Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome

Insights from the LUNG SAFE Study

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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 Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_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 (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 invasively ventilated patients with a Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} lower than 150 mm Hg.

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

Keywords: noninvasive ventilation; acute respiratory distress syndrome

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At a Glance Commentary

Scientific Knowledge on the Subject: Noninvasive 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 patient 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% of patients with ARDS, irrespective of the severity of hypoxemia. Classification of ARDS severity in patients with NIV based on Pa_{O_2}/FI_{O_2} ratio had management and prognostic significance. Use of NIV, in comparison with invasive ventilation, has important implications for patient management. Although 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 intensive care unit outcome than invasive mechanical ventilation in moderate to severe 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 Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} 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 fulfillment of diagnostic criteria for ARDS. Secondary objectives included determining the utility of the Pa_{O_2}/FI_{O_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

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 Pa_{O_2}/FI_{O_2} 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 H_2O, and new radiologic pulmonary parenchymal abnormalities. For

*A complete list of LUNG SAFE national coordinators, site investigators, and national societies endorsing the study may be found in the online supplement.

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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.

Multivariate Cox proportional hazards 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 (*see* Table E2). 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 (SAS Institute, Cary, NC) and R (The R Foundation for Statistical Computing, Vienna, Austria) 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 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 Pa_{O_2}/FI_{O_2} bands in the Berlin definition was associated with a step-wise increase in positive end-expiratory pressure (PEEP) and FI_{O_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 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, Pa_{O_2}/FI_{O_2} ratio was not different between the NIV and invasive-MV patients (Table 1). Pa_{O_2}/FI_{O_2} ratios improved more rapidly in the patients treated with invasive-MV (Figure 2B; *see* Figure E1). Baseline Pa_{CO_2} did not differ between the NIV and invasive-MV patients. However, although baseline Pa_{CO_2} in mild ARDS was higher in NIV compared with invasive-MV patients (48 ± 18 vs. 41 ± 10 mm Hg; $P = 0.002$), Pa_{CO_2} 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 Pa_{CO_2} increased, the Pa_{CO_2} in the NIV group did not change

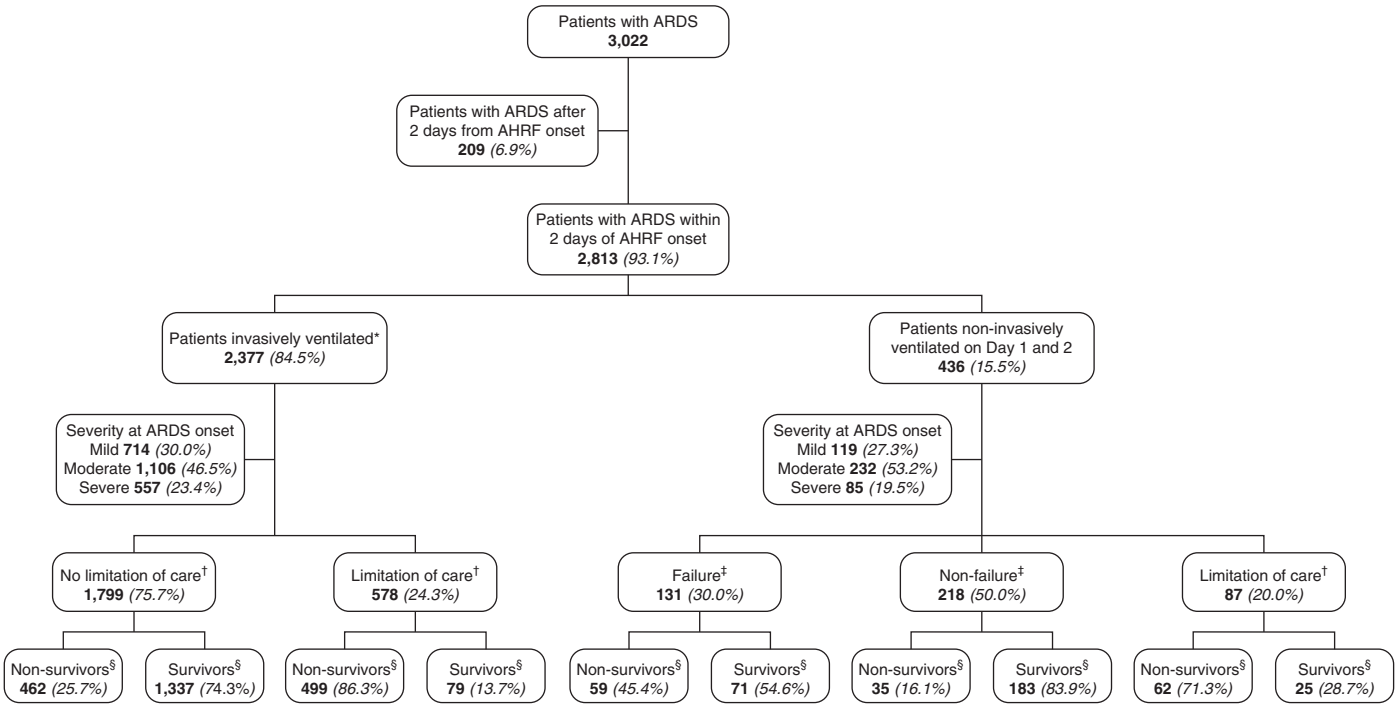

Figure 1. Flowchart of the study population. *Seventy-five patients received noninvasive ventilation on Day 1 and invasive ventilation at Day 2. †Limitation of care before acute hypoxemic respiratory failure (AHRF) onset or within 28 days. ‡Failure of noninvasive ventilation was evaluated within 28 days 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.

($P = 0.134$) with greater ARDS severity (Table 1, Figure 2).

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 Pa_{O_2}/FI_{O_2}, and the percentage increase of Pa_{CO_2} over the first 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 Pa_{O_2}/FI_{O_2} (152 ± 68 vs. 182 ± 95 mm Hg; $P < 0.001$) and Pa_{CO_2} 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 Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_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 Pa_{O_2}/FI_{O_2} ratio between Days 1 and 2, total respiratory rate,

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, yr, median (IQR)	71 (59 to 77)	64 (51 to 75)*	68 (56 to 79)	64 (52 to 74)*	64 (49 to 76)	58 (44 to 70)*	68 (54 to 78)	63 (50 to 73)*	0.110	<0.001
Risk factors for ARDS, n (%)									0.478	<0.001
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)*		
Nonpulmonary	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										
Pa_{O_2}, mm Hg	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*	<0.001	<0.001
FI_{O_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*	<0.001	<0.001
Pa_{O_2}/FI_{O_2}, mm Hg	243 ± 29	246 ± 28	146 ± 29	149 ± 28	79 ± 17	75 ± 17	160 ± 63	161 ± 68	<0.001	<0.001
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	<0.001
Pa_{CO_2}, mm Hg	48 ± 18	41 ± 10*	47 ± 18	46 ± 15	43 ± 14	52 ± 18*	46 ± 17	46 ± 15	0.134	<0.001
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, cm H_2O	7 ± 2	7 ± 3	7 ± 2	8 ± 3*	7 ± 2	10 ± 4*	7 ± 2	8 ± 3*	0.042	<0.001
Total respiratory rate, breaths/min	24 ± 7	19 ± 6*	27 ± 7	21 ± 6*	27 ± 6	23 ± 14*	26 ± 7	21 ± 9*	<0.001	<0.001
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	<0.001
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
Nonpulmonary SOFA score adjusted	3 ± 3	7 ± 4*	3 ± 3	7 ± 4*	3 ± 3	7 ± 4*	3 ± 3	7 ± 4*	0.548	0.370
Use of vasopressors, n (%)	16 (14.4)	342 (51.8)*	37 (17.6)	575 (55.2)*	9 (11.8)	325 (61.2)*	62 (15.6)	1,242 (55.6)*	0.453	0.005
Use of CPAP, n (%)	35 (29.4)	—	65 (28.0)	—	23 (27.0)	—	123 (28.2)	—	0.930	—

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)

	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	—	—
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	<0.001
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	<0.001
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 (d), 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	<0.001
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	<0.001
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	<0.001

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation; NIV = noninvasive ventilation.
Vital status was evaluated at ICU/hospital discharge. Patients who were still in ICU/hospital were censored on Day 90 from acute hypoxemic respiratory failure onset.
*$P < 0.05$, comparison versus NIV group with same ARDS severity.

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 (30.7%) patients, necessitating change to invasive-MV. Classification of ARDS severity based on Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} severity bands also for NIV patients (27), others considered that NIV patients with Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} 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 H_2O) in all the ARDS categories and a predominant use of FI_{O_2} 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

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

	ARDS-NIV (without Treatment Limitations)		
	Success	**Failure**	***P* Value**
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 to 78)	63.0 (53 to 74)	0.081
ICU mortality, n (%)			
All	23 (10.6)	56 (42.7)	<0.001
Patients with $Pa_{O_2}/F_{I_{O_2}}$ ratio <150 mm Hg	13 (14.6)	36 (45.0)	<0.001
Patients with $Pa_{O_2}/F_{I_{O_2}}$ 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 (9.2)	
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			
Pa_{O_2}, mm Hg	88.6 ± 31.6	83.1 ± 30.5	0.097
$F_{I_{O_2}}$	0.58 ± 0.22	0.63 ± 0.21	0.007
$Pa_{O_2}/F_{I_{O_2}}$ ratio, mm Hg	171 ± 65	145 ± 60	<0.001
pH	7.38 ± 0.09	7.38 ± 0.09	0.967
Pa_{CO_2}, mm Hg	48 ± 17	44 ± 17	0.009
Base excess, mmol/L	1.91 ± 6.73	−0.02 ± 6.83	0.002
PEEP, cm H_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
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.

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 Pa_{CO_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 $Pa_{O_2}/F_{I_{O_2}}$ ratios, as well as decreases in tidal volume and respiratory rate leading to an approximately 30% drop of minute ventilation, resulting in an increased Pa_{CO_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. Factors

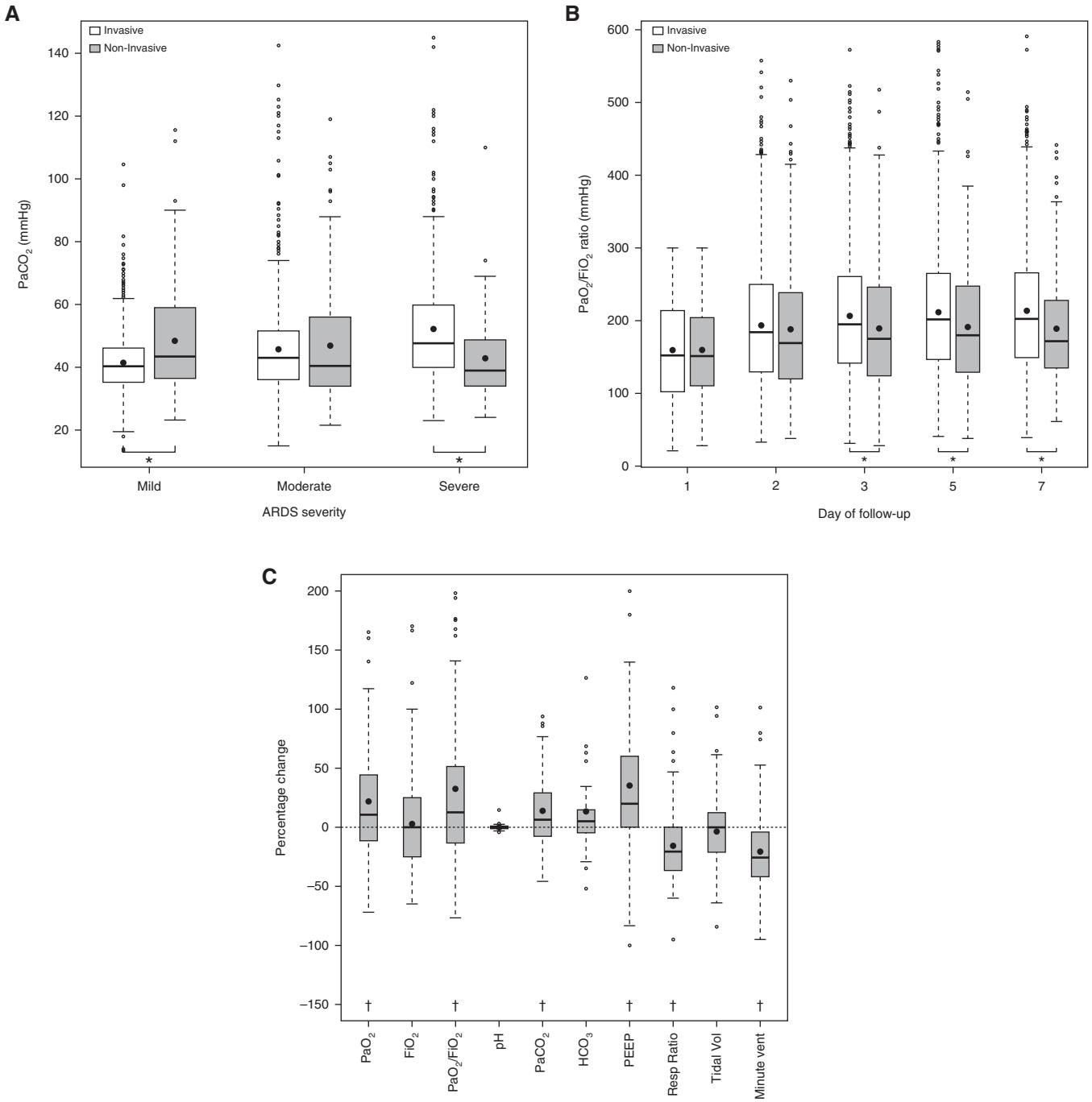

Figure 2. Differences in physiologic variables for patients treated with invasive and noninvasive ventilation. (*A*) Although for mild acute respiratory distress syndrome (ARDS) Pa_{CO_2} was significantly higher in patients managed with noninvasive ventilation, the opposite was true for severe ARDS, for which Pa_{CO_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 $Pa_{O_2}/F_{I_{O_2}}$ 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 of 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 × interquartile range; upper fence = third quartile + 1.5 × 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

	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 Pa_{O_2}/FI_{O_2} ratio <150 mm Hg at ARDS onset, n (%)	174 (49.29)	174 (49.29)	1.000
Parameters at ARDS onset, mean ± SD			
pH	7.35 ± 0.11	7.38 ± 0.09	0.001
FI_{O_2}	0.66 ± 0.24	0.60 ± 0.22	0.001
SP_{O2}, %	94.53 ± 5.51	94.99 ± 3.85	0.660
Total respiratory rate, breaths/min	20.66 ± 6.46	25.63 ± 7.01	<0.001
PEEP, cm H_2O	8.09 ± 3.1	7.02 ± 1.95	<0.001
Peak inspiratory pressure, cm H_2O	26.77 ± 7.66	17.43 ± 7.22	<0.001
Pa_{O_2}, mm Hg	94.64 ± 40.32	87.96 ± 32.55	0.031
Pa_{CO_2}, mm Hg	46.5 ± 14.41	45.8 ± 17.36	0.320
Pa_{O_2}/FI_{O_2}, mm Hg	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	<0.001
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
Nonpulmonary SOFA adjusted	3.26 ± 2.82	3.19 ± 2.84	0.423
Δ (%)* Pa_{O_2}/FI_{O_2} ratio	36.31 ± 76.76	28.17 ± 76.77	0.063
Δ (%)* Pa_{CO_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, d, median (IQR)			
All patients	8 (4 to 15)	9 (5 to 13)	0.293
ICU survivors	7 (4 to 14)	10 (7 to 13)	0.744
Length of ICU stay, d, median (IQR)			
All patients	10 (6 to 18)	7 (4 to 12)	<0.001
ICU survivors	10 (6 to 19)	7 (4 to 12)	<0.001
All-cause in-ICU mortality, n (%)			
All patients	92 (26.06)	99 (28.05)	0.608
Matched patients with Pa_{O_2}/FI_{O_2} ratio <150 mm Hg	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 Pa_{O_2}/FI_{O_2} ratio <150 mm Hg	55 (31.61)	66 (38.15)	0.224

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.

Statistical tests accounted for the matched nature of the sample (paired Student's *t* test or Wilcoxon signed rank test for continuous variables, McNemar test for dichotomous variables). For three patients (two invasive-MV and one NIV) vital status at hospital discharge were missing. Vital status was evaluated at ICU/hospital discharge. Patients who were still in ICU/hospital were censored on Day 90 from AHRF onset.

*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.

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 Pa_{CO_2} over the first 2 days of treatment also associated with NIV failure. A decline of Pa_{O_2}/FI_{O_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 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 Pa_{O_2}/FI_{O_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 Pa_{O_2}/FI_{O_2} 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 Pa_{O_2}/FI_{O_2} 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

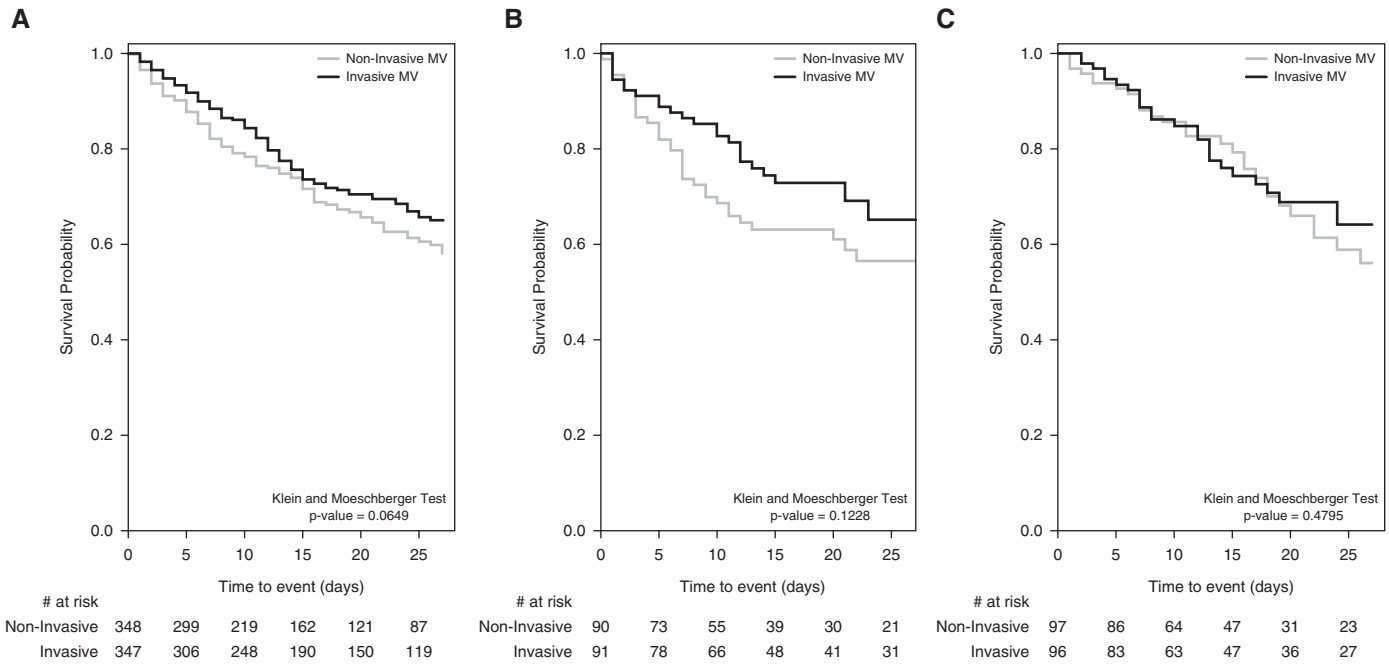

Figure 3. Kaplan-Meier survival curves in the propensity score matched samples of patients managed with noninvasive and invasive ventilation. (*A–C*) Survival over time in the entire sample (n = 706) (*A*), in matched sample with Pa_{O_2}/FI_{O_2} ratio <150 mm Hg (n = 184) (*B*), and in matched sample for Pa_{O_2}/FI_{O_2} ratio ⩾150 mm Hg (n = 194) (*C*). Vital status was evaluated at hospital discharge. Patients were censored on Day 28 from acute hypoxemic respiratory failure (AHRF) onset. Patients discharged alive from hospital before the Day 28 from AHRF onset were considered alive at Day 28. MV = mechanical ventilation.

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 Pa_{O_2}/FI_{O_2} 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.

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