although 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 was not associated with a greater use of NIV in our patients. NIV use seemed associated with other factors, such as preexisting chronic obstructive pulmonary disease, congestive heart failure, and chronic renal failure.

Although 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. Although some authors used the PaO2/FIO2 severity bands also for NIV patients (27), others considered that NIV patients with PaO2/FIO2 less than 200 mm Hg could not be classified according to Berlin definition and these patients were excluded from analysis (25). Our results support the use of PaO2/FIO2 bands to classify NIV patients as 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 underrecognition 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 cm H2O) in all the ARDS categories and a predominant use of FiO2 to correct hypoxemia. This finding is clinically relevant, because application of higher levels of PEEP has been associated with improved outcomes in patients with moderate to severe ARDS (28). Although the use of lower PEEP may be seen as inherent to the use of NIV, because of 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. These data should be interpreted cautiously, because they were 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 $P_{ACO_2}$, 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 $P_{ACO_2}/F_{IO_2}$ ratios, as well as decreases in tidal volume and respiratory rate leading to an approximately 30% drop of minute ventilation, resulting in an increased $P_{ACO_2}$. Ventilator settings in patients transitioned to invasive-MV were closer to protective settings than those seen before 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. Although 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.

### Table 3. Demographic and Clinical Characteristics of ARDS NIV Patients at Baseline (ARDS Onset)

<table>
<thead>
<tr>
<th></th>
<th>ARDS-NIV (without Treatment Limitations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>All</td>
<td>218 (62.5)</td>
</tr>
<tr>
<td>Mild ARDS</td>
<td>77 (77.8)</td>
</tr>
<tr>
<td>Moderate ARDS</td>
<td>105 (57.7)</td>
</tr>
<tr>
<td>Severe ARDS</td>
<td>36 (52.9)</td>
</tr>
</tbody>
</table>
| Male, n (%)           | 129 (59.2) | 80 (61.1) | 0.727
| Age, median (IQR)     | 66.5 (52 to 78) | 63.0 (53 to 74) | 0.081
| ICU mortality, n (%)  | <0.001  |         |
| All                   | 23 (10.6) | 56 (42.7) |
| Patients with $P_{ACO_2}/F_{IO_2}$ ratio <150 mm Hg | 13 (14.6) | 36 (45.9) | <0.001
| Patients with $P_{ACO_2}/F_{IO_2}$ ratio >150 mm Hg | 10 (7.8) | 20 (39.2) | <0.001
| Hospital mortality, n (%) | 35 (16.1) | 59 (45.4) | <0.001
| 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) | <0.001
| Risk factors for ARDS, n (%) | 0.211  |         |
| None                  |        | 33 (15.1) | 12 (8.2) |
| Nonpulmonary          |        | 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
| Neoplasm or immunosuppression | 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 |         |         |
| $P_{ACO_2}$, mm Hg    | 88.6 ± 31.6 | 83.1 ± 30.5 | 0.097
| $F_{IO_2}$            | 0.58 ± 0.22 | 0.63 ± 0.21 | 0.007
| $P_{ACO_2}/F_{IO_2}$ ratio, mm Hg | 171 ± 65 | 145 ± 60 | <0.001
| pH                    | 7.38 ± 0.09 | 7.38 ± 0.09 | 0.967
| $P_{ACO_2}$, mm Hg    | 48 ± 17 | 44 ± 17 | 0.009
| Base excess, mmol/L   | 1.91 ± 6.73 | 9.02 ± 6.83 | 0.002
| PEEP, cm H$_2$O       | 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
| Nonpulmonary 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

Definition of abbreviations: AHRF = acute hypoxemic respiratory failure; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; ICU = intensive care unit; IQR = interquartile range; NIV = noninvasive ventilation; NYHA = New York Heart Association; PBW = predicted body weight; PEEP = positive end-expiratory pressure; SOFA = Sequential Organ Failure Assessment

Population was stratified according to the NIV treatment outcome (success-failure) occurring in ICU during 28 days from AHRF onset. Patients with preintubation treatment limitations were excluded from this analysis. Vital status was evaluated at ICU/hospital discharge. Patients who were still in ICU/hospital were censored on Day 90 from AHRF onset.
Figure 2. Differences in physiologic variables for patients treated with invasive and noninvasive ventilation. (A) Although for mild acute respiratory distress syndrome (ARDS) $\text{PaCO}_2$ was significantly higher in patients managed with noninvasive ventilation, the opposite was true for severe ARDS, for which $\text{PaCO}_2$ was lower in patients treated with noninvasive ventilation. *$P < 0.05$, comparison between invasive mechanical ventilation (MV) and noninvasive ventilation (NIV) group. (B) Although $\text{PaO}_2$/FiO$_2$ was not different over the first 2 days in patients managed with noninvasive 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, and 18, from Day 1 to 28). *$P < 0.05$, comparison between invasive-MV and NIV group. (C) Relative differences (increase or decrease) of selected physiologic variables between the last day of noninvasive ventilation and the first day of invasive ventilation, in the subset of patients with noninvasive ventilation failure. †$P < 0.05$. On each box, the bottom line denotes the first quartile value, the middle line denotes the median value, and the top line represents the third quartile value. The whiskers are drawn out and the extreme values are calculated as: lower fence = first quartile $-1.5 \times$ interquartile range; upper fence = third quartile $+1.5 \times$ interquartile range. PEEP = positive end-expiratory pressure.
Table 4. Effect of Treatment and Clinical Parameters at ARDS Onset for Invasive-MV and NIV Patients in the Propensity Score Matched Sample

<table>
<thead>
<tr>
<th></th>
<th>Invasive-MV Patients (n = 333)</th>
<th>NIV Patients (n = 333)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS severity at onset, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>100 (28.33)</td>
<td>101 (28.61)</td>
<td>1.000</td>
</tr>
<tr>
<td>Moderate</td>
<td>184 (52.12)</td>
<td>165 (46.74)</td>
<td>0.195</td>
</tr>
<tr>
<td>Severe</td>
<td>69 (19.55)</td>
<td>87 (24.65)</td>
<td>0.127</td>
</tr>
<tr>
<td>Patients with PaO2/FiO2 ratio &lt;150 mm Hg at ARDS onset, n (%)</td>
<td>174 (49.29)</td>
<td>174 (49.29)</td>
<td>1.000</td>
</tr>
<tr>
<td>Parameters at ARDS onset, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35 ± 0.11</td>
<td>7.38 ± 0.09</td>
<td>0.001</td>
</tr>
<tr>
<td>FiO2</td>
<td>0.66 ± 0.24</td>
<td>0.60 ± 0.22</td>
<td>0.001</td>
</tr>
<tr>
<td>SPo2, %</td>
<td>94.53 ± 5.51</td>
<td>94.99 ± 3.85</td>
<td>0.660</td>
</tr>
<tr>
<td>Total respiratory rate, breaths/min</td>
<td>20.66 ± 6.46</td>
<td>25.63 ± 7.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PEEP, cm H2O</td>
<td>8.09 ± 3.1</td>
<td>7.02 ± 1.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak inspiratory pressure, cm H2O</td>
<td>26.77 ± 7.66</td>
<td>17.43 ± 7.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>94.64 ± 40.32</td>
<td>87.98 ± 32.55</td>
<td>0.031</td>
</tr>
<tr>
<td>PaCO2/FiO2, mm Hg</td>
<td>46.5 ± 14.41</td>
<td>45.8 ± 17.56</td>
<td>0.328</td>
</tr>
<tr>
<td>PaO2/FiO2, mm Hg</td>
<td>157.62 ± 65.58</td>
<td>160.94 ± 64.29</td>
<td>0.492</td>
</tr>
<tr>
<td>Tidal volume, ml/kg PBW</td>
<td>7.53 ± 1.75</td>
<td>8.46 ± 2.77</td>
<td>0.001</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>9.31 ± 2.90</td>
<td>13.26 ± 5.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Base excess, mmol/L</td>
<td>−0.74 ± 5.93</td>
<td>0.60 ± 6.55</td>
<td>0.002</td>
</tr>
<tr>
<td>HCO3, mmol/L</td>
<td>24.39 ± 5.65</td>
<td>25.4 ± 6.95</td>
<td>0.086</td>
</tr>
<tr>
<td>Nonpulmonary SOFA adjusted</td>
<td>3.26 ± 2.82</td>
<td>3.19 ± 2.84</td>
<td>0.423</td>
</tr>
<tr>
<td>Δ (%)* PaO2/FiO2 ratio</td>
<td>−0.3 ± 29.86</td>
<td>3.37 ± 25.92</td>
<td>0.025</td>
</tr>
<tr>
<td>Use of vasopressors, n (%)</td>
<td>80 (24.32)</td>
<td>49 (15.03)</td>
<td>0.005</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, d, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>8 (4 to 15)</td>
<td>9 (5 to 13)</td>
<td>0.293</td>
</tr>
<tr>
<td>ICU survivors</td>
<td>7 (4 to 14)</td>
<td>10 (7 to 13)</td>
<td>0.744</td>
</tr>
<tr>
<td>Length of ICU stay, d, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>10 (6 to 18)</td>
<td>7 (4 to 12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU survivors</td>
<td>10 (6 to 19)</td>
<td>7 (4 to 12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause in-ICU mortality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>92 (26.06)</td>
<td>99 (28.05)</td>
<td>0.608</td>
</tr>
<tr>
<td>Matched patients with PaO2/FiO2 ratio &lt;150 mm Hg</td>
<td>43 (24.71)</td>
<td>63 (36.21)</td>
<td>0.033</td>
</tr>
<tr>
<td>All-cause in-hospital mortality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>115 (32.76)</td>
<td>117 (33.24)</td>
<td>0.871</td>
</tr>
<tr>
<td>Matched patients with PaO2/FiO2 ratio &lt;150 mm Hg</td>
<td>55 (31.61)</td>
<td>66 (38.15)</td>
<td>0.224</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHRF = acute hypoxemic respiratory failure; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation; NIV = noninvasive ventilation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; SOFA = Sequential Organ Failure Assessment.

Independently associated with NIV failure included higher nonpulmonary SOFA score and higher respiratory rate. Evaluating the patient’s response to NIV is also important, with the percentage increase of PaCO2 over the first 2 days of treatment also associated with NIV failure. A decline of PaO2/FiO2 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 seems to be associated with increased ICU mortality. After adjusting for potential confounders, a patient treated with NIV at ARDS onset seemed to have a 30% increased risk of dying in ICU compared with a similar patient treated with invasive-MV. This result should be interpreted cautiously, because it was not confirmed for the hospital mortality and is partly discrepant with the propensity matched analysis (affected by a lower power because of the smaller number of patients included). Finally, although the model did not highlight any effect of the interaction between NIV and PaO2/FiO2 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 PaO2/FiO2 less than 150 mm Hg. In this respect our data are consistent with previous reports showing an increase in NIV failure rates, in patients with a PaO2/FiO2 ratio less than or equal to 150 mm Hg (29).

The LUNG SAFE study represents one of the largest prospective datasets of patients with ARDS treated with NIV. Nonetheless, it does have limitations. To limit the burden...
on investigators, data were collected as often as once per day and we did not collect hours of duration of NIV treatment, a factor previously thought to be important in NIV success and 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, because 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 Acute Physiology and Chronic Health Evaluation and Simplified Acute Physiology Score, but relied on the SOFA score to characterize the nonpulmonary 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 because of preexisting medical conditions (as suggested, for example, by older age of the NIV patients).

In conclusion, in a large cohort of patients with ARDS, 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 patients with ARDS 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 with a PaO2/FIO2 lower than 150 mm Hg. These findings raise further concerns regarding NIV use in this patient group.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

as a first-line intervention for acute respiratory distress syndrome. 


