

ANESTHESIOLOGY

Outcomes of Patients Presenting with Mild Acute Respiratory Distress Syndrome

Insights from the LUNG SAFE Study

Tài Pham, M.D., Ph.D., Ary Serpa Neto, M.D., Ph.D., Paolo Pelosi, M.D., F.E.R.S., John Gerard Laffey, M.D., M.A., Candelaria De Haro, M.D., Jose Angel Lorente, M.D., Giacomo Bellani, M.D., Ph.D., Eddy Fan, M.D., Ph.D., Laurent Jean Brochard, M.D., Antonio Pesenti, M.D., Marcus Josephus Schultz, M.D., Ph.D., Antonio Artigas, M.D., Ph.D., on behalf of the LUNG SAFE Investigators* and the European Society of Intensive Care Medicine Trials Group

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The Berlin definition of acute respiratory distress syndrome (ARDS) categorizes patients with partial pressure of arterial blood oxygen content to inspired fraction of oxygen ($\text{PaO}_2/\text{fraction of inspired oxygen } [\text{FiO}_2]$) 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

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

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.

Submitted for publication April 25, 2018. Accepted for publication October 5, 2018. From the Interdepartmental Division of Critical Care Medicine (T.P., J.G.L., E.F., L.J.B.), Department of Anesthesia (J.G.L.), and Institute of Health Policy, Management and Evaluation (E.F.), University of Toronto, Toronto, Canada; Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute (T.P., J.G.L., L.J.B.) and Department of Anesthesia (J.G.L.), St. Michael's Hospital, Toronto, Canada; Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil (A.S.N.); Department of Intensive Care (A.S.N., M.J.S.) and Laboratory of Experimental Intensive Care and Anesthesiology (M.J.S.), Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; Department of Clinical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy (P.P.) and San Martino Policlinico Hospital, Istituto di Ricovero e Cura a Carattere Scientifico for Oncology, Genoa, Italy (P.P.); Department of Anaesthesia, School of Medicine, and Regenerative Medicine Institute at CÚRAM Centre for Research in Medical Devices, National University of Ireland Galway, Galway, Ireland (J.G.L.); Critical Care Area, Parc Tauli Hospital University, Autonomous University of Barcelona, Barcelona, Spain (C.D.H.); Respiratory Diseases Network Biomedical Investigation Center, Barcelona, Spain (C.D.H., J.A.L., A.A.); Critical Care Department, University Hospital of Getafe, Madrid, Spain (J.A.L.); European University, Madrid, Spain (J.A.L.); School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy (G.B.); Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy (G.B.); Department of Medicine, University Health Network and Mount Sinai Hospital, Toronto, Canada (E.F.); Department of Anesthesia, Critical Care and Emergency Medicine, Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico Milan, Milan, Italy (A.P.); Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy (A.P.); Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand (M.J.S.); Critical Care Department, Parc Tauli Health Corporation University, Autonomous University of Barcelona, Sabadell and Intensive Care Department, University Hospitals Sagrado Corazon-General de Cataluña, Quiron Salut, Barcelona-Sant Cugat del Valles, Spain (A.A.).

*The LUNG SAFE investigators are listed in the appendix.

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 $\text{PaO}_2/\text{FiO}_2$ 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 $\text{PaO}_2/\text{FiO}_2$ and patients' ventilatory interface to define the following variables:

- Improving: the worst $\text{PaO}_2/\text{FiO}_2$ available on days 2, 3, 5, and 7 was more than 300 mmHg
- Persisting: the worst $\text{PaO}_2/\text{FiO}_2$ available on days 2, 3, 5, and 7 was more than 200 mmHg but 300 mmHg at most
- Worsening: the worst $\text{PaO}_2/\text{FiO}_2$ 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 \pm 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 $\text{PaO}_2/\text{FiO}_2$ 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 $\text{PaO}_2/\text{FiO}_2$ 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, $\text{PaO}_2/\text{FiO}_2$ 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

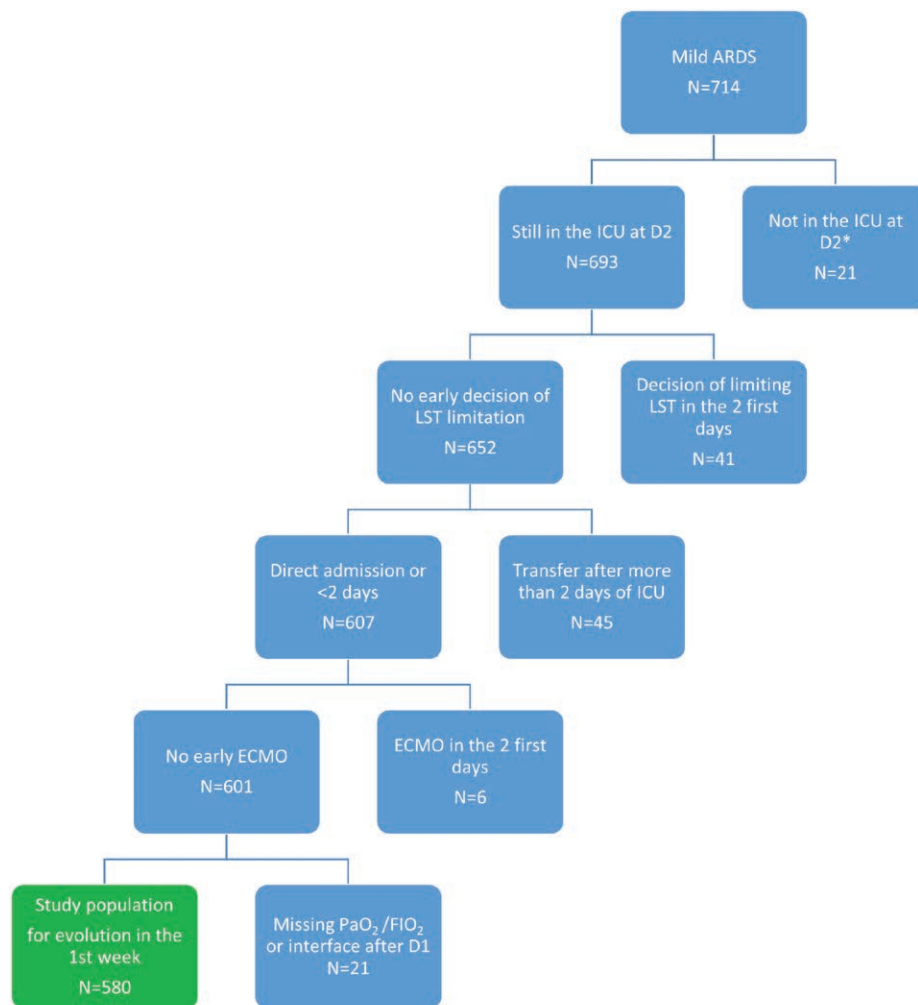


Fig. 1. Flowchart. This figure shows the patient selection process for inclusion in the study. From the 714 patients presenting with mild acute respiratory distress syndrome (ARDS) in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE), 601 fulfilled 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; FiO_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 $\text{PaO}_2/\text{FiO}_2$ 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 $\text{PaO}_2/\text{FiO}_2$, 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 $\text{PaO}_2/\text{FiO}_2$, 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. (%)						
Medical	385 (66.4)	60 (58.3)	136 (64.8)	189 (70.8)	0.013	580
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 ₂ O	7 ± 3.6	7 ± 2	7 ± 3	8 ± 3	0.011	580
Plateau pressure, mean ± SD, cm H ₂ O	21 ± 6	19 ± 5	21 ± 5	21 ± 6	0.423	163
Peak inspiratory pressure, mean ± SD, cm H ₂ O	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 × PaCO₂/40 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; Fio₂, 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.

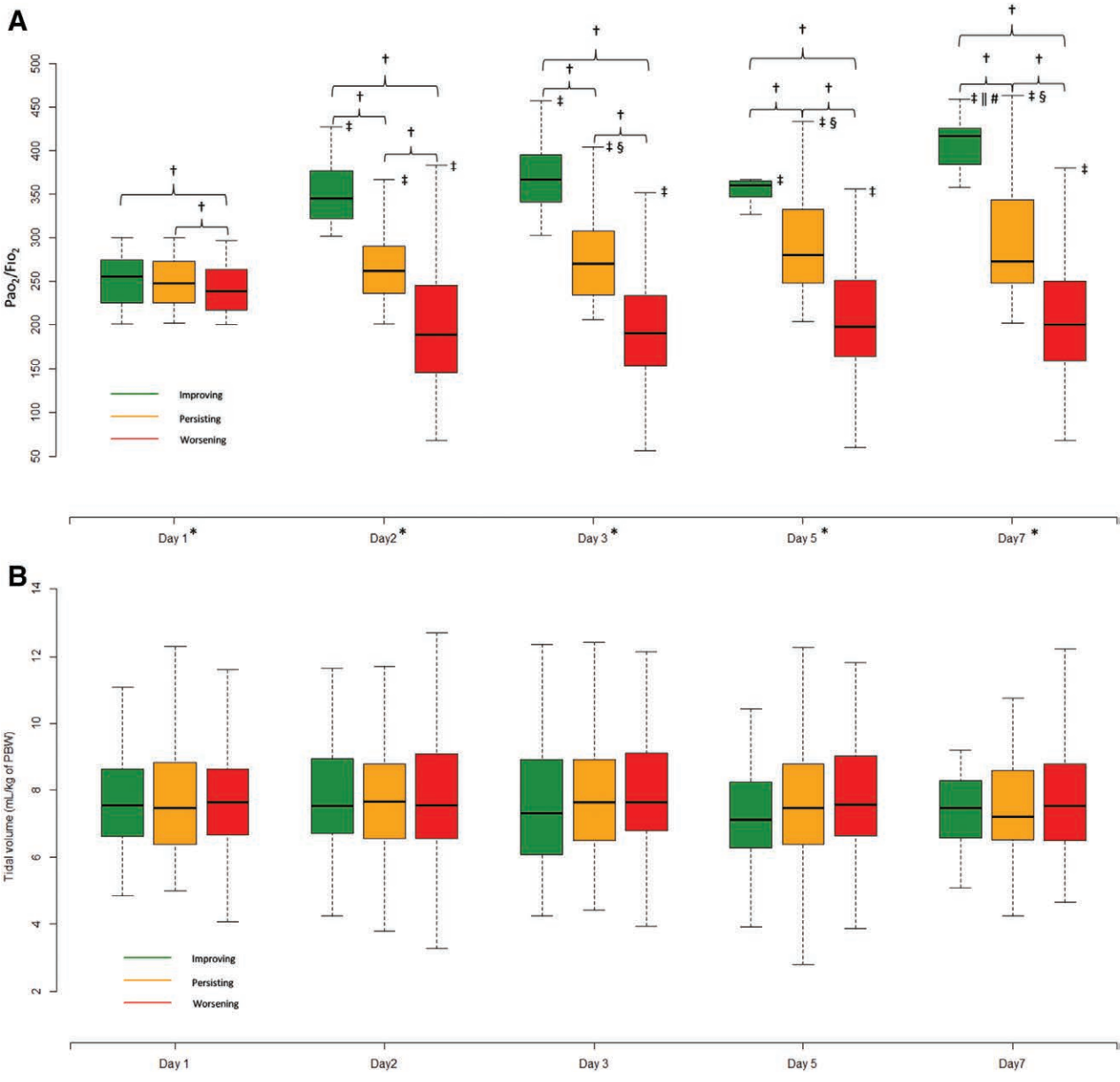


Fig. 2. Evolution of PaO₂/fraction of inspired oxygen (F_iO₂; A), tidal volume (B), and positive end-expiratory pressure (PEEP; C) in the first week after acute respiratory distress syndrome (ARDS) onset according to the evolution group. (A) Evolution of PaO₂/F_iO₂ and comparison between the improving (green), persisting (orange), and worsening (red) categories. On day 1, PaO₂/F_iO₂ 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, PaO₂/F_iO₂ 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, PaO₂/F_iO₂ 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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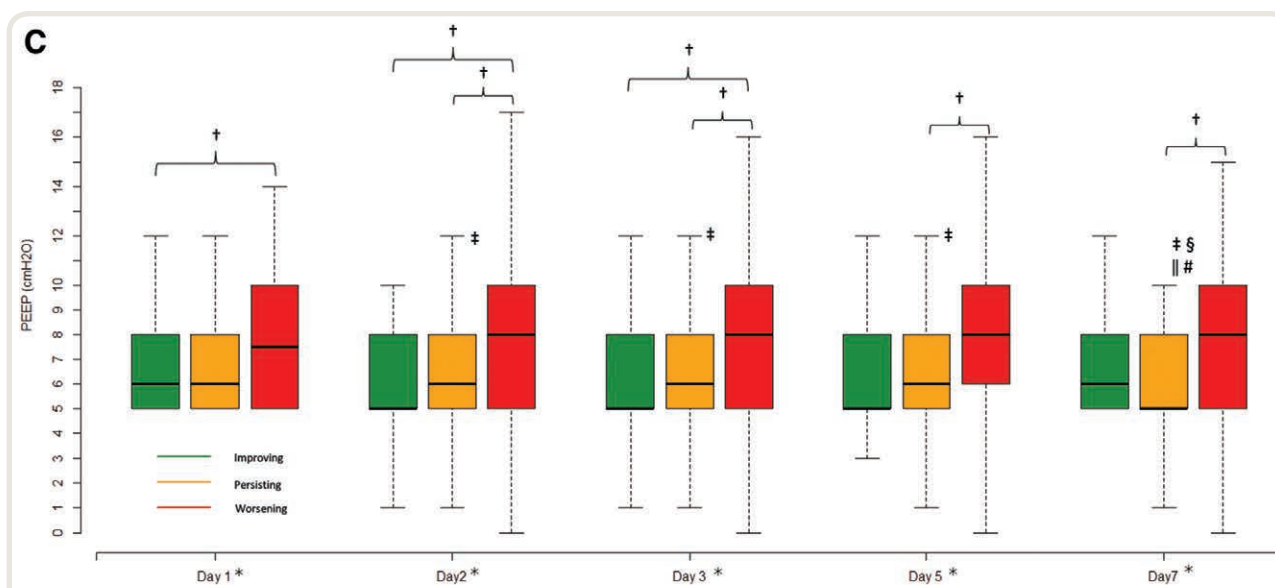


Fig. 2. (Continued). (C) Evolution of PEEP and comparison between the improving (green), persisting (orange), and worsening (red) categories. On days 1, 2, and 3, PEEP was significantly higher in the worsening group as compared to the improving groups. Every day of data collection except on day 1, PEEP 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. (%)				
Medical	196 (62.6)	189 (70.8)	0.002	
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 ₂ O	7 ± 2	8 ± 3	0.007	580
Plateau pressure, mean ± SD, cm H ₂ O	21 ± 5	21 ± 6	0.937	163
Peak inspiratory pressure, mean ± SD, cm H ₂ O	24 ± 9	26 ± 8	0.016	560
Standardized minute ventilation, mean ± SD, l/min	9.1 ± 3.2	9.7 ± 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 × Paco₂/40 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; Fio₂, 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 ₂ O)	1.02	1.00–1.04	0.046

ARDS, acute respiratory distress syndrome; Fio₂, 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.

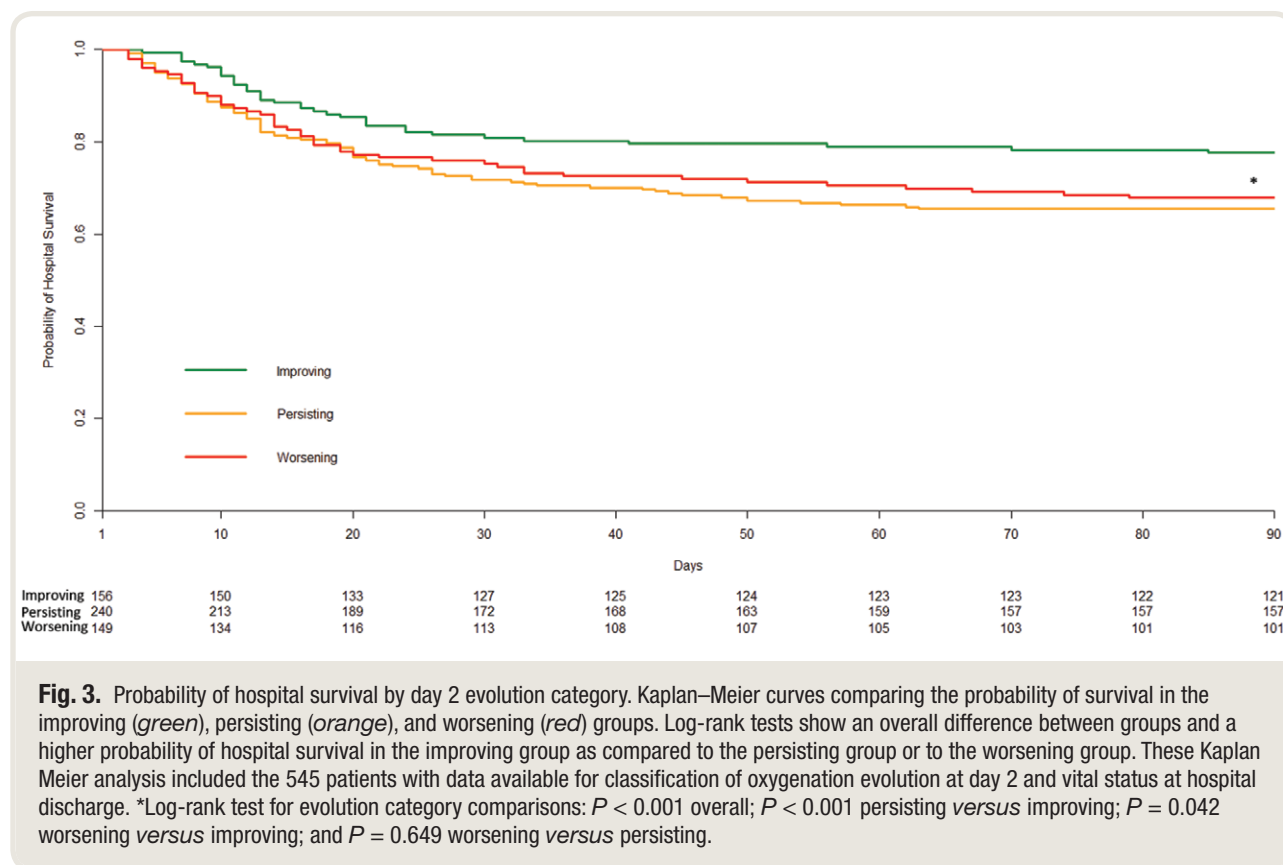
Population Definition

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 burn²² 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.



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 P_{aO_2}/F_{iO_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 (P_{aO_2}/F_{iO_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 period³ 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.

Correspondence

Address correspondence to Dr. Pham: Interdepartmental Division of Critical Care Medicine, University of Toronto, 209 Victoria Street, Toronto, Ontario M5B 1T8, Canada. taiopham@gmail.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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Appendix: LUNG SAFE Investigators

LUNG SAFE Steering Committee: Antonio Pesenti, M.D., John G. Laffey, M.D., Ph.D., Laurent Brochard, M.D., Andres Esteban, M.D., Luciano Gattinoni, M.D., F.R.C.P., Frank van Haren, M.D., Ph.D., Anders Larsson, M.D., Ph.D., Daniel F. McAuley, M.D., Ph.D., Marco Ranieri, M.D., Gordon Rubinfeld, M.D., M.Sc., B. Taylor Thompson, M.D., Hermann Wrigge, M.D., Ph.D., Arthur S. Slutsky, M.D.

LUNG SAFE Executive Committee: John G. Laffey, Giacomo Bellani, Tàì Pham, Eddy Fan

LUNG SAFE National Coordinators: Argentina: Fernando Rios; Australia/New Zealand: Frank Van Haren; Belgium: Thierry Sottiaux, Pieter Depuydt; Bolivia: Fredy S. Lora; Brazil: Luciano Cesar Azevedo; Canada: Eddy Fan; Chile: Guillermo Bugedo; China: Haibo Qiu; Colombia: Marcos Gonzalez; Costa Rica: Juan Silesky; Czech Republic: Vladimir Cerny; Denmark: Jonas Nielsen; Ecuador: Manuel Jibaja; France: Tàì Pham; Germany: Hermann Wrigge; Greece: Dimitrios Matamis; Guatemala: Jorge Luis Ranero; India: Pravin Amin; Iran: S.M. Hashemian; Ireland: Kevin Clarkson; Italy: Giacomo Bellani; Japan: Kiyoyasu Kurahashi; Mexico: Asisclo Villagomez; Morocco: Amine Ali Zeggwagh; Netherlands: Leo M. Heunks; Norway: Jon Henrik Laake; Philippines: Jose Emmanuel Palo; Portugal: Antero do Vale Fernandes; Romania: Dorel Sandesc; Saudi Arabia: Yaasen Arabi; Serbia: Vesna Bumbasierovic; Spain: Nicolas Nin, Jose A. Lorente; Sweden: Anders Larsson; Switzerland: Lise Piquilloud; Tunisia: Fekri Abroug; United Kingdom: Daniel F. McAuley, Lia McNamee; Uruguay: Javier Hurtado; United States: Ed Bajwa; Venezuela: Gabriel Démpaire

LUNG SAFE Site Investigators (by country):

Albania: Uhc Mother Theresa, Tirana: Hektor Sula, Lordian Nunci; University Hospital Shefqet Ndroqi, Tirana: Alma Cani

Argentina: Clinica de Especialidades, Villa Maria: Alan Zazu; Hospital Julio C. Perrando, Resistencia: Christian Delera, Carolina S. Insaurralde; Sanatorio Las Lomas, San Isidro, Buenos Aires: Risso V. Alejandro; Sanatorio de La Trinidad San Isidro, San Isidro: Julio Daldin, Mauricio Vinzio; Hospital Español de Mendoza, Godoy Cruz-Mendoza: Ruben O. Fernandez; Hospital del Centenario, Rosario: Luis P. Cardonnet, Lisandro R. Bettini; San Antonio, Gualeguay, Entre Rios: Mariano Carboni Bisso, Emilio M. Osman; Cemic, Buenos Aires: Mariano G. Setten, Pablo Lovazzano; Hospital Universitario Austral, Pilar: Javier Alvarez, Veronica Villar; Hospital Por + Salud, Pami Dr. Cesar Milstein, Buenos Aires: Norberto C. Pozo, Nicolas Grubissich; Sanatorio Anchorena, Buenos Aires: Gustavo A. Plotnikow, Daniela N. Vasquez; Sanatorio de La Trinidad Mitre, Buenos Aires: Santiago Ilutovich, Norberto Tiribelli; Hospital Luis Lagomaggiore, Mendoza: Ariel Chena, Carlos A. Pellegrini; Hospital

Interzonal General de Agudos, San Martín, La Plata: María G. Saenz, Elisa Estenssoro; Hospital Misericordia, Cordoba: Matias Brizuela, Hernan Gianinetto; Sanatorio Juncal, Temperley: Pablo E. Gomez, Valeria I. Cerrato; Hospital D.F. Santojanni, Buenos Aires: Marco G. Bezzi, Silvina A. Borello; Hospital Alejandro Posadas, Buenos Aires: Flavia A. Loiacono, Adriana M. Fernandez

Australia: St. Vincent's Hospital, Sydney: Serena Knowles, Claire Reynolds; St. George Public Hospital, Kogarah: Deborah M. Inskip, Jennene J. Miller; Westmead Hospital, Westmead: Jing Kong, Christina Whitehead; Flinders Medical Center, Bedford Park: Shailesh Bihari; John Hunter Hospital, Newcastle: Aylin Seven, Amanda Krstevski; Canberra Hospital, Garran: Helen J. Rodgers, Rebecca T. Millar; Calvary Mater Newcastle, Waratah: Toni E. McKenna, Irene M. Bailey; Cabrini Hospital, Melbourne: Gabrielle C. Hanlon; Liverpool Hospital, Liverpool: Anders Aneman, Joan M. Lynch; Coff's Harbour Health Campus, Coff's Harbour: Raman Azad, John Neal; Sir Charles Gairdner Hospital, Nedlands: Paul W. Woods, Brigit L. Roberts; Concord Hospital, Concord: Mark R. Kol, Helen S. Wong

Austria: General Hospital of Vienna/Medical University of Vienna, Vienna: Katharina C. Riss, Thomas Staudinger

Belgium: Cliniques Universitaires St. Luc, Université Catholique de Louvain, Brussels: Xavier Wittebole, Caroline Berghé; Center Hospitalier Universitaire Dinant-Godinne, Yvoir: Pierre A. Bulpa, Alain M. Dive; Acut Ziekenhuis Sint Augustinus Veurne, Veurne: Rik Verstraete, Herve Lebbinck; Ghent University Hospital, Ghent: Pieter Depuydt, Joris Vermassen; University Hospitals Leuven, Leuven: Philippe Meersseman, Helga Ceunen

Brazil: Hospital Renascentista, Pouso Alegre: Jonas I. Rosa, Daniel O. Beraldo; Vitoria Apart Hospital, Serra: Claudio Piras, Adenilton M. Rampinelli; Hospital Das Clinicas, São Paulo: Antonio P. Nassar, Jr.; Hospital Geral Do Grajaú, São Paulo: Sergio Mataloun, Marcelo Moock; Evangelical Hospital, Cachoeiro de Itapemirim/Espírito Santo: Marlus M. Thompson, Claudio H. Gonçalves; Hospital Moinhos de Vento, Porto Alegre: Ana Carolina P. Antônio, Aline Ascoli; Hospital Alvorada Taguatinga, Taguatinga: Rodrigo S. Biondi, Danielle C. Fontenele; Complexo Hospitalar Mngabeira Tarcisio Burity, Joao Pessoa: Danielle Nobrega, Vanessa M. Sales

Brunei: Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan: Ahmad Yazid Bin HJ Abul Wahab, Maizatul Ismail, Suresh Shindhe

Canada: Medical-Surgical Intensive Care Unit of St. Michael's Hospital, Toronto: John Laffey, Francois Beloncle; St. Joseph's Health Center, Toronto: Kyle G. Davies, Rob Cirone; Sunnybrook Health Sciences Center, Toronto: Venika Manoharan, Mehvish Ismail; Toronto Western Hospital, Toronto: Ewan C. Goligher, Mandeep Jassal; Medical Surgical Intensive Care Unit of the Toronto General Hospital, Toronto: Erin Nishikawa, Areej Javeed; Cardiovascular Intensive Care Unit of St. Michael's Hospital, Toronto:

Gerard Curley, Nuttapol Rittayamai; Cardiovascular Intensive Care Unit of the Toronto General Hospital, Toronto: Matteo Parotto, Niall D. Ferguson; Mount Sinai Hospital, Toronto: Sangeeta Mehta, Jenny Knoll; Trauma-Neuro Intensive Care Unit of St. Michael's Hospital, Toronto: Antoine Pronovost, Sergio Canestrini

Chile: Hospital Clínico Pontificia Universidad Católica de Chile, Santiago: Alejandro R. Bruhn, Patricio H. Garcia; Hospital Militar de Santiago, Santiago: Felipe A. Aliaga, Pamela A. Farías; Clínica Davila, Santiago: Jacob S. Yumha; Hospital Guillermo Grant Benavente, Concepcion: Claudia A. Ortiz, Javier E. Salas; Clínica Las Lilas, Santiago: Alejandro A. Saez, Luis D. Vega; Hospital Naval Almirante Nef, Viña del Mar: Eduardo F. Labarca, Felipe T. Martinez; Hospital Luis Tisné Brousse, Penanolen: Nicolás G. Carreño, Pilar Lora

China: Second Affiliated Hospital of Harbin Medical University, Harbin: Haitao Liu; Nanjing Zhong-da Hospital, Southeast University, Nanjing: Haibo Qiu, Ling Liu; First Affiliated Hospital of Anhui Medical University, Hefei: Rui/Tang, Xiaoming Luo; Peking University People's Hospital, Beijing: Youzhong An, Huiying Zhao; Fourth Affiliated Hospital of Harbin Medical University, Harbin: Yan Gao, Zhe Zhai; Nanjing Jiangbei People's Hospital Affiliated to Medical School of Southeast University, Nanjing: Zheng L. Ye, Wei Wang; First Affiliated Hospital of Dalian Medical University, Dalian: Wenwen Li, Qingdong Li; Subei People's Hospital of Jiangsu Province, Yangzhou: Ruiqiang Zheng; Jinling Hospital, Nanjing: Wenkui Yu, Juanhong Shen; Urumqi General Hospital, Urumqi: Xinyu Li; Intensive Care Unit, First Affiliated Hospital of Wannan Medical College, Yijishan Hospital, Wuhu: Tao Yu, Weihua Lu; Sichuan Provincial People's Hospital, Chengdu: Ya Q. Wu, Xiao B. Huang; Hainan Province People's Hospital, Haikou: Zhenyang He; People's Hospital of Jiangxi Province, Nanchang: Yuanhua Lu; Qilu Hospital of Shandong University, Jinan: Hui Han, Fan Zhang; Zhejiang Provincial People's Hospital, Hangzhou: Renhua Sun; First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui: Hua X. Wang, Shu H. Qin; Nanjing Municipal Government Hospital, Nanjing: Bao H. Zhu, Jun Zhao; First Hospital of Lanzhou University, Lanzhou: Jian Liu, Bin Li; First Affiliated Hospital of Chongqing University of Medical Science, Chongqing: Jing L. Liu, Fa C. Zhou; Xuzhou Central Hospital, Xuzhou: Qiong J. Li, Xing Y. Zhang; First People's Hospital of Foshan, Foshan: Zhou Li-Xin, Qiang Xin-Hua; First Affiliated Hospital of Guangxi Medical University, Nanning: Liangyan Jiang; Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai: Yuan N. Gao, Xian Y. Zhao; First Hospital of Shanxi Medical University, Taiyuan: Yuan Y. Li, Xiao L. Li; Shandong Provincial Hospital, Jinan: Chunting Wang, Qingcun Yao; Fujian Provincial Hospital, Fuzhou: Rongguo Yu, Kai Chen; Henan Provincial People's Hospital, Zhengzhou: Huanzhang Shao, Bingyu Qin; Second Affiliated Hospital

of Kunming Medical University, Kunming City: Qing Q. Huang, Wei H. Zhu; Xiangya Hospital, Central South University, Changsha: Ai Y. Hang, Ma X. Hua; First Affiliated Hospital of Guangzhou Medical University, Guangzhou: Yimin Li, Yonghao Xu; People's Hospital of Hebei Province, Shijiazhuang: Yu D. Di, Long L. Ling; Guangdong General Hospital, Guangzhou: Tie H. Qin, Shou H. Wang; Beijing Tongren Hospital, Beijing: Junping Qin; Jiangsu Province Hospital, Nanjing: Yi Han, Suming Zhou

Colombia: Fundación Valle del Lili, Cali: Monica P. Vargas
Costa Rica: Hospital San Juan De Dios, San Jose: Juan I. Silesky Jimenez, Manuel A. González Rojas, Jaime E. Solis-Quesada, Christian M. Ramirez-Alfaro

Czech Republic: University Hospital of Ostrava, Ostrava: Jan Máca, Peter Sklienka

Denmark: Aarhus Universitetshospital, Aarhus: Jakob Gjedsted, Aage Christiansen; Rigshospitalet: Jonas Nielsen

Ecuador: Hospital Militar, Quito: Boris G. Villamagua, Miguel Llano

France: Clinique du Millenaire, Montpellier: Philippe Burtin, Gautier Buzancais; Center Hospitalier, Roanne: Pascal Beuret, Nicolas Pelletier; Center Hospitalier Universitaire d'Angers, Angers: Satar Mortaza, Alain Mercat; Hôpital Marc Jacquet, Melun: Jonathan Chelly, Sébastien Jochmans; Center Hospitalier Universitaire Caen, Caen: Nicolas Terzi, Cédric Daubin; Henri Mondor Hospital, Créteil: Guillaume Carreaux, Nicolas de Prost; Cochin Hospital, Paris: Jean-Daniel Chiche, Fabrice Daviaud; Hôpital Tenon, Paris: Tâi Pham, Muriel Fartoukh; CH Mulhouse-Emile Muller, Mulhouse: Guillaume Barberet, Jerome Biehler; Archet 1 University Hospital, Nice: Jean Dellamonica, Denis Doyen; Hopital Sainte Musse, Toulon: Jean-Michel Arnal, Anais Briquet; Hopital Nord-Réanimation des Détresses Respiratoires et Infections Sévères, Marseille: Sami Hraiech, Laurent Papazian; Hôpital Européen Georges Pompidou, Paris: Arnaud Follin; Louis Mourier Hospital, Colombes: Damien Roux, Jonathan Messika; Center Hospitalier de Dax, Dax: Evangelos Kalaitzis; Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière, Paris: Laurence Dangers, Alain Combes; Assistance Publique-Hôpitaux de Paris Ambroise Paré, Boulogne-Billancourt: Siu-Ming Au; University Hospital Rouen, Rouen: Gaetan Béduneau, Dorothee Carpentier; Center Hospitalier Universitaire Amiens, Amiens-Salouel: Elie H. Zogheib, Herve Dupont; Center Hospitalier Intercommunal Robert Ballanger, Aulnay-sous-Bois: Sylvie Ricome, Francesco L. Santoli; Center Hospitalier René Dubos, Pontoise: Sebastien L. Besset; Center Hospitalier Intercommunal Portes de l'Oise, Beaumont-sur-Oise: Philippe Michel, Bruno Gelée; Archet 2 University Hospital, Nice: Pierre-Eric Danin, Bernard Goubaux; Center Hospitalier Pierre Oudot, Bourgoin Jallieu: Philippe J. Crova, Nga T. Phan; Center Hospitalier Dunkerque, Dunkerque: Frantz Berkelmans; Center Hospitalier de Belfort Montbéliard, Belfort: Julio C. Badie, Romain Taponnier; Center

Hospitalier Emile Muller, Mulhouse: Josette Gally, Samy Khebbeb; Hôpital de Haute-pierre-Hôpitaux Universitaires de Strasbourg, Strasbourg: Jean-Etienne Herbrecht, Francis Schneider; Center Hospitalier de Dieppe, Dieppe: Pierre-Louis M. Declercq, Jean-Philippe Rigaud; Bicetre, Le Kremlin-Bicetre: Jacques Duranteau, Anatole Harrois; Center Hospitalier Universitaire Gabriel Montpied, Clermont-Ferrand: Russell Chabanne, Julien Marin; Center Hospitalier Universitaire Estaing, Clermont-Ferrand: Charlene Bigot, Sandrine Thibault; Center Hospitalier Intercommunal Eure-Seine Evreux, Evreux: Mohammed Ghazi, Messabi Boukhazna; Center Hospitalier de Châlons en Champagne, Châlons en Champagne: Salem Ould Zein; CH Beauvais, Beauvais: Jack R. Richecoeur, Daniele M. Combaux; Center Hospitalier Le Mans, Le Mans: Fabien Grelon, Charlene Le Moal; Hôpital Fleury, Bourges: Elise P. Sauvadet, Adrien Robine; Hôpital Saint Louis, Paris: Virginie Lemiale, Danielle Reuter; Service de Pneumologie Pitié-Salpêtrière, Paris: Martin Dres, Alexandre Demoule; Center Hospitalier Gonesse, Gonesse: Dany Goldgran-Toledano; Hôpital Croix Rousse, Lyon: Loredana Baboi, Claude Guérin

Germany: St. Nikolaus-Stiftshospital, Andernach: Ralph Lohner; Fachkrankenhaus Coswig GmbH, Coswig: Jens Kraßler, Susanne Schäfer; University Hospital Frankfurt, Frankfurt am Main: Kai D. Zacharowski, Patrick Meybohm; Department of Anesthesia and Intensive Care Medicine, University Hospital of Leipzig, Leipzig: Andreas W. Reske, Philipp Simon; Asklepios Klinik Langen, Langen: Hans-Bernd F. Hopf, Michael Schuetz; Städtisches Krankenhaus Heinsberg, Heinsberg: Thomas Baltus

Greece: Hippokrateion General Hospital of Athens, Athens: Metaxia N. Papanikolaou, Theonymfi G. Papavasiliopoulou; Gh Ahepa, Thessaloniki: Giannis A. Zacharas, Vasilis Ourailogloy; Hippokration General Hospital of Thessaloniki, Thessaloniki: Eleni K. Mouloudi, Eleni V. Massa; Hospital General of Kavala, Kavala: Eva O. Nagy, Electra E. Stamou; Papageorgiou General Hospital, Thessaloniki: Ellada V. Kiourtzieva, Marina A. Oikonomou

Guatemala: Hospital General de Enfermedades, Instituto Guatemalteco de Seguridad Social, Ciudad de Guatemala: Luis E. Avila; Centro Médico Militar, Guatemala: Cesar A. Cortez, Johanna E. Citalán

India: Deenanath Mangeshkar Hospital and Research Center, Pune: Sameer A. Jog, Safal D. Sable; Care Institute of Medical Sciences Hospital, Ahmedabad: Bhagyesh Shah; Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow: Mohan Gurjar, Arvind K. Baronia; Rajasthan Hospital, Ahmedabad: Mohammedfaruk Memon; National Institute of Mental Health and Neuro Sciences, Bangalore: Radhakrishnan Muthuchellappan, Venkatapura J. Ramesh; Anesthesiology Unit of the Kasturba Medical College and Department of Respiratory Therapy, School of Allied Health Sciences, Manipal University, Manipal: Anitha Shenoy, Ramesh Unnikrishnan; Sanjeevan Hospital, Pune: Subhal B. Dixit, Rachana V. Rhayakar; Apollo

Hospitals, Chennai: Nagarajan Ramakrishnan, Vallish K. Bhardwaj; Medicine Unit of the Kasturba Medical College and Department of Respiratory Therapy, School of Allied Health Sciences, Manipal University, Manipal: Heera L. Mahto, Sudha V. Sagar; G. Kuppaswamy Naidu Memorial Hospital, Coimbatore: Vijayanand Palaniswamy, Deeban Ganesan

Iran: National Research Institute of Tuberculosis and Lung Disease/Masih Daneshvari, Tehran: Seyed Mohammad Hashemian, Hamidreza Jamaati; Milad Hospital, Tehran: Farshad Heidari

Ireland: St. Vincent's University Hospital, Dublin: Edel A. Meaney, Alistair Nichol; Mercy University Hospital, Cork: Karl M. Knapman, Donall O'Croinin; Cork University Hospital, Cork: Eimhin S. Dunne, Dorothy M. Breen; Galway University Hospital, Galway: Kevin P. Clarkson, Rola F. Jaafar; Beaumont Hospital, Dublin: Rory Dwyer, Fahd Amir; Mater Misericordiae University Hospital, Dublin: Olaitan O. Ajetunmobi, Aogan C. O'Muircheartaigh; Tallaght Hospital, Dublin: Colin S. Black, Nuala Treanor; Saint James's Hospital, Dublin: Daniel V. Collins, Wahid Altaf

Italy: Santa Maria delle Croci Hospital, Ravenna: Gianluca Zani, Maurizio Fusari; Arcispedale Sant'Anna Ferrara, Ferrara: Savino Spadaro, Carlo A. Volta; Ospedale Profili, Fabriano, Ancona: Romano Graziani, Barbara Brunettini; Umberto I. Nocera Inferiore, Nocera Inferiore Salerno: Salvatore Palmese; Azienda Ospedaliera San Paolo-Polo Universitario-Università degli Studi di Milano, Milan: Paolo Formenti, Michele Umbrello; Sant'Anna, San Fermo Della Battaglia, Como: Andrea Lombardo; Spedali Civili Brescia, Brescia: Elisabetta Pecci, Marco Botteri; Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca Granda, Ospedale Maggiore Policlinico, Milan: Monica Savioli, Alessandro Protti; University Campus Bio-Medico of Rome, Rome: Alessia Mattei, Lorenzo Schiavoni; Azienda Ospedaliera "Mellino Mellini," Chiari, Brescia: Andrea Tinnirello, Manuel Todeschini; Policlinico P. Giaccone, University of Palermo, Palermo: Antonino Giarratano, Andrea Cortegiani; Niguarda Cà Granda Hospital, Milan: Sara Sher, Anna Rossi; A. Gemelli University Hospital, Rome: Massimo M. Antonelli, Luca M. Montini; Ospedale "Sandro Pertini," Rome: Paolo Casalena, Sergio Scafetti; Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione; Istituto Di Ricovero e Cura a Carattere Scientifico; University of Pittsburgh Medical Center, Palermo: Giovanna Panarello, Giovanna Occhipinti; Ospedale San Gerardo, Monza: Nicolò Patroniti, Matteo Pozzi; Santa Maria Della Scaletta, Imola: Roberto R. Biscione, Michela M. Poli; Humanitas Research Hospital, Rozzano: Ferdinando Raimondi, Daniela Albiero; Ospedale Desio-Ao Desio-Vimercate, Desio: Giulia Crapelli, Eduardo Beck; Pinetragrande Private Hospital, Castelvoturno: Vincenzo Pota, Vincenzo Schiavone; Istituto di Ricovero e Cura a Carattere Scientifico San Martino Ist, Genova: Alexandre Molin, Fabio Tarantino; Ospedale San Raffaele,

Milano: Giacomo Monti, Elena Frati; Ospedali Riuniti Di Foggia, Foggia: Lucia Mirabella, Gilda Cinnella; Azienda Ospedaliera Luigi Sacco–Polo Universitario, Milano: Tommaso Fossali, Riccardo Colombo.; Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin: Pierpaolo Terragni Iliara Pattarino; Università degli Studi di Pavia-Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia: Francesco Mojoli, Antonio Braschi; Ao Ospedale Civile Legnano, Legnano: Erika E. Borotto; Arnas Ospedale Civico Di Cristina Benfratelli, Palermo: Andrea N. Cracchiolo, Daniela M. Palma; Azienda Ospedaliera Della Provincia Di Lecco–Ospedale “A. Manzoni,” Lecco: Francesco Raponi, Giuseppe Foti; A.O. Provincia Di Lecco–Ospedale Alessandro Manzoni, Lecco: Ettore R. Vascotto, Andrea Coppadoro; Cliniche Universitarie Sassari, Sassari: Luca Brazzi, Leda Floris; Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia: Giorgio A. Iotti, Aaron Venti

Japan: Yokohama City University Hospital, Yokohama: Osamu Yamaguchi, Shunsuke Takagi; Toyooka Hospital, Toyooka City: Hiroki N. Maeyama; Chiba University Hospital, Chiba City: Eizo Watanabe, Yoshihiro Yamaji; Okayama University Hospital, Okayama: Kazuyoshi Shimizu, Kyoko Shiozaki; Japanese Foundation for Cancer Research, Cancer Institute Hospital, Department of Emergency Medicine and Critical Care, Tokyo: Satoru Futami; Ibaraki Prefectural Central Hospital, Kasama: Sekine Ryo-suke; Tohoku University Hospital, Sendai-Shi: Koji Saito, Yoshinobu Kameyama; Tokyo Medical University Hachioji Medical Center, Hachioji, Tokyo: Keiko Ueno; Tokushima University Hospital, Tokushima: Masayo. Izawa, Nao Okuda; Maebashi Red Cross Hospital, Gunma Maebashi: Hiroyuki Suzuki, Tomofumi Harasawa; Urasoe General Hospital, Urasoe: Michitaka Nasu, Tadaaki Takada; Ohta General Hospital Foundation Ohta Nishinouchi Hospital, Fukushima: Fumihito Ito; Jichi Medical University Hospital, Shimotsuke: Shin Nunomiya, Kansuke Koyama; Mito Kyodo General Hospital, Tsukuba University Hospital Mito Medical Center, Mito: Toshikazu Abe; Sendai City Hospital, Sendai: Kohkichi Andoh, Kohei Kusumoto; Ja Hiroshima General Hospital, Hatsukaichi City, Hiroshima: Akira Hirata, Akihiro Takaba; Yokohama Rosai Hospital, Yokohama: Hiroyasu Kimura; Nagasaki University Hospital, Nagasaki: Shuhei Matsumoto, Ushio Higashijima; Niigata University Medical and Dental Hospital, Niigata: Hiroyuki Honda, Nobumasa Aoki; Mie University Hospital, Tsu, Mie: Hiroshi Imai; Yamaguchi University Hospital, Ube, Yamaguchi: Yasuaki Ogino, Ichiko Mizuguchi; Saiseikai Kumamoto Hospital, Kumamoto City: Kazuya Ichikado; Shinshu University School of Medicine, Matsumoto City: Kenichi Nitta, Katsunori Mochizuki; Kuki General Hospital, Kuki: Tomoaki Hashida; Kyoto Medical Center, Kyoto: Hiroyuki Tanaka; Fujita Health University, Toyooka: Tomoyuki Nakamura, Daisuke Niimi; Rakwakai

Marutamachi Hospital, Kyoto: Takeshi Ueda; Osaka University Hospital, Suita City, Osaka Prefecture: Yozo Kashiwa, Akinori Uchiyama

Latvia: Paul Stradins Clinical University Hospital, Riga: Olegs Sabelnikovs, Peteris Oss

Lebanon: Kortbawi Hospital, Jounieh: Youssef Haddad

Malaysia: Hospital Kapit, Kapit: Kong Y. Liew

Mexico: Instituto Nacional de Cancerología, Mexico City: Silvio A. Namendys-Silva, Yves D. Jarquin-Badiola; Hospital de Especialidades “Antonio Fraga Mouret” Centro Medico Nacional La Raza Instituto Mexicano del Seguro Social, Mexico City: Luis A. Sanchez-Hurtado, Saira S. Gomez-Flores; Hospital Regional 1° de Octubre, Mexico City: Maria C. Marin, Asisclo J. Villagomez; Hospital General Dr. Manuel Gea Gonzalez, Mexico City: Jordana S. Lemus, Jonathan M. Fierro; Hospital General de Zona No. 1 Instituto Mexicano del Seguro Social Tepic Nayarit, Tepic: Mavy Ramirez Cervantes, Francisco Javier Flores Mejia; Centro Medico Dalinde, Mexico City: Dulce Dec-tor, Alejandro Rojas; Opd Hospital Civil de Guadalajara Hospital Juan I. Menchaca, Guadalajara: Daniel R. Gonzalez, Claudia R. Estrella; Hospital Regional de Ciudad Madero Pemex, Ciudad Madero: Jorge R. Sanchez-Medina, Alvaro Ramirez-Gutierrez; Centro Médico American British Cowdray, Mexico City: Fernando G. George, Janet S. Aguirre; Hospital Juarez de Mexico, Mexico City: Juan A. Buensuseso, Manuel Poblano

Morocco: Mohammed V University, University Teaching Ibn Sina Hospital, Rabat: Tarek Dendane, Amine Ali Zeggwagh; Hopital Militaire D’Instruction Mohammed V, Rabat: Hicham Balkhi; Errazi, Marrakech: Mina Elkhayari, Nacer Samkaoui; University Teaching Hospital Ibn Rushd, Casablanca: Hanane Ezzouine, Abdellatif Benslama; Hôpital des Spécialités de Rabat, Rabat: Mourad Amor, Wajdi Maazouzi

Netherlands: Tjongerschans, Heerenveen: Nedim Cimic, Oliver Beck; Cwz, Nijmegen: Monique M. Bruns, Jeroen A. Schouten; Rijnstate Hospital, Arnhem: Myra Rinia, Monique Raaijmakers; Radboud Umc, Nijmegen: Leo M. Heunks, Hellen M. Van Wezel; Maastricht University Medical Center, Maastricht: Serge J. Heines, Ulrich Strauch; Catharinaziek-enhuis, Eindhoven: Marc P. Buijs; Academic Medical Center, Amsterdam: Fabienne D. Simonis, Marcus J. Schultz

New Zealand: Tauranga Hospital, Tauranga: Jennifer C. Goodson, Troy S. Browne; Wellington Hospital, Wellington: Leanlove Navarra, Anna Hunt; Dunedin Hospital, Dunedin: Robyn A. Hutchison, Mathew B. Bailey; Auckland City Hospital, Auckland: Lynette Newby, Colin McArthur; Whangarei Base Hospital, Whangarei: Michael Kalkoff, Alex Mcleod; North Shore Hospital, Auckland: Jonathan Casement, Danielle J. Hacking

Norway: Ålesund Hospital, Ålesund: Finn H. Andersen, Merete S. Dolva; Oslo University Hospital, Rikshospitalet Medical Center, Oslo: Jon H. Laake, Andreas Barratt-Due; Stavanger University Hospital, Stavanger: Kim Andre L.

Noremark, Eldar Søreide; Haukeland University Hospital, Bergen: Brit Å. Sjøbø, Anne B. Guttormsen

Peru: Hospital Nacional Edgardo Rebagliati Martins, Lima: Hector H. Leon Yoshido; Clínica Ricardo Palma, Lima: Ronald Zumaran Aguilar, Fredy A. Montes Oscanoa

Philippines: The Medical City, Pasig: Alain U. Alisis, Joanne B. Robles; Chong Hua Hospital, Cebu: Rossini Abbie B. Pasanting-Lim, Beatriz C. Tan

Poland: Warsaw University Hospital, Warsaw: Pawel Andruszkiewicz, Karina Jakubowska

Portugal: Centro Hospitalar Da Cova Da Beira, Covilhã: Cristina M. Coxo; Hospital Santa Maria, Chln, Lisboa: António M. Alvarez, Bruno S. Oliveira; Centro Hospitalar Trás-Os-Montes E. Alto Douro, Hospital de S. Pedro-Vila Real, Vila Real: Gustavo M. Montanha, Nelson C. Barros; Hospital Beatriz Ângelo, Loures: Carlos S. Pereira, António M. Messias; Hospital de Santa Maria, Lisboa: Jorge M. Monteiro; Centro Hospitalar Médio Tejo-Hospital de Abrantes, Abrantes: Ana M. Araujo, Nuno T. Catorze; Instituto Português de Oncologia de Lisboa, Lisboa: Susan M. Marum, Maria J. Bouw; Hospital Garcia de Orta, Almada: Rui M. Gomes, Vania A. Brito; Centro Hospitalar Do Algarve, Faro: Silvia Castro, Joana M. Estilita; Hospital de Cascais, Alcabideche: Filipa M. Barros; Hospital Prof. Doutor Fernando Fonseca Epe, Amadora: Isabel M. Serra, Aurelia M. Martinho

Romania: Fundeni Clinical Institute, Bucharest: Dana R. Tomescu, Alexandra Marcu; Emergency Clinical County Hospital Timisoara, Timisoara: Ovidiu H. Bedreag, Marius Papurica; Elias University Emergency Hospital, Bucharest: Dan E. Corneci, Silviu Ioan Negoita

Russian Federation: University Hospital, Kemerovo: Evgeny Grigoriev; Krasnoyarsk Regional Hospital, Krasnoyarsk State Medical University, Krasnoyarsk: Alexey I. Gritsan, Andrey A. Gzenkampf

Saudi Arabia: General Intensive Care Unit of Prince Sultan Military Medical City, Riyadh: Ghaleb Almekhlafi, Mohamad M. Albarrak; Surgical Intensive Care Unit of Prince Sultan Military Medical City, Riyadh: Ghanem M. Mustafa; King Faisal Hospital and Research Center, Riyadh: Khalid A. Maghrabi, Nawal Salahuddin; King Fahad Hospital, Baha: Tharwat M. Aisa; Neuro Critical Care Unit, King Abdulaziz Medical City, Riyadh: Ahmed S. Al Jabbar, Edgardo Tabhan; Intensive Care Unit, King Abdulaziz Medical City, Riyadh: Yaseen M. Arabi; Surgical Intensive Care Unit, King Abdulaziz Medical City, Riyadh: Yaseen M. Arabi, Olivia A. Trinidad; Trauma Intensive Care Unit, King Abdulaziz Medical City, Riyadh: Hasan M. Al Dorzi, Edgardo E. Tabhan

South Africa: Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg: Stefan Bolon, Oliver Smith

Spain: Hospital Sant Pau, Barcelona: Jordi Mancebo, Hernan Aguirre-Bermeo; Hospital Universitari Bellvitge, L'Hospitalet de Llobregat, Barcelona: Juan C. Lopez-Delgado, Francisco Esteve; Hospital Son Llatzer, Palma de

Mallorca: Gemma Rialp, Catalina Forteza; Sabadell Hospital, Centro de Investigación Biomédica en Red Enfermedades Respiratorias, Sabadell: Candelaria De Haro, Antonio Artigas; Hospital Universitario Central de Asturias, Oviedo: Guillermo M. Albaiceta, Sara De Cima-Iglesias; Complejo Hospitalario Universitario A Coruña, A Coruña: Leticia Seoane-Quiroga, Alexandra Ceniceros-Barros; Hospital Universitario Miguel Servet, Zaragoza: Antonio L. Ruiz-Aguilar, Luis M. Claraco-Vega; Morales Meseguer University Hospital, Murcia: Juan Alfonso Soler, Maria del Carmen Lorente; Hospital Universitario del Henares, Coslada: Cecilia Hermosa, Federico Gordo; Complejo Asistencial de Palencia, Hospital Rio Carrión, Palencia: Miryam Prieto-González, Juan B. López-Messa; Fundación Jiménez Díaz, Madrid: Manuel P. Perez, Cesar P. Perez; Hospital Clínico Universitario Lozano Blesa, Zaragoza: Raquel Montoiro Allue; Hospital Verge de la Cinta, Tortosa: Ferran Roche-Campo, Marcos Ibañez-Santacruz; Hospital Universitario 12 de Octubre, Madrid: Susana Temprano; Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid: Maria C. Pintado, Raul De Pablo; Hospital Universitari Germans Trias I Pujol, Badalona: Pilar Ricart Aroa Gómez; Hospital Universitario Arnau de Vilanova de Lleida, Lleida: Silvia Rodriguez Ruiz, Silvia Iglesias Moles; Cst Terrassa, Barcelona: M^a Teresa Jurado, Alfons Arizmendi; Hospital Universitari Mútua Terrassa, Terrassa: Enrique A. Piacentini; Hospital Universitario de Móstoles, Mostoles: Nieves Franco, Teresa Honrubia; Complejo Asistencial de Salamanca, Salamanca: Meisy Perez Cheng, Elena Perez Losada; Hospital General Universitario de Ciudad Real, Ciudad Real: Javier Blanco, Luis J. Yuste; Torrecardenas, Almeria: Cecilia Carbayo-Gorrioz, Francisca G. Cazorla-Barranquero; Hospital Universitario Donostia, San Sebastian: Javier G. Alonso, Rosa S. Alda; Hospital Universitario de Torrejón, Madrid: Ángela Algaba, Gonzalo Navarro; Hospital Universitario de La Princesa, Madrid: Enrique Cereijo, Esther Diaz-Rodriguez; Hospital Universitario Lucus Augusti, Lugo: Diego Pastor Marcos, Laura Alvarez Montero; Hospital Universitario Santa Lucia, Cartagena: Luis Herrera Para, Roberto Jimenez Sanchez; Hospital Universitario Severo Ochoa, Leganes, Madrid: Miguel Angel Blasco Navalpotro, Ricardo Diaz Abad; University Hospital of Nuestra Señora de Candelaria, Santa Cruz de Tenerife: Raquel Montiel González, Dácil Parrilla Toribio; Hospital Universitario Marques de Valdecilla, Santander: Alejandro G. Castro, Maria Jose D. Artiga; Hospital Infanta Cristina, Parla, Madrid: Oscar Penuelas; Hospital General de Catalunya, Sant Cugat del Valles: Tomas P. Roser, Moreno F. Olga; San Pedro de Alcántara, Cáceres: Elena Gallego Curto, Rocío Manzano Sánchez; Sant Joan de Reus, Reus: Vallverdu P. Imma, Garcia M. Elisabet; Hospital Joan XXIII, Tarragona: Laura Claverias, Monica Magret; Hospital Universitario de Getafe, Madrid: Ana M. Pellicer, Lucia L. Rodriguez; Hospital Universitario Río Hortega, Valladolid: Jesús Sánchez-Ballesteros, Ángela González-Salamanca;

Hospital Arquitecto Marcide, Ferrol, La Coruña: Antonio G. Jimenez, Francisco P. Huerta; Hospital General Universitario Gregorio Marañón, Madrid: Juan Carlos J. Sotillo Diaz, Esther Bermejo Lopez; Hospital General de Segovia, Segovia: David D. Llinares Moya, Alec A. Tallet Alfonso; Hospital General Universitario Reina Sofia, Murcia: Palazon Sanchez Eugenio Luis, Palazon Sanchez Cesar; Complejo Hospitalario Universitario de Albacete, Albacete: Sánchez I. Rafael, Corcoles G. Virgilio; Hospital Infanta Elena, Valdemoro: Noelia N. Recio

Sweden: Sahlgrenska University Hospital, Gothenburg: Richard O. Adamsson, Christian C. Rylander; Karolinska University Hospital, Stockholm: Bernhard Holzgraefe, Lars M. Broman; Akademiska Sjukhuset Uppsala, Uppsala: Joanna Wessbergh, Linnea Persson; Vrinnevisjukhuset, Norrköping: Fredrik Schiöler, Hans Kedelv; Linköping University Hospital, Linköping: Anna Oscarsson Tibblin, Henrik Appelberg; Skellefteå Lasarett, Skellefteå: Lars Hedlund, Johan Helleberg; Karolinska University Hospital Solna, Stockholm: Karin E. Eriksson, Rita Glietsch; Umeå University Hospital, Umeå: Niklas Larsson, Ingela Nygren; Danderyd Hospital, Stockholm: Silvia L. Nunes, Anna-Karin Morin; Lund University Hospital, Lund: Thomas Kander, Anne Adolfsson

Switzerland: Center Hospitalier Universitaire Vaudois, Lausanne: Lise Piquilloud; Hôpital neuchâtelois–La Chaux-de-Fonds, La Chaux-de-Fonds: Hervé O. Zender, Corinne Leemann-Refondini

Tunisia: Hôpital Taher Sfar Mahdia, Mahdia: Souheil Elatrous; University Hospital Farhat Hached Sousse, Sousse: Slaheddine Bouchoucha, Imed Chouchene; Center Hospitalier Universitaire F. Bourguiba, Monastir: Islem Ouanes; Mongi Slim University Hospital, La Marsa: Asma Ben Souissi, Salma Kamoun

Turkey: Cerrahpasa Medical Faculty Emergency Intensive Care Unit, Istanbul: Oktay Demirkiran; Cerrahpasa Medical Faculty Sadi Sun Intensive Care Unit, Istanbul: Mustafa Aker, Emre Erbabacan; Uludag University Medical Faculty, Bursa: Ilkay Ceylan, Nermin Kelebek Girgin; Ankara University Faculty of Medicine, Reanimation 3rd Level Intensive Care Unit, Ankara: Menekse Ozcelik, Necmettin Ünal; Ankara University Faculty of Medicine, 2nd Level Intensive Care Unit–Postoperative Intensive Care Unit, Ankara: Basak Ceyda Mec; Istanbul Kartal Egitim Ve Arastirma Hastanesi, Istanbul: Onat O. Akyol, Suleyman S. Derman

United Kingdom: Papworth Hospital, Cambridge: Barry Kennedy, Ken Parhar; Royal Glamorgan Hospital, Llantrisant: Latha Srinivasa; Royal Victoria Hospital, Belfast: Lia McNamee, Danny McAuley; Jack Steinberg Intensive Care Unit of the King's College, London: Phil Hopkins, Clare Mellis; Frank Stansil Intensive Care Unit of the King's College Hospital, London: Vivek Kakar; Liver Intensive Care Unit of the King's College, London: Dan Hadfield; Christine Brown Intensive Care Unit of the King's College, London:

Andre Vercueil; West Suffolk Hospital, Bury St. Edmunds: Kaushik Bhowmick, Sally K. Humphreys; Craigavon Area Hospital, Portadown: Andrew Ferguson, Raymond Mckee; Barts Health National Health Service Trust, Whipps Cross Hospital, Leytonstone: Ashok S. Raj, Danielle A. Fawkes; Kettering General Hospital, Foundation National Health Service Trust, Northamptonshire: Philip Watt, Linda Twohey; Barnet General Hospital, Barnet: Rajeev R. Jha, Matthew Thomas, Alex Morton, Varsha Kadaba; Rotherham General Hospital, Rotherham: Mark J. Smith, Anil P. Hormis; City Hospital, Birmingham: Santhana G. Kannan, Miriam Namih; Poole Hospital National Health Service Foundation Trust, Poole: Henrik Reschreiter, Julie Camsooksai; Weston General Hospital, Weston-Super-Mare: Alek Kumar, Szabolcs Rugonfalvi; Antrim Area Hospital, Antrim: Christopher Nutt, Orla Oneill; Aintree University Hospital, Liverpool: Colette Seaman, Ged Dempsey; Northern General Hospital, Sheffield: Christopher J. Scott, Helen E. Ellis; John Radcliffe Hospital, Oxford: Stuart Mckechnie, Paula J. Hutton; St. Georges Hospital, London: Nora N. Di Tomasso, Michela N. Vitale; Hillingdon Hospital, Uxbridge: Ruth O. Griffin, Michael N. Dean; Royal Bournemouth and Christchurch National Health Service Foundation Trust, Bournemouth: Julius H. Cranshaw, Emma L. Willett; Guy's and St. Thomas' National Health Service Foundation Trust, London: Nicholas Ioannou, Guy's and St. Thomas' Severe Respiratory Failure Service, Whittington Hospital, London: Sarah Gillis; Wexham Park Hospital, Slough: Peter Csabi; Western General Hospital, Edinburgh: Rosaleen Macfadyen, Heidi Dawson; Royal Preston Hospital, Preston: Pieter D. Preez, Alexandra J. Williams; Brighton and Sussex University Hospitals National Health Service Trust, Brighton: Owen Boyd, Laura Ortiz-Ruiz de Gordo; East and North Herts National Health Service Trust, Stevenage: Jon Bramall, Sophie Symmonds; Barnsley Hospital, Barnsley: Simon K. Chau, Tim Wenham; Prince Charles Hospital, Merthyr Tydfil: Tamas Szakmany, Piroska Toth-Tarsoly; University Hospital of South Manchester National Health Service Foundation Trust, Manchester: Katie H. Mcalman, Peter Alexander; Harrogate District Hospital, Harrogate: Lorraine Stephenson, Thomas Collyer; East and North Herts National Health Service Trust, Welwyn Garden City: Rhiannon Chapman, Raphael Cooper; Western Infirmary, Glasgow: Russell M. Allan, Malcolm Sim; Dumfries and Galloway Royal Infirmary, Dumfries: David W. Wrathall, Donald A. Irvine; Charing Cross Hospital, London: Kim S. Zantua, John C. Adams; Worcestershire Royal Hospital, Worcester: Andrew J. Burtenshaw, Gareth P. Sellors; Royal Liverpool University Hospital, Liverpool: Ingeborg D. Welters, Karen E. Williams; Royal Alexandra Hospital, Glasgow: Robert J. Hessel, Matthew G. Oldroyd; Morriston Hospital, Swansea: Ceri E. Battle, Suresh Pillai; Frimley Park Hospital, Frimley: Istvan Kajtor, Mageswaran Sivashanmugavel; Altnagelvin Hospital, Derry: Sinead C. Okane, Adrian Donnelly; Buckinghamshire Healthcare National Health Service

Trust, High Wycombe, Buckinghamshire: Aniko D. Frigyk, Jon P. Careless; Milton Keynes Hospital, Milton Keynes: Martin M. May, Richard Stewart; Ulster Hospital, Belfast: T. John Trinder, Samantha J. Hagan; University Hospital of Wales, Cardiff: Jade M. Cole; Freeman Hospital, Newcastle upon Tyne: Caroline C. MacFie, Anna T. Dowling

Uruguay: Hospital Español, Montevideo: Javier Hurtado, Nicolás Nin; Cudam, Montevideo: Javier Hurtado; Sanatorio Mautone, Maldonado: Edgardo Nuñez; Sanatorio Americano, Montevideo: Gustavo Pittini, Ruben Rodriguez; Hospital de Clínicas, Montevideo: María C. Imperio, Cristina Santos; Circulo Católico Obreros Uruguay-Sanatorio Juan Pablo II, Montevideo: Ana G. França, Alejandro Ebeid; Centro de Asistencia del Sindicato Médico del Uruguay, Montevideo: Alberto Deicas, Carolina Serra

United States: St. Louis University Hospital, St. Louis, Missouri: Aditya Uppalapati, Ghassan Kamel; Beth Israel Deaconess Medical Center, Boston, Massachusetts: Valerie M. Banner-Goodspeed, Jeremy R. Beitler; Memorial Medical Center, Springfield, Illinois: Satyanarayana Reddy Mukhera, Shreedhar Kulkarni; Massachusetts General Hospital, Boston, Massachusetts: Jarone Lee, Tomaz Mesar; University of Cincinnati Medical Center, Cincinnati, Ohio: John O. Shinn III, Dina Gomaa; Massachusetts General Hospital, Boston, Massachusetts: Christopher Tainter, Jarone Lee; Massachusetts General Hospital, Boston, Massachusetts: Tomaz Mesar, Jarone Lee; R. Adams Cowley Shock Trauma Center, Baltimore, Maryland: Dale J. Yeatts, Jessica Warren; Intermountain Medical Center, Murray, Utah: Michael J. Lanspa, Russel R. Miller; Intermountain Medical Center, Murray, Utah: Colin K. Grissom, Samuel M. Brown; Mayo Clinic, Rochester, Minnesota: Philippe R. Bauer; North Shore Medical Center, Salem, Massachusetts: Ryan J. Goselin, Barrett T. Kitch; Albany Medical Center, Albany, New York: Jason E. Cohen, Scott H. Beegle, Shazia Choudry; John H. Stoger Hospital of Cook County, Chicago, Illinois: Renaud M. Gueret, Aiman Tulaimat; University of

Alabama at Birmingham, Birmingham, Alabama: William Stigler, Hitesh Batra; Duke University Hospital, Durham, North Carolina: Nidhi G. Huff; Iowa Methodist Medical Center, Des Moines, Iowa: Keith D. Lamb, Trevor W. Oetting; Surgical and Neurosciences Intensive Care Unit of the University of Iowa Hospitals and Clinics, Iowa City, Iowa: Nicholas M. Mohr, Claine Judy; Medical Center of Louisiana at New Orleans, New Orleans, Louisiana: Shigeki Saito, Fayez M. Kheir; Tulane University, New Orleans, Louisiana: Fayez Kheir; Critical Care Unit of the University of Iowa Hospitals and Clinics, Iowa City, Iowa: Adam B. Schlichting, Angela Delsing; University of California, San Diego Medical Center, San Diego, California: Daniel R. Crouch, Mary Elmasri; University of California San Diego Thornton Hospital, La Jolla, California: Daniel R. Crouch, Dina Ismail; University Hospital, Cincinnati, Ohio: Kyle R. Dreyer, Thomas C. Blakeman, Dina Gomaa; Tower 3B Medical Intensive Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Rebecca M. Baron, Carolina Quintana Grijalba; Tower 8C Burn/Trauma Intensive Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Peter C. Hou; Tower 8D Surgical Intensive Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Raghu Seethala; Tower 9C Neurosurgical Intensive Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Imo Aisiku; Tower 9D Neurological Intensive Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Galen Henderson; Tower 11C Thoracic Intensive Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Gyorgy Frenzl; Shapiro 6W Cardiac Surgery Intensive Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Sen-Kuang Hou; Shapiro 9E Coronary Care Unit of Brigham and Women's Hospital, Boston, Massachusetts: Robert L. Owens, Ashley Schomer

Serbia: Clinical Center of Serbia, Belgrade: Vesna Bumbasirevic, Bojan Jovanovic; Military Medical Academy, Belgrade: Maja Surbatovic, Milic Veljovic