ANESTHESIOLOGY

Outcomes of Patients Presenting with Mild Acute Respiratory Distress Syndrome

Insights from the LUNG SAFE Study

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ABSTRACT

Background: Patients with initial mild acute respiratory distress syndrome are often underrecognized and mistakenly considered to have low disease severity and favorable outcomes. They represent a relatively poorly characterized population that was only classified as having acute respiratory distress syndrome in the most recent definition. Our primary objective was to describe the natural course and the factors associated with worsening and mortality in this population.

Methods: This study analyzed patients from the international prospective Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) who had initial mild acute respiratory distress syndrome in the first day of inclusion. This study defined three groups based on the evolution of severity in the first week: "worsening" if moderate or severe acute respiratory distress syndrome criteria were met, "persisting" if mild acute respiratory distress syndrome criteria were the most severe category, and "improving" if patients did not fulfill acute respiratory distress syndrome criteria any more from day 2.

Results: Among 580 patients with initial mild acute respiratory distress syndrome, 18% (103 of 580) continuously improved, 36% (210 of 580) had persisting mild acute respiratory distress syndrome, and 46% (267 of 580) worsened in the first week after acute respiratory distress syndrome onset. Global in-hospital mortality was 30% (172 of 576; specifically 10% [10 of 101], 30% [63 of 210], and 37% [99 of 265] for patients with improving, persisting, and worsening acute respiratory distress syndrome, respectively), and the median (interquartile range) duration of mechanical ventilation was 7 (4, 14) days (specifically 3 [2, 5], 7 [4, 14], and 11 [6, 18] days for patients with improving, persisting, and worsening acute respiratory distress syndrome, respectively). Admissions for trauma or pneumonia, higher nonpulmonary sequential organ failure assessment score, lower partial pressure of alveolar oxygen/fraction of inspired oxygen, and higher peak inspiratory pressure were independently associated with worsening.

Conclusions: Most patients with initial mild acute respiratory distress syndrome continue to fulfill acute respiratory distress syndrome criteria in the first week, and nearly half worsen in severity. Their mortality is high, particularly in patients with worsening acute respiratory distress syndrome, emphasizing the need for close attention to this patient population.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hospital mortality in acute respiratory distress syndrome is approximately 40%, but mortality and trajectory in "mild" acute respiratory distress syndrome (classified only since 2012) are unknown, and many cases are not detected

What This Article Tells Us That Is New

- Approximately 80% of cases of mild acute respiratory distress syndrome persist or worsen in the first week; in all cases, the mortality is substantial (30%) and is higher (37%) in those in whom the acute respiratory distress syndrome progresses

The Berlin definition of acute respiratory distress syndrome (ARDS) categorizes patients with partial pressure of arterial blood oxygen content to inspired fraction of oxygen (Pa_{O_2}/fraction of inspired oxygen [$F_{I_{O_2}}$]) ranging from 200 to 300 mmHg as "mild ARDS."[1] In the preceding American European Consensus Conference, this population was defined as having "non-ARDS acute lung injury."[2] Some clinicians continue to overlook these less severely hypoxemic patients and instead pay closer attention to patients they consider to have "actual" ARDS (*i.e.*, moderate and severe ARDS groups). This group has not been included in some recent studies recruiting patients with ARDS.[3–6] Patients with mild ARDS have better unadjusted outcomes than patients with more severe hypoxemia in terms of ventilator-free days, lengths of stay in the intensive care unit and in the hospital, and mortality.[7–11] Nevertheless, intensive care unit and hospital mortality of this group of patient remains as high as 40%,[7,11–13] emphasizing the need to better understand this patient cohort.

To date, the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) is the largest prospective study having collected data on patients with ARDS according to the Berlin definition.[7]

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Almost one third of the 2,377 patients fulfilling the criteria for ARDS within 48 h of respiratory failure initially had mild ARDS at first assessment. Recent research showed different subphenotypes of patients with ARDS had distinct presentations and outcomes,[4,14] and autopsy studies showed that patients with mild ARDS displayed different histologic features with a lower proportion of diffuse alveolar damage.[15,16]

We hypothesized that patients presenting with mild ARDS constitute a heterogeneous group with diverse evolutions, and that in this group, the evolution in the first week after ARDS onset would be associated with patient outcome. Our primary objective was to characterize patients with initial mild ARDS and to describe their management, their evolution over the first week of critical illness, and their outcomes. Secondary objectives included identifying factors associated with progression to a more severe ARDS category, as well as factors associated with hospital mortality.

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue. This article is featured in "This Month in Anesthesiology," page 5A. Corresponding article on page 190. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version. Part of the work presented in this article has been presented at the American Thoracic Society meeting in Washington, D.C., May 23, 2017. M.J.S. and A.A. contributed equally to this article.

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Materials and Methods

Study Design

LUNG SAFE (ClinicalTrials.gov identifier NCT02010073) was an international multicenter prospective observational study performed in 2014 that recruited nearly 13,000 patients from 459 intensive care units from 50 different countries. A total of 4,499 patients had acute respiratory hypoxemic failure defined by a $Pa_{O_2}/F_{I_{O_2}}$ of 300 mmHg or less, new pulmonary infiltrates on chest imaging, and ventilator support with a positive end-expiratory pressure (PEEP) of 5 cm H_2O or more. Among them, 3,022 patients presented the Berlin criteria for ARDS during their intensive care unit stay. The present study was designed after LUNG SAFE data collection, but the analysis and the different groups were planned before starting the data analyzing. The detailed methods and design of LUNG SAFE have previously been described,[7] and further details are available in the Supplemental Digital Content (http://links.lww.com/ALN/B814). Some of the results of this study have been previously reported in the form of abstracts.[17]

Participants

We included intubated patients with mild ARDS on the first day they fulfilled ARDS criteria and within the first 2 days of fulfilling criteria for acute respiratory hypoxemic failure. Patients initially managed with noninvasive ventilation and not intubated in the first 2 days were excluded. We excluded patients based on the following criteria: (1) patients transferred to a participating intensive care unit more than 2 days after being admitted in another intensive care unit; (2) patients not present in the participating intensive care unit the day after meeting criteria for mild ARDS; (3) patients with a decision to limit life-sustaining treatment in the first 2 days; and (4) patients treated with extracorporeal membrane oxygenation in the first 2 days of ARDS.

Definitions

On days 2, 3, 5, and 7 after the patient fulfilled criteria for mild ARDS, we assessed $Pa_{O_2}/F_{I_{O_2}}$ and patients' ventilatory interface to define the following variables:

- Improving: the worst $Pa_{O_2}/F_{I_{O_2}}$ available on days 2, 3, 5, and 7 was more than 300 mmHg
- Persisting: the worst $Pa_{O_2}/F_{I_{O_2}}$ available on days 2, 3, 5, and 7 was more than 200 mmHg but 300 mmHg at most
- Worsening: the worst $Pa_{O_2}/F_{I_{O_2}}$ available on days 2, 3, 5, and 7 was 200 mmHg at most

To determine the factors associated with worsening oxygenation in the first week after mild ARDS onset, we also dichotomized patients into "worsening in the first week" *versus* all other patients (*i.e.*, combination of the persisting and improving groups). When items for sequential organ failure assessment score calculations were missing, the missing values were omitted, and the denominator was adjusted accordingly.

Statistical Analysis

Continuous variables are reported as means ± SD or median (first, third quartiles), and categorical variables as count and proportion. Normality of the data distribution was visually assessed by means of histograms. Comparisons of proportions were made using chi-square and Fisher exact tests. Continuous variables were compared using Student's *t* tests or Wilcoxon rank sum test when two groups were compared; using paired Student's *t* test or paired Wilcoxon rank sum test when variables were compared at two time points in the same group; and one-way ANOVA or Kruskal–Wallis tests when more than two groups were compared, as appropriate. Tukey's range tests were then used to compare all possible pairs of means within the three groups.

We performed bivariate analyses to identify factors potentially associated with the worsening group and with hospital mortality. We assumed that patients discharged alive from hospital before 90 days were alive on day 90. To determine the association of statistically significant variables with the outcomes of interest while controlling for confounders, covariates found to be associated with the dependent variable (worsening group or hospital mortality) in the bivariate analysis with a *P* value less than or equal to 0.20 were entered in stepwise (forward and backward) multivariable logistic regression analyses with significance α levels of 0.05 or less for retention. Multicollinearity was assessed calculating a variance inflation factor of each variable and ruled out if the variance inflation factor was lower than 4. The results are shown as odds ratios with 95% CI, and models' performance was assessed using the Hosmer–Lemeshow goodness-of-fit test statistic. We computed Kaplan–Meier analysis to estimate the likelihood of hospital mortality within 90 days of onset of ARDS. To check the validity of the logistic regression to determine factors associated with hospital mortality, a Cox proportional hazard model and a time-varying Cox model (taking into account the subjects' variability over time) were performed as sensitivity analyses.

No statistical power calculation was conducted before the study, and sample size was based on available data. For all numerical variables, outliers were assessed and corrected by contacting site investigators if needed. The remaining outliers were plausible values that were kept in the analysis. No assumptions were made for missing data, and we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[18] Statistical analyses were done with R (version 3.5.1, http://cran.r-project.org, accessed July 2018). All *P* values were two-sided, and values less than 0.05 were deemed statistically significant. The study protocol and case-report form, as well as additional methodologic information, are in the Supplemental Digital Content (http://links.lww.com/ALN/B814).

Results

Patient Characteristics

The Berlin definition of ARDS at day 1 or 2 of acute respiratory hypoxemic failure was fulfilled by 2,377 of the 12,906 patients enrolled in the LUNG SAFE study: 714 had mild ARDS, 1,106 had moderate ARDS, and 557 had severe ARDS. Of the 714 patients with mild ARDS, 693 were still present in the intensive care unit on the day after fulfilling ARDS criteria, and 601 did not have any of the prespecified exclusion criteria (fig. 1). Characteristics and outcomes of patients discharged from the participating intensive care unit before day 2 are presented in table 1 in the Supplemental Digital Content (http://links.lww.com/ALN/B814). Because of missing data, 21 additional patients could not be classified. Finally, a total of 580 patients were included in the analyses, and their main characteristics, ventilator management, and outcomes are presented in table 1 and in table 2 in the Supplemental Digital Content (http://links.lww.com/ALN/B814). Their mean Pao_2/Fio_2 at ARDS onset was 246 ± 28 mmHg, and 92% (529 of 577) were still intubated the day after fulfilling mild ARDS. Half of them were recognized by clinicians as having ARDS. Their median (interquartile range) lengths of stay in the intensive care unit and in the hospital were, respectively, 11 (6, 19) and 19 (11, 37) days, whereas hospital mortality was 30% (172 of 576).

Comparison According to the Evolution in the First Week

Based on the worst evolution category in the first 7 days after the onset of ARDS, 18% (103 of 580) showed only improvement, 36% (210 of 580) remained stable, and 46% (267 of 580) worsened at least 1 day in the first 7 days after mild ARDS onset (table 1; table 2 in the Supplemental Digital Content, http://links.lww.com/ALN/B814). The rate of pneumonia differed among the three groups ($P = 0.008$), being highest in patients from the worsening group compared to each other group (56% *vs.* 47%, $P = 0.047$ for comparison with the persisting group and 56% *vs.* 39%, $P = 0.003$ for comparison with the improving group).

Within each group, comparing Pao_2/Fio_2 from one day to the following day of data collection, the only differences were between the day of ARDS onset and the next day ($P < 0.001$ for each group) and for the improving group between days 5 and 7 (tables 2 and 3 in the Supplemental Digital Content, http://links.lww.com/ALN/B814; table 4); after day 2, Pao_2/Fio_2 remained stable in the worsening group (fig 2A; tables 2 and 3 in the Supplemental Digital Content, http://links.lww.com/ALN/B814). Tidal volumes of mechanically ventilated patients remained stable over the first week of evolution

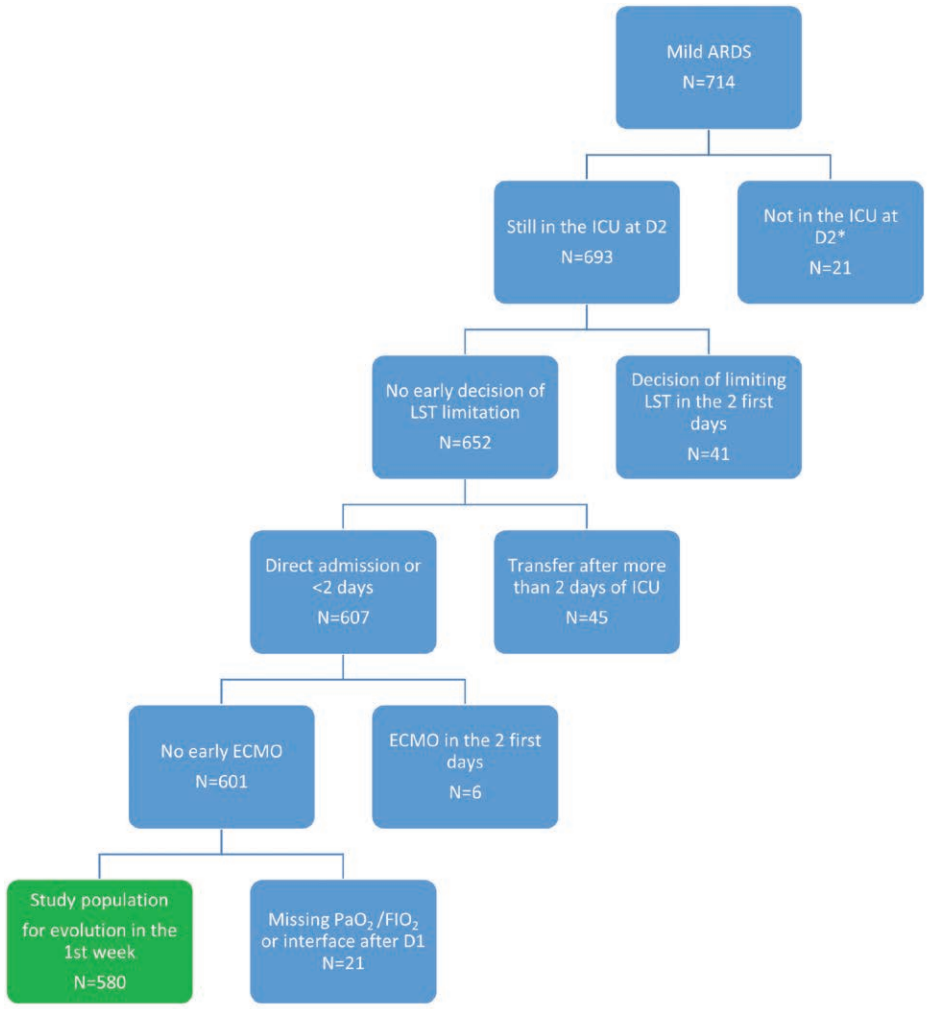

Fig. 1. Flowchart. This figure shows the patient selection process for inclusion in the study. From the 714 patients presenting with mild acute respiratory distress syndrome (ARDS) in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE), 601 fulfilled the criteria for inclusion, and 580 had data allowing classification in the defined categories after day 1 (D1; *green box*). *Twenty-one not in the intensive care unit (ICU) at ARDS day 2 (D2): 12 died, 5 were transferred to another ICU, and 4 were discharged alive from the ICU. ECMO, extracorporeal membrane oxygenation; F_{IO_2}, fraction of inspired oxygen; LST, life-sustaining treatment.

and did not differ between the different evolution groups (tables 2–4 in the Supplemental Digital Content, http://links.lww.com/ALN/B814; fig. 2B). Respectively, 61% (338 of 550), 80% (438 of 550), and 89% (492 of 550) of the patients had tidal volume of less than 8, 9, and 10 ml/kg of predicted body weight. Each day, PEEP settings were overall different between groups with the use of a higher PEEP in the group with worsening ARDS (fig. 2C; tables 2–4 in the Supplemental Digital Content, http://links.lww.com/ALN/B814).

In the worsening ARDS group, the first day with P_{AO_2}/F_{IO_2} of less than 200 mmHg was day 2 for 149 (56%), day 3 for 53 (20%), day 5 for 40 (15%), and day 7 for 25 patients (9%). To determine the factors associated with worsening of mild ARDS, we compared the group worsening to the other patients (*i.e.*, improving and persisting mild ARDS); the results are shown in table 2. Patients in the worsening group had a higher rate of medical (71% *vs.* 63%, $P = 0.038$) and trauma causes for admission (9% *vs.* 4%, $P = 0.029$) and a lower rate of surgical causes (21% *vs.* 33%, $P < 0.001$), whereas more of these patients had pneumonia as a risk factor (56% *vs.* 43%, $P = 0.006$), and they had a significantly lower initial P_{AO_2}/F_{IO_2}, higher PEEP, and higher peak inspiratory pressure (table 2). In a multivariable logistic regression including data collected on the first day of ARDS, only admission for trauma, pneumonia as a risk factor for ARDS, higher nonpulmonary sequential organ failure assessment score, lower initial P_{AO_2}/F_{IO_2}, and higher peak inspiratory pressures

Table 1. Patients' Baseline Characteristics and Outcomes According to Their Evolution Categories

	All N = 580	Improving N = 103	Persisting N = 210	Worsening N = 267	*P* value	N
Baseline						
Age, mean ± SD, yr	61 ± 17	61 ± 18	61 ± 17	61 ± 16	0.884	580
Weight, mean ± SD, kg	75.9 ± 20.0	72.8 ± 18.8	75.5 ± 17.3	77.4 ± 22.1	0.142	545
Female sex (%)	214 (36.9)	29 (28.2)	81 (38.6)	104 (39.0)	0.128	580
Comorbidities, No. (%)						
Diabetes	121 (20.9)	17 (16.5)	41 (19.5)	63 (23.6)	0.270	580
COPD	110 (19.0)	23 (22.3)	31 (14.8)	56 (21.0)	0.144	580
Chronic renal failure	56 (9.7)	13 (12.6)	17 (8.1)	26 (9.7)	0.443	580
Immunosuppression	116 (20.0)	16 (15.5)	44 (21.0)	56 (21.0)	0.458	580
Chronic heart failure	60 (10.3)	10 (9.7)	17 (8.1)	33 (12.4)	0.307	580
Chronic liver failure	20 (3.4)	5 (4.9)	7 (3.3)	8 (3.0)	0.657	580
Type of admission, No. (%)					0.013	580
Medical	385 (66.4)	60 (58.3)	136 (64.8)	189 (70.8)		
Postoperative (elective)	47 (8.1)	12 (11.7)	19 (9.0)	16 (6.0)		
Surgical	112 (19.3)	27 (26.2)	46 (21.9)	39 (14.6)		
Trauma	36 (6.2)	4 (3.9)	9 (4.3)	23 (8.6)		
Risk factor for ARDS, No. (%)						
Pneumonia	287 (49.5)	40 (38.8)	98 (46.7)	149 (55.8)	0.008	580
Extrapulmonary sepsis	113 (19.5)	20 (19.4)	48 (22.9)	45 (16.9)	0.259	580
Aspiration	85 (14.7)	24 (23.3)	30 (14.3)	31 (11.6)	0.017	580
Trauma	35 (6.0)	5 (4.9)	11 (5.2)	19 (7.1)	0.595	580
Pancreatitis	12 (2.1)	1 (1.0)	4 (1.9)	7 (2.6)	0.743	580
Pulmonary contusion	26 (4.5)	5 (4.9)	8 (3.8)	13 (4.9)	0.863	580
Pulmonary vasculitis	5 (0.9)	1 (1.0)	3 (1.4)	1 (0.4)	0.415	580
Noncardiogenic shock	45 (7.8)	8 (7.8)	15 (7.1)	22 (8.2)	0.906	580
Overdose	14 (2.4)	5 (4.9)	5 (2.4)	4 (1.5)	0.186	580
TRALI	27 (4.7)	5 (4.9)	12 (5.7)	10 (3.7)	0.588	580
No identified risk factor	53 (9.1)	12 (11.7)	19 (9.0)	22 (8.2)	0.593	580
First day of ARDS						
SOFA adjusted, mean ± SD	8.6 ± 3.6	8.0 ± 3.4	8.3 ± 3.6	8.9 ± 3.7	0.049	580
Nonpulmonary SOFA, mean ± SD	6.4 ± 3.7	5.9 ± 3.5	6.2 ± 3.7	6.8 ± 3.8	0.037	576
$Paco_2$, mean ± SD, mmHg	42 ± 10	41 ± 8	42 ± 10	42 ± 11	0.653	579
pH, mean ± SD	7.36 ± 0.10	7.38 ± 0.09	7.37 ± 0.09	7.36 ± 0.11	0.104	578
Fio_2, median (IQR)	0.4 (0.4, 0.5)	0.4 (0.4, 0.5)	0.4 (0.4, 0.5)	0.4 (0.4, 0.6)	0.002	580
VT, mean ± SD, ml/kg PBW	7.8 ± 1.7	7.7 ± 1.6	7.8 ± 1.7	7.9 ± 1.7	0.715	549
Pao_2/Fio_2 ratio, mean ± SD, mmHg	246 ± 28	251 ± 29	248 ± 28	242 ± 27	0.004	580
Total respiratory rate, mean ± SD, 1/min	19 ± 6	18 ± 6	19 ± 5	20 ± 6	0.078	576
PEEP, mean ± SD, cm H_2O	7 ± 36	7 ± 2	7 ± 3	8 ± 3	0.011	580
Plateau pressure, mean ± SD, cm H_2O	21 ± 6	19 ± 5	21 ± 5	21 ± 6	0.423	163
Peak inspiratory pressure, mean ± SD, cm H_2O	25 ± 9	22 ± 8	25 ± 9	26 ± 8	0.001	560
Standardized minute ventilation, mean ± SD, l/min	9.4 ± 3.5	8.9 ± 2.8	9.3 ± 3.4	9.7 ± 3.8	0.134	569
Outcome						
Clinician recognition of ARDS, No. (%)	292 (50.3)	30 (36.9)	108 (51.4)	146 (54.7)	0.008	580
Decision of withholding or withdrawing life-sustaining treatments, No. (%)	105 (18.1)	7 (6.8)	37 (17.6)	61 (22.8)	0.002	580
Duration of mechanical ventilation, median (IQR), days	8 (4, 14)	3 (2, 5)	7 (4, 14)	11 (6, 18)	< 0.001	550
Ventilator-free days, median (IQR), days	18 (0, 24)	25 (22, 26)	19 (0, 24)	9 (0, 20)	< 0.001	550
ICU length of stay, median (IQR), days	11 (6, 19)	6 (4, 10)	10 (7, 19)	14 (8, 22)	< 0.001	580
ICU mortality, No. (%)	142 (24.5)	8 (7.8)	45 (21.4)	89 (33.3)	< 0.001	580
Hospital length of stay, median (IQR), days	19 (11, 37)	17 (10, 32)	21 (12, 42)	19 (11, 37)	0.104	564
Hospital mortality, No. (%)	172 (29.9)	10 (9.9)	63 (30.0)	99 (37.4)	< 0.001	576

P values represent comparisons across the evolution categories for each variable. For all sequential organ failure assessment (SOFA) scores for which data points were missing, this value was omitted, and the denominator was adjusted accordingly. The nonpulmonary SOFA score and the pulmonary component of the score were omitted, and the denominator was adjusted accordingly. Plateau pressure values are limited to patients in whom this value was reported and in whom either an assist control mode was used or in whom a control mode permitting spontaneous ventilation was used. Standardized minute ventilation = minute ventilation × $Paco_2$/40 mmHg. Ventilator-free days: calculated as the number of days from weaning from invasive ventilation to day 28. Patients who died before weaning were considered to have a ventilator-free day value of 0. Clinical recognition of acute respiratory distress syndrome (ARDS): on the day of inclusion, investigators were asked whether the patient presented ARDS. At the time patient exited the study, the investigators were asked whether the patient presented ARDS at any stage during his/her intensive care unit (ICU) stay. ARDS was deemed to have been clinician-recognized if either question was answered positively. Four patients had missing status at hospital discharge or day 90.

COPD, chronic obstructive pulmonary disease; Fio_2, fraction of inspired oxygen; IQR, interquartile range; PBW, predicted body weight; PEEP, positive end-expiratory pressure; TRALI, transfusion-related acute lung injury; VT, tidal volume.

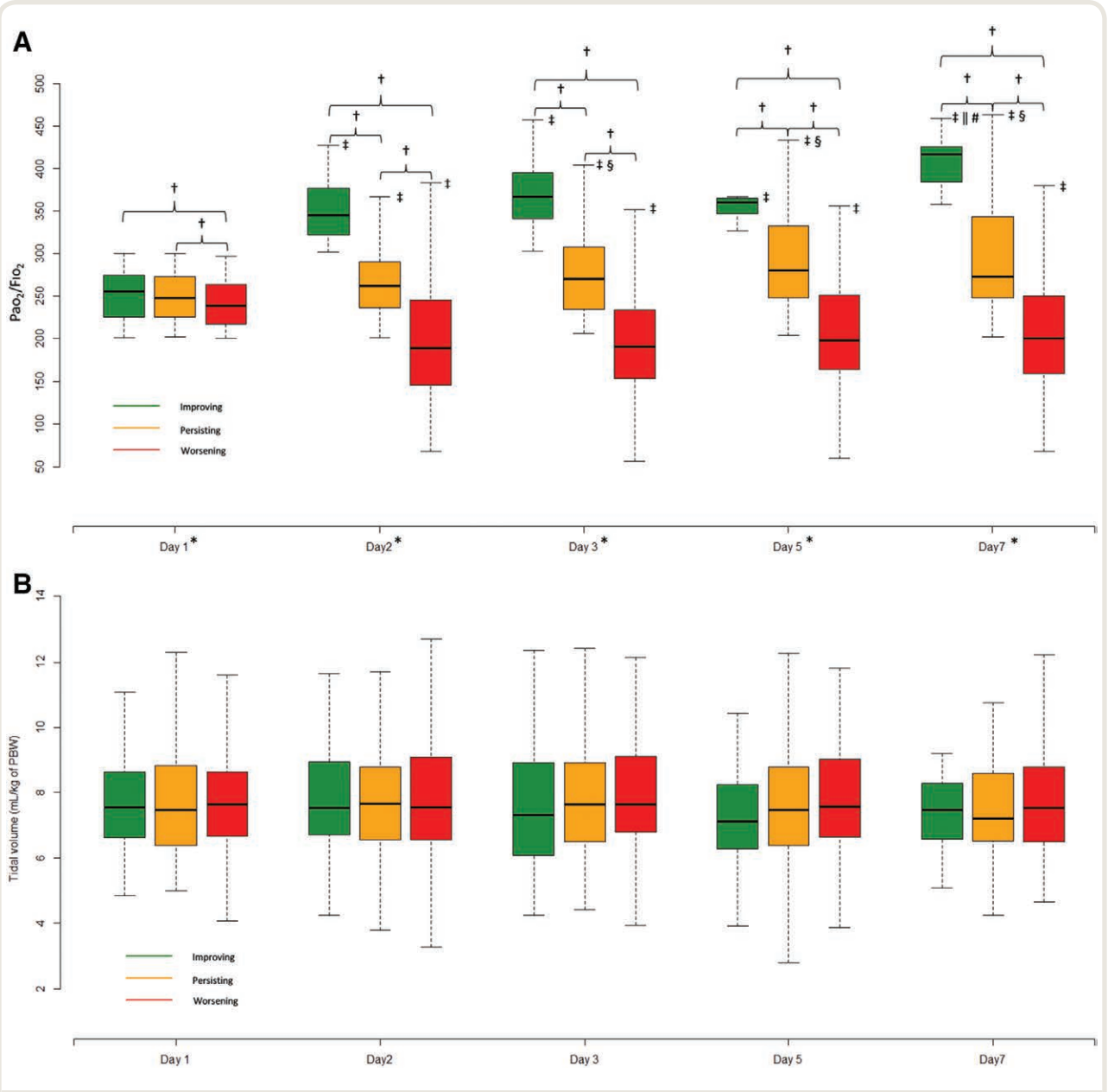

Fig. 2. Evolution of $Pa_{O_2}/F_{I_{O_2}}$; (*A*), tidal volume (*B*), and positive end-expiratory pressure (PEEP; *C*) in the first week after acute respiratory distress syndrome (ARDS) onset according to the evolution group. (*A*) Evolution of $Pa_{O_2}/F_{I_{O_2}}$ and comparison between the improving (*green*), persisting (*orange*), and worsening (*red*) categories. On day 1, $Pa_{O_2}/F_{I_{O_2}}$ was significantly lower in the worsening group as compared to the improving group ($P = 0.009$) and the persisting group ($P = 0.031$). Each following day, $Pa_{O_2}/F_{I_{O_2}}$ was significantly different between each of the three groups with a gradual increase from the worsening to the persisting and to the improving group. As compared to day 1, $Pa_{O_2}/F_{I_{O_2}}$ on day 2 significantly decreased in the worsening group and then remained stable, whereas it increased in the improving and persisting groups. (*B*) Evolution of tidal volume and comparison between the improving (*green*), persisting (*orange*), and worsening (*red*) categories. Tidal volume was similar between groups at day 1 and remained similar each day of data collection. Within each group, tidal volume also remained similar to the initial one at each day of follow-up.

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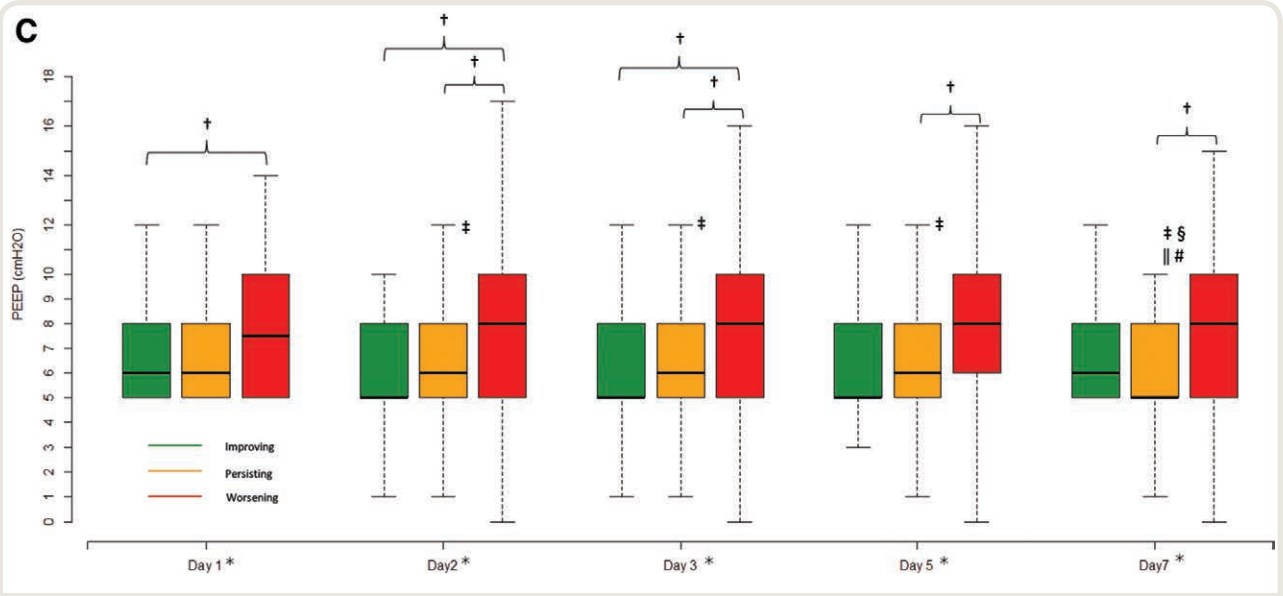

Fig. 2. (*Continued*). (*C*) Evolution of PEEP and comparison between the improving (*green*), persisting (*orange*), and worsening (*red*) categories. On days 1, 2, and 3, PEEP was significantly higher in the worsening group as compared to the improving groups. Every day of data collection except on day 1, PEEP was higher in the worsening group as compared to the persisting groups. In the persisting groups, PEEP decreased from day 1 to day 2 and remained stable the following days. Detailed *P* values are shown in tables 2–4 in the Supplemental Digital Content (http://links.lww.com/ALN/B814). **P* < 0.05 for overall comparison; †*P* < 0.05 for two-by-two comparison; ‡*P* < 0.05 *versus* day 1 for the same group; §*P* < 0.05 *versus* day 2 for the same group; ‖*P* < 0.05 *versus* day 3 for the same group; #*P* < 0.05 *versus* day 5 for the same group. PBW, predicted body weight.

were independently associated with higher risk of worsening in the 7 days after mild ARDS onset (table 3). The model showed good fit ($P = 0.183$ on the Hosmer–Lemeshow goodness-of-fit test).

Comparison According to Hospital Mortality

Of 580 patients with initial mild ARDS, 142 died in the intensive care unit (24.5%), and an additional 30 patients died in the hospital after intensive care unit discharge, resulting in total hospital mortality of 29.9% (272 of 576). Patients who died in the hospital had more comorbidities, including a higher rate of diabetes, immunosuppression, and chronic liver failure (table 5 in the Supplemental Digital Content, http://links.lww.com/ALN/B814). Their main cause for admission was more frequently medical than surgical or trauma, and they had a higher rate of pneumonia as a risk factor for ARDS. They also displayed a more severe baseline severity, with higher sequential organ failure assessment scores, lower arterial pH, and fewer patients with improving oxygenation the day after ARDS onset.

Kaplan–Meier hospital survival curves for each category of ARDS evolution the day after ARDS onset (fig. 3) demonstrated different survival probability overall ($P < 0.001$) and comparing the improving group to the persisting group ($P < 0.001$) or the worsening group ($P = 0.043$) but not comparing the worsening group to the persisting group ($P = 0.649$).

In a multivariable logistic regression, higher age, medical history of diabetes or immunosuppression, higher nonpulmonary admission sequential organ failure assessment scores, and extrapulmonary sepsis as a risk factor for ARDS were associated with higher risk of death in the hospital, whereas admission for surgery or being in the group with improving oxygenation the day after ARDS onset was associated with increased hospital survival (table 4). The model showed good fit ($P = 0.749$ on the Hosmer–Lemeshow goodness-of-fit test). As a sensitivity analysis, both the Cox proportional hazard model and the time-varying Cox model found the same factors as the logistic regression associated with hospital mortality (tables 6 and 7 in the Supplemental Digital Content, http://links.lww.com/ALN/B814).

Discussion

This analysis of the characteristics and evolution of patients classified as mild ARDS at initial presentation revealed several new and relevant results. First, despite being in the lowest severity group of ARDS, patients with initial mild ARDS had a hospital mortality of 30%. Second, 82% had persistent ARDS, whereas 46% worsened within the first week; this latter group had a mortality of 37%. Third, no modifiable factor was independently associated with this deterioration. Taken together, these findings demonstrate

Table 2. Characteristics and Outcome of Worsening *versus* Nonworsening Patients

	Nonworsening, N = 313	Worsening, N = 267	*P* value	N
Baseline				
Age, mean ± SD, yr	61 ± 17	61 ± 16	0.659	580
Weight, mean ± SD, kg	74.6 ± 17.8	77.4 ± 22.1	0.109	545
Female sex (%)	110 (35.1)	104 (39.0)	0.389	580
Comorbidities, No. (%)				
Diabetes	58 (18.5)	63 (23.6)	0.163	580
COPD	54 (17.3)	56 (21.0)	0.302	580
Chronic renal failure	30 (9.6)	26 (9.7)	1.000	580
Immunosuppression	60 (19.2)	56 (21.0)	0.662	580
Chronic heart failure	27 (8.6)	33 (12.4)	0.182	580
Chronic liver failure	12 (3.8)	8 (3.0)	0.747	580
Type of admission, No. (%)			0.002	
Medical	196 (62.6)	189 (70.8)		
Postoperative (elective)	31 (9.9)	16 (6.0)		
Surgical	73 (23.3)	39 (14.6)		
Trauma	13 (4.2)	23 (8.6)		
Risk factor for ARDS, No. (%)				
Pneumonia	138 (44.1)	149 (55.8)	0.006	580
Extrapulmonary sepsis	68 (21.7)	45 (16.9)	0.170	580
Aspiration	54 (17.3)	31 (11.6)	0.072	580
Trauma	16 (5.1)	19 (7.1)	0.403	580
Pancreatitis	5 (1.6)	7 (2.6)	0.568	580
Pulmonary contusion	13 (4.2)	13 (4.9)	0.831	580
Pulmonary vasculitis	4 (1.3)	1 (0.4)	0.381	580
Noncardiogenic shock	23 (7.3)	22 (8.2)	0.807	580
Overdose	10 (3.2)	4 (1.5)	0.291	580
TRALI	17 (5.4)	10 (3.7)	0.446	580
No identified risk factor	31 (9.9)	22 (8.2)	0.583	580
First day of ARDS				
SOFA adjusted, mean ± SD	8.2 ± 3.5	8.9 ± 3.7	0.018	580
Nonpulmonary SOFA, mean ± SD	6.1 ± 3.6	6.8 ± 3.8	0.013	576
$Paco_2$, mean ± SD, mmHg	42 ± 9	42 ± 11	0.561	579
pH, mean ± SD	7.37 ± 0.09	7.36 ± 0.11	0.050	578
Fio_2, median (IQR)	0.4 (0.4; 0.5)	0.4 (0.4; 0.6)	< 0.001	580
VT, mean ± SD, ml/kg PBW	7.8 ± 1.7	7.9 ± 1.7	0.415	549
Pao_2/Fio_2 ratio, mean ± SD, mmHg	249 ± 28	242 ± 27	0.001	580
Total respiratory rate, mean ± SD, 1/min	19 ± 6	20 ± 6	0.061	576
PEEP, mean ± SD, cm H_2O	7 ± 2	8 ± 3	0.007	580
Plateau pressure, mean ± SD, cm H_2O	21 ± 5	21 ± 6	0.937	163
Peak inspiratory pressure, mean ± SD, cm H_2O	24 ± 9	26 ± 8	0.016	560
Standardized minute ventilation, mean ± SD, l/min	9.1 ± 3.2	97 ± 3.7	0.076	569
Outcome				
Clinician recognition of ARDS, No. (%)	146 (46.6)	146 (54.7)	0.065	580
Decision of withholding or withdrawing life-sustaining treatments, No. (%)	44 (14.1)	61 (22.8)	0.008	580
Duration of mechanical ventilation, median (IQR), days	5 (3, 11)	11 (6, 18)	< 0.001	550
Ventilator-free days, median (IQR), days	22 (6, 25)	9 (0, 20)	< 0.001	550
ICU length of stay, median (IQR), days	9 (5, 17)	14 (8, 22)	< 0.001	580
ICU mortality, No. (%)	53 (16.9)	89 (33.3)	< 0.001	580
Hospital length of stay, median (IQR), days	20 (11, 38)	19 (11, 37)	0.950	564
Hospital mortality, No. (%)	73 (23.5)	99 (37.4)	< 0.001	576

The *P* value represents comparisons across the evolution categories for each variable. For all sequential organ failure assessment (SOFA) scores for which data points were missing, this value was omitted, and the denominator was adjusted accordingly. The nonpulmonary SOFA score and the pulmonary component of the score were omitted, and the denominator was adjusted accordingly. Plateau pressure values are limited to patients in whom this value was reported and in whom either an assist control mode was used or in whom a control mode permitting spontaneous ventilation was used. Standardized minute ventilation = minute ventilation × $Paco_2$/40 mmHg. Ventilator-free days: calculated as the number of days from weaning from invasive ventilation to day 28. Patients who died before weaning were considered to have a ventilator-free day value of 0.

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; Fio_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; PBW, predicted body weight; PEEP, positive end-expiratory pressure; TRALI, transfusion related acute lung injury; VT, tidal volume.

Table 3. Multivariable Analysis of Factors Associated with Worsening ARDS

	Odds Ratio	95% CI	*P* value
Admission for trauma	2.74	1.33–5.88	0.007
Pneumonia	1.69	1.19–2.40	0.004
Nonpulmonary SOFA score (for 1 point)	1.07	1.02–1.12	0.005
Pao_2/Fio_2 ratio (per decrease of 10 mmHg)	1.09	1.03–1.17	0.004
Peak inspiratory pressure (for 1 cmH_2O)	1.02	1.00–1.04	0.046

ARDS, acute respiratory distress syndrome; Fio_2, fraction of inspired oxygen; SOFA, sequential organ failure assessment.

Table 4. Multivariable Analysis of Factors Associated with Hospital Death

	Odds Ratio	95% CI	*P* value
Age (for 1 yr)	1.03	1.02–1.05	< 0.001
Diabetes	1.75	1.09–2.481	0.018
Immunosuppression	2.20	1.37–3.55	< 0.001
Nonpulmonary SOFA score (for 1 point)	1.14	1.08–1.22	< 0.001
Extrapulmonary sepsis	1.99	1.19–3.34	0.009
Surgical cause of admission	0.39	0.24–0.64	< 0.001
Improving oxygenation in the first 24 h	0.57	0.35–0.91	0.020

SOFA, sequential organ failure assessment.

that patients with initial "mild" ARDS are a critically ill cohort with a high risk of worsening ARDS severity and a high mortality that may require greater attention and/or preventive measures. These findings illustrate the importance of raising clinicians' awareness regarding patients with mild ARDS and considering them for inclusion in research studies with a specific focus on preventing worsening of ARDS.

Population Definition

Patients initially presenting with mild ARDS are a poorly characterized cohort. Relatively few epidemiologic studies[7,9–11,13,19–21] included patients with mild ARDS, and they found a wide mortality range from 15%[9] to 42%[19] and even higher in burn[22] and cancer patients.[23] None of these studies provided a daily reassessment of the patients' management and evolution. More than 80% of the patients in our cohort continued to have ARDS on the days after onset, corroborating the rationale of including the mild category in the most recent definition of ARDS.[1] Despite a high global mortality of 30%, only half of them were recognized as having ARDS by their clinicians, highlighting the need to better characterize and understand this group to ultimately optimize their management. Of importance, hospital mortality was relatively low in the improving group (10%) as compared to the persisting and worsening group (30 and 37%, respectively), emphasizing the importance of monitoring ARDS evolution over the first week. Evolution of oxygenation in the first week was the main criterion of the group definitions; thus it was expected that patients with worsening oxygenation within this relatively long period would have a poorer outcome. To avoid this bias, we only used classification at day 2 of ARDS for mortality analyses.

Risk Factors for Progression of ARDS

Predicting the evolution of patients with initial mild ARDS facilitates identification of patients that may benefit from specific managements or closer monitoring, as well as optimizing inclusion criteria selection in future studies. As previously described, trauma and pneumonia were the ARDS risk factors independently associated with worsening severity over the first week.[8,24–26] We could not identify any modifiable factor independently associated with worsening oxygenation. Most of the literature on patients' oxygenation evolution was obtained in patients at risk of developing ARDS,[27] but we lack evidence regarding the strategy that would avoid worsening of patients presenting mild ARDS. Similar to ARDS prevention, an optimized management combining protective ventilation, restrictive fluids and transfusion management, and etiologic treatment seems appropriate but still has to be tested.[28,29] Given the high rate of patients worsening within the first week in our cohort, patients with mild ARDS appear to be an appropriate population to test such interventions in the future.

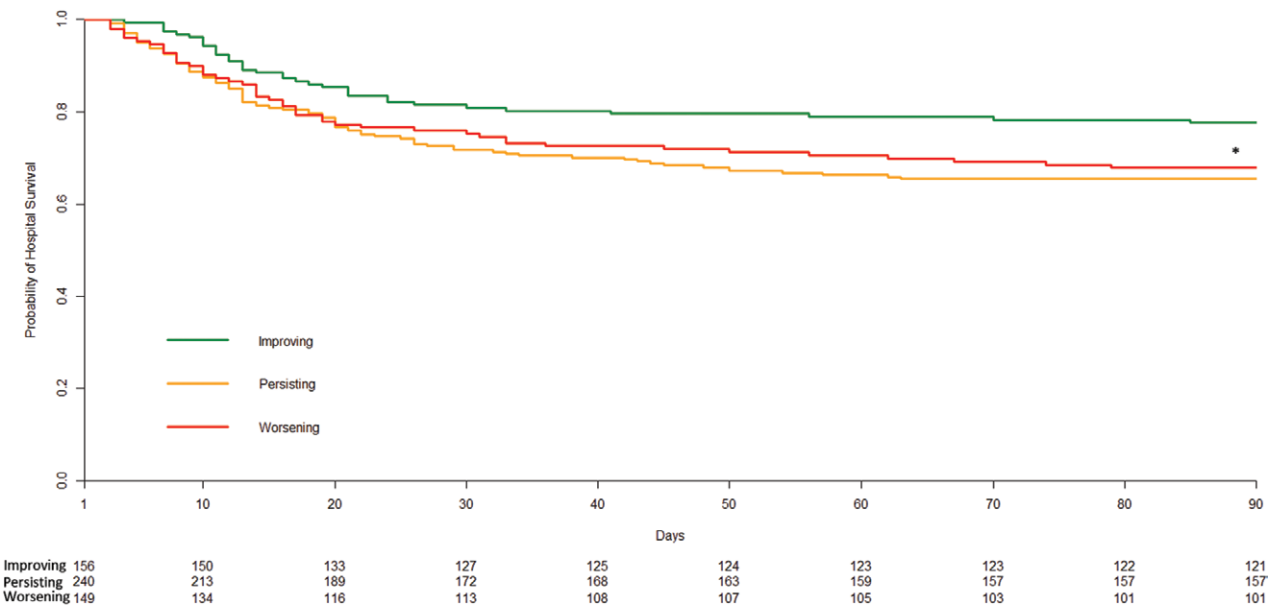

Fig. 3. Probability of hospital survival by day 2 evolution category. Kaplan–Meier curves comparing the probability of survival in the improving (*green*), persisting (*orange*), and worsening (*red*) groups. Log-rank tests show an overall difference between groups and a higher probability of hospital survival in the improving group as compared to the persisting group or to the worsening group. These Kaplan Meier analysis included the 545 patients with data available for classification of oxygenation evolution at day 2 and vital status at hospital discharge. *Log-rank test for evolution category comparisons: $P < 0.001$ overall; $P < 0.001$ persisting *versus* improving; $P = 0.042$ worsening *versus* improving; and $P = 0.649$ worsening *versus* persisting.

Patients' Initial Characteristics, Severity, and Ventilation Parameters

Contrasting with previous literature, diabetes was associated with mortality in our cohort of patients with mild ARDS. Diabetes may decrease the risk of developing ARDS.[30,31] In patients with ARDS, diabetes either had no effect[32,33] or was associated with a better outcome.[34] Chronic diseases and complication of diabetes such as kidney failure or cardiovascular disease may play a more important role in patients with initial mild ARDS as opposed to patients with more severe hypoxemia.

Illness severity at ARDS onset, whether related to the lung injury (lower Pao_2/Fio_2 and higher peak inspiratory pressure) or other organ dysfunctions (higher nonpulmonary sequential organ failure assessment), was associated with worsening oxygenation. The sequential organ failure assessment score has consistently been reported as a good predictor for outcomes in critically ill patients.[35–38] The association between driving pressure or plateau pressure and mortality has been previously described.[39,40] These variables were reported only in 28% of the patients either because the mode of ventilation did not allow a reliable assessment (patients showing evidence of spontaneous breathing) or because they were not measured. We used the peak inspiratory pressure as a surrogate of airway pressures, because this is a measurement available in all modes of mechanical ventilation, and its association with mortality was shown in a recent cohort of ventilated patients.[41] Peak inspiratory pressure increased sequentially with severity of evolution categories, and in multivariable analysis, higher peak inspiratory pressure was associated with an increased risk of being in the group with worsening evolution.

Tidal volumes and PEEP are potentially modifiable factors in the management of patients with ARDS.[42–45] In accordance with the observational study design, no recommendations regarding ventilator settings were given to investigators, and mean tidal volumes around 8 ml/kg predicted body weight used in this study were higher than the 6 ml/kg usually recommended.[42,46] Modes of ventilation allowing spontaneous breathing were used for more than 40% of patients on the day of ARDS onset. Clinicians tolerated these modes and higher tidal volumes maybe because they considered patients with mild ARDS less severe than more hypoxemic patients. We could not find any association between tidal volume and outcomes (evolution of oxygenation or mortality) likely because despite being higher than recommended, tidal volumes were in a narrow range (7.8 ± 1.7 ml/kg predicted body weight). It is still unclear whether larger tidal volumes generated by patients should be tolerated in less severe patients or are harmful[47–49]; however, most of the patients had tidal volumes remaining in reasonable ranges, well below the demonstrated injurious 12 ml/kg predicted body weight.[42] Patients in

the worsening group received higher PEEP, but this was probably confounded by severity because PEEP was not found to be associated with worsening of increased mortality in multivariable analyses. Although we have evidence for the benefit of higher PEEP in moderate to severe ARDS and in the overall LUNG SAFE patient cohort,[50] the impact of PEEP in mild ARDS remains unclear.[51,52]

Outcome from ARDS

Early improvement ($Pa_{O_2}/F_{I_{O_2}}$ more than 300 mmHg or extubation) was associated with a better survival, whereas patients in the persisting and worsening groups had a comparable evolution and worse outcome. It has been previously proposed to reassess ARDS criteria after a stabilization period[3] or standardizing ventilation parameters to better predict outcomes.[53–55] However, these authors mainly focused on moderate to severe ARDS. In our mild ARDS cohort, 13.6% of the patients with an initial improvement on the day after ARDS onset worsened later during their intensive care unit stay. We have recently demonstrated that reclassifying ARDS severity at day 2 identifies a subgroup with severe ARDS at day 2 as being at high risk for mortality.[56] In contrast, reclassifying ARDS severity at day 2 regardless of initial severity in the whole LUNG SAFE ARDS cohort showed limited additional predictive value.[56] We demonstrate here that most patients with initial mild ARDS continue to have ARDS over the course of the first week, with many progressing to higher-severity ARDS, and have a high mortality. This highlights that patients with initial mild ARDS constitute a critically ill group with a high mortality that require greater attention.

Limitations

By design, observational studies cannot adjust for unmeasured confounders and rely on the quality of the data collected by the investigators. However, most of the common important data for characterization of patients with ARDS were available; the amount of missing data at baseline was low except for plateau pressure, and outliers were confirmed or corrected by contacting site investigators. The data were collected only once a day, which makes it impossible to get more granular information. We acknowledged these limitations when designing LUNG SAFE. We deliberately balanced the quantity of data collected with investigator workload to enhance feasibility. Here, we provide a real-life prospective assessment of nonselected patients with mild ARDS using the most rigorous methods of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[18]

Conclusions

Most of the patients initially presenting with mild ARDS continue to fulfill criteria over the following days, and nearly half of them worsen in terms of ARDS severity category over the first week. Their mortality is high, particularly in patients with worsening ARDS, emphasizing the need for greater clinical attention and the necessity to include them in specific clinical trials and to develop strategies to prevent worsening of ARDS severity in these patients.

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Competing Interests

The authors declare no competing interests.

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