ditions, most notably cancer, were previously described in a similar manner but are now further characterized based not just on anatomic location and cell type but most recently on expression of specific biomarkers, including cellular receptors, activation of intracellular pathways, and genomic alterations. Such characterization has enabled development of therapies targeted to specific patients, with remarkable improvements in outcome. Although the present definition for sepsis provides needed evolution in categorization of this syndrome, incorporation of more information about the molecular and cellular characterization of sepsis may have been helpful. Hopefully, the next iteration of this consensus process will take full advantage of the rapidly advancing understanding of molecular processes that lead from infection to organ failure and death so that sepsis and septic shock will no longer need to be defined as a syndrome but rather as a group of identifiable diseases, each characterized by specific cellular alterations and linked biomarkers. Such evolution will be required to truly transform care for the millions of patients worldwide who develop these life-threatening conditions.

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The Acute Respiratory Distress Syndrome
Dialing in the Evidence?

Brendan J. Clark, MD; Marc Moss, MD

Acute respiratory distress syndrome (ARDS) could be regarded as a prototypical disorder that has benefited from a bench to bedside research approach. After its original description in 1967, the complex pathophysiology of ARDS has been slowly unraveled through extensive basic and translational research. Based on this improved understanding of the mechanisms responsible for ARDS, a variety of major clinical trials were subsequently designed and conducted. Several of these clinical trials identified relatively simple and biologically plausible interventions that reduced mortality for patients with ARDS. For example, the ARDS network trial established that low tidal volume ventilation (6 mL/kg of predicted body weight) reduced mortality from 40% to 31%.[1] A meta-analysis of 3 other trials demonstrated that a strategy of high positive end-expository pressure (PEEP) was associated with decreased mortality for patients with moderate to severe ARDS.[2] In addition, ventilation in the prone position early in the course of moderate to severe ARDS resulted in a 16% absolute risk reduction in mortality.[3] In theory, these beneficial therapies should be relatively easy to implement. They are essentially free, involve adjusting the dials on the ventilator or positioning patients, and are relatively safe.

Related article page 788

As the mechanistic and clinical understanding of ARDS advanced, concerns arose about the diagnostic criteria used to define ARDS. A panel of experts was convened to evaluate the objective performance of various diagnostic criteria for ARDS using a consensus process. The result was that the 2012 Berlin Definition changed several the diagnostic criteria for ARDS. The Berlin criteria included a graded severity based on the degree of hypoxemia was created (mild, moderate, or severe ARDS), a minimal amount of PEEP was added as a specific diagnostic criterion, and the intubation requirement was removed for patients with mild ARDS.[4]

Until the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study, reported by Bellani and colleagues in this

issue of *JAMA*, little was known about how the Berlin Definition of ARDS was being used and whether the results of clinical trials were being implemented in clinical practice.[5] For 4 weeks during the winter of 2014, LUNG SAFE investigators conducted a large multinational prospective cohort study, including 29 144 patients from 459 intensive care units (ICUs) from 50 countries. This study has many strengths including its large sample size, rigorous data collection, and provocative results.

The study confirmed that ARDS is common, accounting for 10.4% of all ICU admissions (3022 patients) and 23.4% of 12 906 patients breathing with the aid of mechanical ventilation. However, despite the relatively high prevalence of ARDS, the rate of clinician recognition was surprisingly low. Only 60% of ARDS cases were identified at any point during their clinical course, and only 34% of cases were identified at the initial time that ARDS criteria were met. Therefore, the findings suggest that the diagnosis of ARDS was frequently delayed and often was not made. These low rates of ARDS recognition are particularly concerning given that clinicians likely knew their hospital was participating in an ARDS study. Thus, it is possible that there was a Hawthorne effect in the study and that these low rates of clinician recognition of ARDS are overestimates of what likely happens in daily practice.

Moreover, clinicians frequently failed to deliver interventions with proven efficacy. For example, 36% of patients with ARDS did not receive low tidal volume ventilation and instead received potentially deleterious high tidal volumes of greater than 8 mL/kg of predicted body weight. Patients with ARDS also routinely received low levels of PEEP, well below the amount used for a high-PEEP strategy. In addition, prone positioning, a therapy found to significantly decrease mortality in moderate to severe ARDS, was rarely used and indeed was used no more commonly than other purported rescue therapies (inhaled nitric oxide and systemic corticosteroids) for which previous randomized trials failed to demonstrate clinical benefit. Perhaps most importantly, the study confirmed that the in-hospital ARDS mortality remained high, with 34.9% mortality for mild, 40.3% mortality for moderate, and 46.1% mortality for severe ARDS.

What can be done to lower the unacceptably high mortality rate in ARDS? Even though there is room to deepen current understanding of the pathophysiology of ARDS and to develop new targeted treatments, the LUNG SAFE study demonstrates that improved recognition of ARDS might be the best place to start. A recent report from the Institute of Medicine highlights that diagnostic errors harm an unacceptable number of patients, are more costly today than ever before, and are a substantial source of avoidable death.[6] Why do well-intentioned, experienced, and knowledgeable physicians fail to recognize ARDS? The Institute of Medicine report underscores that diagnostic errors are "a consequence of the interplay between cognitive and system-related vulnerabilities" and that measurement plays a critical role in reducing diagnostic errors.[7,8] From a cognitive standpoint, one hypothesis is that overreliance on short-term memory, which may only be able to hold 4 "chunks" of information at any one time, could impair decision making.[9] Although it is a coincidence that the Berlin Definition has 4 major diagnostic categories, it is easy to see how a critical care clinician could have difficulty connecting and processing specific elements of patient data, especially when barraged with hundreds of pieces of clinical information during the initial phase of a patient's critical illness.

Several potential strategies may enhance the clinician's ability to recognize ARDS. In hospitals with electronic health record systems, an electronic surveillance system may be able to screen the medical record and proactively prompt clinicians when ARDS is suspected based on clinical data. Electronic surveillance tools for ARDS have been developed, have been validated in single centers, and have shown promise as highly sensitive tools that outperform manual screening.[10,11] Therefore, larger scale research studies are needed to determine whether these electronic tools accurately raise signals that help identify patients with ARDS.

To diagnose ARDS, a clinician must also be able to perform specific tests such as arterial blood gases and chest radiographs. In resource limited settings, these tests may not be routinely performed or available at the time of the clinician's initial evaluation. Increasing evidence suggests that the more readily available pulse oximetry may be used to determine an arterial oxygen saturation to fraction of inspired oxygen (Spo_2/Fio_2) ratio and identify hypoxemia; instead of requiring an arterial blood gas to calculate a Pao_2/Fio_2 ratio. In a recent epidemiological study examining the incidence of ARDS in a Rwandan referral hospital, investigators used prespecified Spo_2/Fio_2 ratios to determine the hypoxemia diagnostic criteria. Similarly, lung ultrasonography may be able to identify bilateral infiltrates in place of a chest radiograph.[12] As the evidence supporting the validity of Spo_2/Fio_2 ratios and lung ultrasonography accumulates, an addendum to the Berlin hypoxemia and chest radiographic criteria may be necessary to facilitate and expedite the diagnosis of ARDS.

Even if the clinical recognition of ARDS were substantially improved, a large gap still exists between evidence and practice. One explanation for this gap might be that the critical care community has become somewhat cautious about adopting new therapies. The initial results of several critical care trials including intensive insulin therapy and activated protein C were not replicated in subsequent clinical trials.[13,14] However, changing clinical behavior to improve quality of care is difficult. Implementation science can help identify methods that effectively translate research findings into clinical practice. Traditional educational methods such as guidelines, presentations at conferences, and publications in journals clearly are not sufficient to change ARDS treatment practices. The failure to implement effective strategies for ARDS likely goes beyond a lack of knowledge and extends to the attitudes and beliefs of nurses, respiratory therapists, and critical care physicians.[15] Therefore, more effective implementation strategies may require multiple approaches such as identification of an ICU or hospital-specific physician (or another health care professional) who will serve as a champion and advocate to improve clinical practice, engagement of multiple members of the interprofessional team that provides care for patients with

ARDS, and involvement in a network of health care professionals dedicated to quality. In support of these implementation approaches, a multifaceted knowledge transfer intervention was able to enhance adherence with 6 ICU process measures in 15 ICUs in Ontario, Canada.[16]

An additional barrier to the implementation of low tidal volume ventilation, higher PEEP, and prone ventilation may be that no manufacturer or proprietary interest has a direct financial incentive to increase uptake and utilization. However, there are other important stakeholders. Research funding agencies have invested a tremendous amount of money to advance the understanding of ARDS and test novel therapies in clinical trials. If the ultimate goal of this investment is to improve outcomes, it makes sense that research funding agencies would also develop an implementation research portfolio. For example, the National Heart, Lung, and Blood Institute recently created the Center for Translational Research and Implementation Science to focus on narrowing the gap between evidence and practice. Other important stakeholders could include hospital administrators, patient advocacy groups, policy makers, as well as payers. When evidence is not translated into practice, payers potentially bear the financial burden. A financial investment in implementation science by payers could lead to a sound return—with both improved patient outcomes and decreased costs.[17]

Even though important advances have been made in the care of patients with ARDS, high-quality care has not routinely reached the bedside of every patient. Proven therapies such as low tidal volume ventilation are not being effectively used in many clinical settings around the world. The medical and critical care community should prioritize the proper implementation of beneficial therapies, engage the necessary stakeholders, and take the next steps to dial in the evidence to improve the treatment and outcomes of patients with ARDS.

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Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

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IMPORTANCE Limited information exists about the epidemiology, recognition, management, and outcomes of patients with the acute respiratory distress syndrome (ARDS).

OBJECTIVES To evaluate intensive care unit (ICU) incidence and outcome of ARDS and to assess clinician recognition, ventilation management, and use of adjuncts—for example prone positioning—in routine clinical practice for patients fulfilling the ARDS Berlin Definition.

DESIGN, SETTING, AND PARTICIPANTS The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) was an international, multicenter, prospective cohort study of patients undergoing invasive or noninvasive ventilation, conducted during 4 consecutive weeks in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across 5 continents.

EXPOSURES Acute respiratory distress syndrome.

MAIN OUTCOMES AND MEASURES The primary outcome was ICU incidence of ARDS. Secondary outcomes included assessment of clinician recognition of ARDS, the application of ventilatory management, the use of adjunctive interventions in routine clinical practice, and clinical outcomes from ARDS.

RESULTS Of 29 144 patients admitted to participating ICUs, 3022 (10.4%) fulfilled ARDS criteria. Of these, 2377 patients developed ARDS in the first 48 hours and whose respiratory failure was managed with invasive mechanical ventilation. The period prevalence of mild ARDS was 30.0% (95% CI, 28.2%-31.9%); of moderate ARDS, 46.6% (95% CI, 44.5%-48.6%); and of severe ARDS, 23.4% (95% CI, 21.7%-25.2%). ARDS represented 0.42 cases per ICU bed over 4 weeks and represented 10.4% (95% CI, 10.0%-10.7%) of ICU admissions and 23.4% of patients requiring mechanical ventilation. Clinical recognition of ARDS ranged from 51.3% (95% CI, 47.5%-55.0%) in mild to 78.5% (95% CI, 74.8%-81.8%) in severe ARDS. Less than two-thirds of patients with ARDS received a tidal volume 8 of mL/kg or less of predicted body weight. Plateau pressure was measured in 40.1% (95% CI, 38.2-42.1), whereas 82.6% (95% CI, 81.0%-84.1%) received a positive end-expository pressure (PEEP) of less than 12 cm H_2O. Prone positioning was used in 16.3% (95% CI, 13.7%-19.2%) of patients with severe ARDS. Clinician recognition of ARDS was associated with higher PEEP, greater use of neuromuscular blockade, and prone positioning. Hospital mortality was 34.9% (95% CI, 31.4%-38.5%) for those with mild, 40.3% (95% CI, 37.4%-43.3%) for those with moderate, and 46.1% (95% CI, 41.9%-50.4%) for those with severe ARDS.

CONCLUSIONS AND RELEVANCE Among ICUs in 50 countries, the period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be underrecognized and undertreated and associated with a high mortality rate. These findings indicate the potential for improvement in the management of patients with ARDS.

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Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung injury, associated with increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue.[1] Although prior epidemiologic studies have provided substantial insights into ARDS,[2-5] there remains limited information about the epidemiology, recognition, management, and outcomes of patients with the ARDS, especially in the era of the current Berlin Definition.[1] This definition was constructed empirically and validated using retrospective cohorts[1]; however, prospective studies of the Berlin Definition have been limited to small numbers of centers and patients.[6,7]

We set out to address some clinically important questions regarding ARDS. The current incidence and mortality of ARDS in a large international cohort is not known. Large regional differences have been suggested; for example, the incidence of ARDS in Europe[5] is reported to be 10-fold lower than in the United States.[4] A number of ventilatory interventions, such as lower tidal volumes,[8] higher positive end-expiratory pressure (PEEP),[9] and adjuncts such as prone positioning,[10] neuromuscular blockade,[11] and extracorporeal membrane oxygenation[12] for ARDS have been proposed. It is not clear how these interventions are applied in routine practice in the broader international context. Implementation of effective therapies may be limited by lack of recognition of ARDS by clinicians.[13,14] Understanding the factors associated with ARDS recognition and its effect on management could lead to effective interventions to improve care.

Therefore, we undertook the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) to determine the intensive care unit (ICU) epidemiology and outcomes from ARDS, assess clinician recognition of ARDS, and understand how clinicians use mechanical ventilation and adjunctive interventions in routine clinical practice.

Methods

Study Design

This study was an international, multicenter, prospective cohort study. The enrollment window consisted of 4 consecutive winter weeks (February-March 2014 in the Northern hemisphere and June-August 2014 in the Southern hemisphere), as selected by each ICU. We aimed to recruit a broadly representative sample of ICUs by public announcements by the European Society of Intensive Care Medicine, by national societies and networks endorsing the study, and by designated national coordinators (eAppendix 1 in the Supplement). The study ICUs represent a convenience sample of those that agreed to participate in the study and had enrolled at least 1 patient. Different ICUs from the same hospital were considered as separate centers; each ICU provided baseline data concerning its resources (eTable 1 in the Supplement). All participating ICUs obtained ethics committee approval and obtained either patient consent or ethics committee waiver of consent. We recruited physicians from each participating country as lead site investigators and national coordinators. Site investigators (eAppendix 2 in the Supplement) were also responsible for ensuring data integrity and validity, and were offered web-based training to enhance chest x-ray interpretation reliability as part of a substudy.

Patients, Study Design, and Data Collection

All patients, including ICU transfers, admitted to an ICU within the 4-week enrollment window and receiving invasive or noninvasive ventilation were enrolled. Exclusion criteria were age younger than 16 years or inability to obtain informed consent, when required. Following enrollment, patients were evaluated daily for acute hypoxemic respiratory failure, defined as the concurrent presence of (1) ratio of arterial oxygen tension to inspired fraction of oxygen (Pao_2/Fio_2) of 300 mm Hg or less; (2) new pulmonary parenchymal abnormalities on chest x-ray or computed tomography; and (3) ventilatory support with continuous positive airway pressure (CPAP), expiratory positive airway pressure (EPAP), or positive end-expiratory pressure (PEEP) of 5 cm H_2O or more

Day 1 was defined as the first day that acute hypoxemic respiratory failure criteria were satisfied, irrespective of ICU admission date. The case report form (eAppendix 3 in the Supplement) automatically prompted investigators to provide an expanded data set for days 1, 2, 3, 5, 7, 10, 14, 21, and 28 or at ICU discharge or death. All data were recorded at the same time, normally as close as possible to 10 AM each day. Patient outcomes included date of liberation from mechanical ventilation and vital status at ICU discharge and at either hospital discharge or at day 90, whichever occurred earlier.

Quality Control

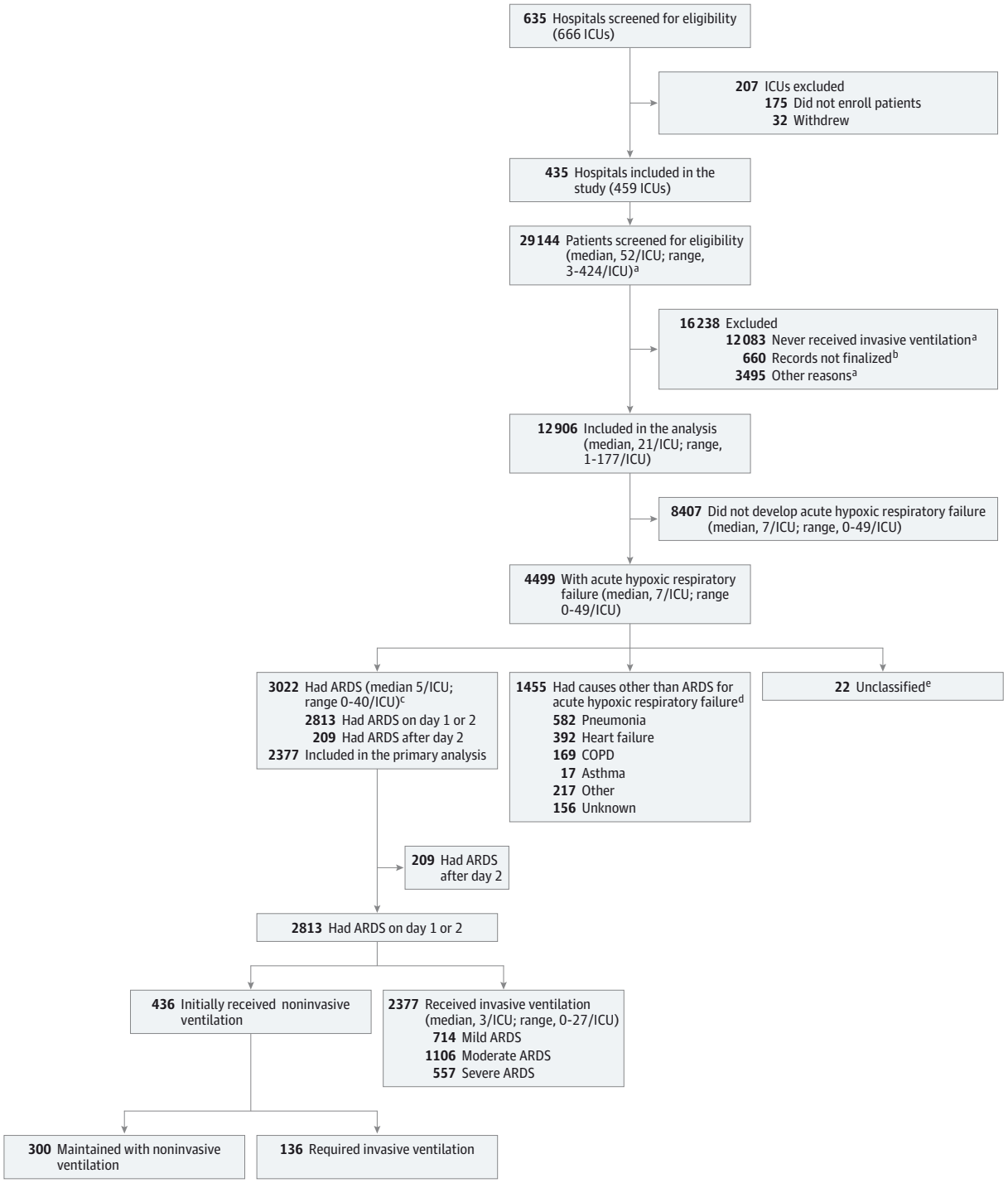
At the time of data entry, the site investigators were required to answer all queries raised by the case report form before they could electronically finalize a patient data set. Patient data sets that were not finalized were not included in the analysis (**Figure 1**). In addition, prior to analysis, all data were screened for potentially erroneous data and outliers. These data were verified or corrected by site investigators. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for observational cohort studies.[15]

Identification and Recognition of ARDS

The diagnosis of ARDS was made by a computer algorithm in the analysis phase of the study using the raw data that made up the various components of the Berlin ARDS Definition: (1) presence of acute hypoxemic respiratory failure criteria, (2) onset within 1 week of insult, or new (within 7 days) or worsening respiratory symptoms; (3) bilateral airspace disease on chest x-ray or computed tomography not fully explained by effusions, lobar or lung collapse, or nodules; and (4) cardiac failure not the primary cause of acute hypoxemic respiratory failure.

We assessed clinician recognition of ARDS at 2 time points. On day 1 of study entry, site investigators indicated the reasons for the patient's hypoxemia, with ARDS included as a potential cause. If the answer was "yes," ARDS was deemed to have been clinician-recognized on day 1. When patients exited the study, investigators were asked if the patient had ARDS at any stage during their ICU stay. ARDS was deemed to have

Figure 1. Flow of Patient Screening and Enrollment



[a] Projected from data provided by 360 intensive care units (ICUs [78%]). Data specifying other reasons were not collected during the study.

[b] Patient electronic case report forms that were not fully complete were excluded.

[c] Number included in the primary analysis.

[d] Patients could have more than one cause for acute hypoxic respiratory failure.

[e] For unclassified patients it was not possible to determine whether they fulfilled the criteria for acute respiratory distress syndrome (ARDS) due to incomplete data.

been clinician-recognized at any point if either question was answered positively. Although clinicians were offered participation in a substudy to evaluate a training module on chest x-ray diagnosis of ARDS, they were not specifically prompted with the Berlin criteria when answering the questions about ARDS diagnosis. Criteria for other diagnoses, such as chronic

obstructive pulmonary disease, pneumonia, etc were left to clinician discretion.

ARDS Severity and Mechanical Ventilation Parameters

Patients with ARDS undergoing invasive ventilation were categorized on the day of ARDS diagnosis based on their Pao_2/Fio_2 ratio into mild (200 $<Pao_2/Fio_2 \leq 300$ mm Hg), moderate (100 $<Pao_2/Fio_2 \leq 200$ mm Hg), and severe (Pao_2/Fio_2 <100 mm Hg) based on the Berlin Definition.[1] Given the lack of clarity in the Berlin Definition regarding the severity classification of patients managed with noninvasive ventilation, and the difficulty in comparing noninvasive ventilation settings to invasive modes, we excluded patients ventilated on noninvasive ventilation from the analyses pertaining to severity, ventilator management or outcome. To ensure a more homogenous data set, we restricted subsequent analyses to the large subset of patients (93.1%) fulfilling ARDS criteria on day 1 or 2 from onset of acute hypoxemic respiratory failure.

Invasive ventilator-free days were 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. Driving pressure was defined as plateau pressure (P_{plat}) minus PEEP.

Patients were considered to have no evidence for spontaneous ventilation when set and measured respiratory rates were equal.

Calculation of Period Prevalence and Per-ICU-Bed ARDS Incidence

The period prevalence of patients with ARDS was calculated by dividing the number of patients fulfilling ARDS criteria by the total number of patients admitted to the ICU in the 28-day study period (ie, 29 160). The number of patients with ARDS per ICU bed over the 4-week study period was calculated as number of patients with ARDS/number of ICU beds available.

ICU Enrollment and Statistical Analysis

The primary outcome was to determine the ICU incidence of ARDS. Secondary outcomes included assessment of clinician recognition of ARDS, the application of ventilatory management, the use of adjunctive interventions in routine clinical practice, and the outcomes from ARDS. We wished to enroll at least 1000 patients with ARDS. Assuming a 30% mortality, 300 deaths would allow us to evaluate at least 30 associated variables in multivariable models.[16] Prior epidemiological studies reported an ARDS incidence ranging between 2.2% and 19% of ICU patients.[2-5] Based on a conservative a priori estimate that 5% of ICU admissions would have ARDS and projecting that a medium-sized ICU admits 50 patients per month, we planned to enroll at least 500 ICUs worldwide.

Descriptive statistics included proportions for categorical and mean (standard deviation) or median (interquartile range [IQR]) for continuous variables. The amount of missing data was low, with the exception of plateau pressure P_{plat} and arterial oxygen saturation (Sao_2), and is detailed in eTable 2 in the Supplement). No assumptions were made for missing data. Data were unadjusted unless specifically stated otherwise. Proportions were compared using χ^2 or Fisher exact tests and continuous variables were compared using the *t* test or Wilcoxon rank-sum test, as appropriate. To evaluate variables associated with clinician recognition of ARDS, covariates determined a priori to be associated with ARDS recognition and covariates associated with ARDS recognition with $P < .20$ in bivariate analyses were entered into multivariable regression models with variable selection based on a stepwise backward elimination pro-

Table 1. Characteristics of Patients With Acute Respiratory Distress Syndrome

Parameter	Value
No. of patients	
ARDS	3022
ARDS in first 48 h after AHRF	2813
No longer fulfill ARDS criteria after 24 h, No. (%) [95% CI]	486 (17) [15.9-18.7]
Clinician recognition of ARDS, No. (%) [95% CI]	1820 (60) [59-62.0]
Age, mean (95% CI)y	61.5 (60.9-62.1)
Women, No. (%)	1151 (38)
Height, mean (95% CI), cm	168 (167.6-168.4)
Weight, mean (95% CI), kg	78.0 (77-79)
Chronic disease, No. (%)	
COPD	657 (21.7)
Diabetes	657 (21.7)
Immunoincompetence	365 (12.1)
Chronic cardiac failure	314 (10.4)
Chronic renal failure	306 (10.1)
Active neoplasm	258 (8.5)
Hematological disease	142 (4.7)
Risk factor for ARDS, No. (%)[a]	
Pneumonia	1794 (59.4)
Extrapulmonary sepsis	484 (16.0)
Aspiration	430 (14.2)
Noncardiogenic shock	226 (7.5)
Trauma	127 (4.2)
Blood transfusion	118 (3.9)
Pulmonary contusion	97 (3.2)
Inhalation	72 (2.3)
Drug overdose	56 (1.9)
Pulmonary vasculitis	41 (1.4)
Burn	9 (0.3)
Drowning	2 (0.1)
Other risk factor	82 (2.7)
No risk factor	252 (8.3)
Duration of invasive mechanical ventilation, median (IQR), d	8 (4-16)
Duration of ICU stay, median (IQR), d	10 (5-19)
ICU survival, No. (%) [95% CI]	1994 (66.0) [64.3-67.7]
Duration of hospital stay, median (IQR), d	17 (9-32)
Hospital survival, No. (%) [95% CI][b]	1826 (60.4) [58.7-62.2]

Abbreviations: AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR (interquartile range).

[a] Total is greater than 100%, because patients could have more than 1 risk factor.

[b] Data are missing for 10 patients.

Table 2. Organizational and Patient Factors Associated With Clinician Recognition of ARDS in Invasively Ventilated Patients

	ARDS Recognized, No./Total No. (%)	Absolute Difference (95% CI)	Bivariate OR (95% CI)	*P* Value[a]	Multivariable OR (95% CI)	*P* Value[b]
No. of patients/staff physician, for each additional patient		−1.20 (−0.74 to −1.66)[c]	0.960 (0.945 to 0.976)	<.001	0.959 (0.942 to 0.977)	<.001
No. of patients/nurse, for each additional patient		−0.34 (−0.55 to −0.13)[c]	0.911 (0.860 to 0.957)	<.001	0.920 (0.870 to 0.968)	.002
Age, per year		−4.03 (−5.43 to −2.65)[c]	0.985 (0.980 to 0.990)	<.001	0.987 (0.980 to 0.993)	<.001
Predicted body weight per kg		−1.27 (−2.18 to −0.36)[c]	0.989 (0.980 to 0.997)	.006	0.984 (0.974 to 0.993)	<.001
Nonpulmonary SOFA per point		0.81 (0.48 to 1.12)[c]	1.054 (1.031 to 1.077)	<.001	1.057 (1.030 to 1.085)	<.001
Pao_2:FIO_2 ratio, per mm Hg		−30.0 (−35.5 to −24.4)[c]	0.993 (0.992 to 0.995)	<.001	0.993 (0.992 to 0.995)	<.001
Medical or surgical Admission with trauma						
No	1477/2274 (65.0)		1 [Reference]		1 [Reference]	
Yes	48/103 (46.6)	−18.4 (−28.7 to −8.0)	0.471 (0.316 to 0.700)	<0.001	0.539 (0.334 to 0.868)	.011
Neoplastic or immune or hematologic disease						
No	1173/1892 (62.0)		1 [Reference]		1 [Reference]	
Yes	352/485 (72.6)	10.6 (6.0 to 15.1)	1.623 (1.305 to 2.027)	<.001	1.396 (1.079 to 1.816)	.012
Pneumonia						
No	440/1002 (43.9)		1 [Reference]		1 [Reference]	
Yes	963/1375 (70.0)	26.1 (22.2 to 30.0)	1.830 (1.544 to 2.170)	<.001	1.339 (1.073 to 1.670)	.01
Pancreatitis						
No	844/2328 (36.3)		1 [Reference]		1 [Reference]	
Yes	41/49 (83.7)	47.4 (36.9 to 58.0)	2.915 (1.436 to 6.733)	.006	3.506 (1.439 to 10.543)	.01
ARDS risk factors						
Yes	1454/2187 (66.5)		1 [Reference]		1 [Reference]	
No	71/190 (37.4)	−29.1 (−36.3 to −22.0)	0.301 (0.220 to 0.408)	<.001	0.408 (0.280 to 0.591)	<.001
With heart failure						
No	1347/2027 (66.5)		1 [Reference]		1 [Reference]	
Yes	178/350 (50.9)	−15.6 (−21.2 to −10.0)	0.522 (0.415 to 0.657)	<.001	0.496 (0.377 to 0.652)	<.001

Abbreviations. ARDS, acute respiratory distress syndrome; Pao_2/FIO2; partial pressure of oxygen to fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

[a] Bivariate analysis.

[b] All variables included in the multivariable analysis are reported in this Table.

[c] These values are the mean difference (95% CI).

cedure using *P* values. The association of clinician recognition with ventilatory management of ARDS was determined for tidal volume, PEEP, P_{plat} measurement, and use of prone positioning and neuromuscular blockade in separate multivariable stepwise backward logistic or multiple linear regression models as appropriate. We did not perform any longitudinal data analyses. A Kaplan-Meier estimate of the cumulative probability of unassisted breathing and survival to day 28 was performed. Patients discharged from the hospital before day 28 were assumed alive at this time point. Statistical analyses were performed with R 3.2.3 (http://www.R-project.org). All *P* values were 2-sided, with *P* values <.05 considered statistically significant. The study protocol, case report form and full statistical analysis plan are included in eAppendix 3 in the Supplement.

Results

Participating ICUs and Patients Enrolled

Six hundred sixty-six ICUs registered for the study. Following data verification and elimination of nonrecruiting sites, 459 ICUs from 50 countries were included in the final analysis (eTable 1 and eTable 3 in the Supplement). Of the 29 144 patients admitted to these ICUs during the enrollment period, 13 566 patients receiving ventilatory support were enrolled. Complete data sets from 12 906 patients were analyzed (Figure 1). **Table 1** outlines their key characteristics.

Characteristics of Patients Enrolled

Of 4499 patients with acute hypoxemic respiratory failure, 3022 (67.2%) fulfilled ARDS criteria during their ICU stay. Of these, 2813 (93.1%) developed ARDS at day 1 (n = 2665) or day 2 (n = 148), whereas 209 patients (6.9%) developed ARDS after day 2 of acute hypoxemic respiratory failure (Figure 1). The 436 patients (14.4%) with ARDS who received noninvasive ventilation were excluded from analyses regarding ARDS severity, mechanical ventilation settings, and outcome.

ICU Incidence of ARDS

ARDS represented 10.4% (95% CI, 10.0%-10.7%) of total ICU admissions and 23.4% (95% CI, 21.7%-25.2%)of all patients requiring mechanical ventilation and constituted 0.42 cases/ICU bed over 4 weeks. There was some geographic variation, with Europe having an incidence of 0.48 cases/ICU bed over 4 weeks; North America, 0.46; South America, 0.31; Asia, 0.27; Africa, 0.32; and Oceania, 0.57 cases/ICU bed per 4 weeks.

Table 3. Baseline Characteristics of Patients With Acute Respiratory Distress Syndrome Treated With Invasive Ventilation by Severity Category at Diagnosis

Parameter	All (N = 2377)	Mild (n = 714)	Moderate (n = 1106)	Severe (n = 557)	*P* Value[a]
Age, median (IQR), y	61 (61-62)	61 (60-63)	62 (62-63)	57 (55-58)	<.001
No longer meet ARDS criteria after 24 h, No. (%) [95% CI]	486 (17.3) [15.9-18.7]	190 (26.6) [23.4-30.0]	152 (13.7) [11.8-15.9]	71 (12.8) [10.1-15.8]	<.001
Severity of illness, mean (95% CI), SOFA score[b]					
Day 1	10.1 (9.9-10.2)	8.8 (8.6-9.1)	10.2 (9.9-10.4)	11.4 (11.1-11.8)	<.001
Day 1 nonpulmonary[c]	6.9 (6.7-7.0)	6.7 (6.4-7.0)	6.9 (6.7-7.1)	7.0 (6.7-7.4)	.34
Worst	11.1 (10.9-11.3)	10.3 (10.0-10.6)	11.8 (11.5-12.0)	13.0 (12.6-13.3)	<.001
Worst nonpulmonary	8.0 (7.8-8.2)	8.0 (7.7-8.3)	8.7 (8.4-8.9)	9.0 (8.4-8.9)	<.001
Ventilator settings, first day of ARDS					
F_{IO_2}, mean (95% CI)	0.65 (0.64-0.65)	0.48 (0.47-0.50)	0.62 (0.61-0.63)	0.90 (0.88-0.91)	<.001
Median (IQR)	0.6 (0.45-0.85)	0.4 (0.4-0.5)	0.6 (0.5-0.7)	1 (0.8-1)	
Set respiratory rate, mean (95% CI), 1/min	18.6 (18.3-19.0)	17.4 (16.9-17.8	18.4 (18.0-18.5)	20.4 (19.2-21.6)	<.001
Total respiratory rate, mean (95% CI), 1/min	20.8 (21.5-21.2)	19.5 (19.0-19.9)	20.7 (20.3-21.1)	22.7 (21.5-23.8)	<.001
VT, mean (95% CI), mL/kg PBW	7.6 (7.5-7.7)	7.8 (7.6-7.9	7.6 (7.5-7.7)	7.5 (7.3-7.6)	.02
Control vent mode	7.5 (7.4-7.6)	7.6 (7.5-7.8)	7.4 (7.3-7.6)	7.4 (7.2-7.6)	.06
Spontaneous vent mode	7.9 (7.8-8.1)	7.9 (7.7-8.2)	8.0 (7.7-8.2)	7.7 (7.4-8.1)	.55
P value (control vs spont mode)	<.001	.049	<.001	.053	
Set PEEP, mean (95% CI), cm H_2O	8.4 (8.3-8.6)	7.4 (7.2-7.6)	8.3 (8.1-8.5)	10.1 (9.8-10.4)	<.001
Peak pressure, mean (95% CI), cm H_2O[d]	27.0 (26.7-27.4)	24.7 (24.1-25.4)	26.9 (26.5-27.4)	30.3 (29.6-30.9)	<.001
Patients in whom P_{PLAT} measured, No. (%)					
Among all invasively ventilated patients, No. (%) [95% CI]	954 (40.1) [38.2-42.1]	260 (36.4) [32.9-40.1]	463 (41.9) [38.9-44.8]	231 (41.5) [37.3-45.7]	.05
Among patients with controlled ventilation, No. (%) [95% CI]	756 (48.5) [46.0-51.0]	198 (46.1) [41.3-51.0]	363 (49.8) [46.1-53.5]	195 (48.5) [43.5-53.5]	.49
P_{PLAT}, mean (95% CI), cm H_2O[e]	23.2 (22.6-23.7)	20.5 (19.8-21.3)	23.1 (22.6-23.7)	26.2 (25.2-27.1)	<.001
Standardized minute ventilation, mean (95% CI), l/min[f]	10.8 (10.6-11.0)	9.3 (9.1-9.6)	10.7 (10.5-11.0)	12.8 (12.3-13.3)	<.001
Spontaneous ventilation, No. (%) [95% CI]	723 (30.4 [8.6-32.3]	260 (36.4) [32.9-40.0]	336 (30.4) [29.7-35.3]	127 (22.8) [19.3-26.5]	<.001
Gas exchange, first day of ARDS					
Pa_{O_2}/F_{IO_2} ratio, mean (95% CI), mmHg	161 (158-163)	246 (244-248)	149 (147-150)	75 (74-77)	<.001
Sp_{O_2}, mean (95% CI)	95 (94-95)	97 (97-98)	95 (95-96)	90 (89-91)	<.001
Median (IQR)	96 (93-98)	98 (96-99)	96 (94-98)	92 (88-95)	
Pa_{CO_2}, mean (95% CI), mm Hg	46.0 (45.4-46.6)	41.5 (40.7-42.2)	45.8 (44.9-46.6)	52.2 (50.7-53.7)	<.001
pH, mean (95% CI)	7.33 (7.32-7.33)	7.36 (7.36-7.37)	7.33 (7.32-7.33)	7.27 (7.26-7.29)	<.001

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; PBW; predicted body weight; PEEP, positive end-expiratory pressure; Pa_{O_2}/F_{IO_2}, partial pressure of oxygen to fraction of inspired oxygen; P_{PLAT}, plateau pressure; SOFA, Sequential Organ Failure Assessment; VT, tidal volume; Sp_{O_2}, peripheral arterial oxygen saturation.

[a] *P* value represents comparisons across the ARDS severity categories for each variable.

[b] For all SOFA scores for which data points were missing, this value was omitted and the denominator adjusted accordingly.

[c] The nonpulmonary SOFA score and the pulmonary component of the score was omitted and the denominator adjusted accordingly.

[d] For peak pressure measurements, patients receiving high-frequency oscillatory ventilation (HFOV) or extracorporeal membrane oxygenation (ECMO) were excluded.

[e] 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 mode permitting spontaneous ventilation was used. The set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded.

[f] Standardized minute ventilation = minute ventilation × Pa_{CO_2}/40 mm Hg.

Recognition of ARDS

ARDS was underdiagnosed, with 60.2% of all patients with ARDS being clinician-recognized. Clinician recognition of ARDS ranged from 51.3% (95% CI, 47.5%-55.0%) for mild ARDS to 78.5% (95% CI, 74.8%-81.8%) for severe ARDS (eTable 4 in the Supplement). Clinician recognition of ARDS at the time of fulfillment of ARDS criteria was 34.0% (95% CI, 32.0-36.0), suggesting that diagnosis of ARDS was frequently delayed.

A multivariable analysis including variables from the bivariable analyses (eTable 5 in the Supplement), revealed several patient and organizational factors associated with clinician recognition of ARDS. Higher nurse-to-patient ratios, higher physician-to-patient ratios, younger patient age and a lower Pa_{O_2}/F_{IO_2} ratio, and the presence of pneumonia or pancreatitis were factors independently associated with higher probability of clinician recognition (**Table 2**). Absence of a risk factor and presence of concomitant

Table 4. Use of Adjunctive and Other Optimization Measures in Invasively Ventilated Patients With Acute Respiratory Distress Syndrome[a]

	Patients of No. (%) [95% CI]				
	All (n = 2377)	Mild[a] (n = 498)	Moderate[a] (n = 1150)	Severe[a] (n = 729)	*P* Value[b]
Neuromuscular blockade	516 (21.7) [20.1-23.4]	34 (6.8) [4.8-9.4]	208 (18.1) [15.9-20.4]	274 (37.8) [34.1-41.2]	<.001
Recruitment maneuvers	496 (20.9) [19.2-22.6]	58 (11.7) [9.0-14.8]	200 (17.4) [15.2-19.7]	238 (32.7) [29.3-36.2]	<.001
Prone positioning	187 (7.9) [6.8-9.0]	5 (1.0) [0.3-2.3]	63 (5.5) [4.2-7.0]	119 (16.3) [13.7-19.2]	<.001
ECMO	76 (3.2) [2.5-4.0]	1 (0.2) [0.05-1.2]	27 (2.4) [1.6-3.4]	48 (6.6) [4.9-8.6]	<.001
Inhaled vasodilators	182 (7.7) [6.6-8.8]	17 (3.4) [02.0-5.4]	70 (6.1) [4.8-7.6]	95 (13.0) [10.7-15.7]	<.001
HFOV	28 (1.2) [0.8-1.7]	3 (0.6) [0.1-1.7]	14 (1.2) [0.7-2.0]	11 (1.5) [0.8-2.7]	.347
None of the above	1431 (60.2) [58.2-62.2]	397 (79.7) [75.9-83.2]	750 (65.2) [62.4-68.0]	284 (39.0) [35.4-42.6]	<.001
Esophageal pressure catheter	19 (0.8) [0.04-1.4]	2 (0.4) [0.04-1.4]	8 (0.7) [0.3-1.3]	9 (1.2) [0.6-2.3]	.233
Tracheostomy	309 (13.0) [11.6-14.4]	48 (9.6) [7.1-12.6]	155 (13.5) [11.6-15.6]	106 (14.5) [12.1-17.3]	.034
High-dose corticosteroids[c]	425 (17.9) [16.4-19.5]	61 (12.3) [9.5-15.5]	194 (16.9) [14.7-19.2]	170 (23.3) [20.3-26.6]	<.001
Pulmonary artery catheter	107 (4.5) [3.7-5.4]	9 (1.8) [0.8-3.4]	53 (4.6) [3.4-6.0]	45 (6.2) [4.5-8.2]	.001

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; PEEP, positive end-expiratory pressure.

[a] For this analysis, ARDS severity was defined based on the patients' worst severity category over the course of their ICU stay in patients who developed ARDS on day 1 or 2.

[b] *P* value represents comparisons across the ARDS severity categories for each variable.

[c] High-dose corticosteroids was defined as doses that were equal to or greater than the equivalent of 1 mg/kg of methylprednisolone.

Table 5. Outcome of Invasively Ventilated Patients by Acute Respiratory Distress Syndrome Severity at Diagnosis

Parameter	All (n = 2377)	Mild (n = 714)	Moderate (n = 1106)	Severe (n = 557)	*P* Value[a]
Progression of ARDS severity, No (%) [95% CI][b]					
Progression to moderate[c]		184 (25.8) [22.6-29.1]	N/A	N/A	
Progression to severe[c]		32 (4.5) [3.1-6.3]	140 (12.7) [10.8-14.8]	N/A	
Death in the 1st wk without category change		63 (8.8) [6.8-11.1]	126 (11.4) [9.6-13.4]	117 (21.0) [17.7-24.6]	
Invasive ventilation-free days to day 28, median (IQR), d[d]	10 (0-22)	16 (0-24)	11 (0-21)	0 (0-18)	<.001
Duration of invasive ventilation, median (IQR), d					
All patients	8 (4-15)	7 (3-14)	8 (4-16)	9 (4-16)	.04
Surviving patients	8 (4-15)	6 (3-13)	8 (4-15)	11 (6-18)	<.001
ICU length of stay, median (IQR), d					
All patients	10 (5-20)	10 (5-19)	11 (6-20)	11 (5-19)	.39
Surviving patients	11 (7-21)	10 (6-19)	12 (7-21)	14 (7-23)	.03
ICU mortality, No. (%) [95% CI]	838 (35.3) [33.3-37.2]	212 (29.7) [26.4-33.2]	387 (35.0) [32.2-37.9]	239 (42.9) [38.8-47.1]	<.001
Day 28 mortality, No. (%) [95% CI]	828 (34.8) [32.9-36.8]	211 (29.6) [26.2-33.0]	389 (35.2) [32.4-38.1]	228 (40.9) [36.8-45.1]	<.001
Hospital length of stay, median (IQR), d					
All patients	17 (8-33)	18 (10-33)	17 (8-33)	16 (6-31)	.22
Surviving patients	23 (14-40)	23 (14-40)	22 (13-40)	26 (14-43)	.41
Hospital mortality, No. (%) [(95% CI]	952 (40.0) [38.1-42.1]	249 (34.9) [31.4-38.5]	446 (40.3) [37.4-43.3]	257 (46.1) [41.9-50.4]	<.001

Abbreviations: ARDS, acute respiratory distress syndrome, ICU, intensive care unit; IQR, interquartile range.

[a] *P* value represents comparisons across the ARDS severity categories for each variable.

[b] Initial ARDS severity determined from worst partial pressure of oxygen to fraction of inspired oxygen ratio within first 24 hours following ARDS diagnosis.

[c] Most severe is calculated for time period up to day 7 postdiagnosis of ARDS. Analysis was limited to the first 7 days due to the less frequent sampling after that day.

[d] In patients in whom death occurs while receiving invasive mechanical ventilation, invasive ventilation-free days are counted as 0.

cardiac failure were associated with reduced likelihood of clinician recognition of ARDS (Table 2). The mean tidal volume was 7.5 mL/kg (95% CI, 7.4-7.6 mL/kg) of predicted body weight (PBW) among patients whose physicians recognized ARDS, marginally lower than that of 7.7 mL/kg (95% CI, 7.6-7.9 mL/kg) in patients whose ARDS was not recognized (P = .01). The mean PEEP level was 8.9 cm H_2O (95% CI, 8.8-9.1 cm H_2O) in patients whose ARDS was recognized, higher than that of 7.5 cm H_2O (95% CI, 7.3-7.7 cm H_2O) in patients whose ARDS was not recognized (P < .001). Physicians who recognized ARDS used adjunctive treatments more than physicians who did not (43.9% vs 21.7%, P < .001; eTable 4 in the Supplement). After adjusting for potentially confounding variables, there was no statistically significant association between clinician-recognized ARDS and tidal volumes (eTable 6 in the Supplement) or P_{plat} recording (eTable 7 in the Supplement). In contrast, clinician recognition of ARDS was statistically associated with the use of higher levels of PEEP, and greater use of prone positioning and neuromuscular blockade (eTables 8-10 in the Supplement).

ARDS Severity

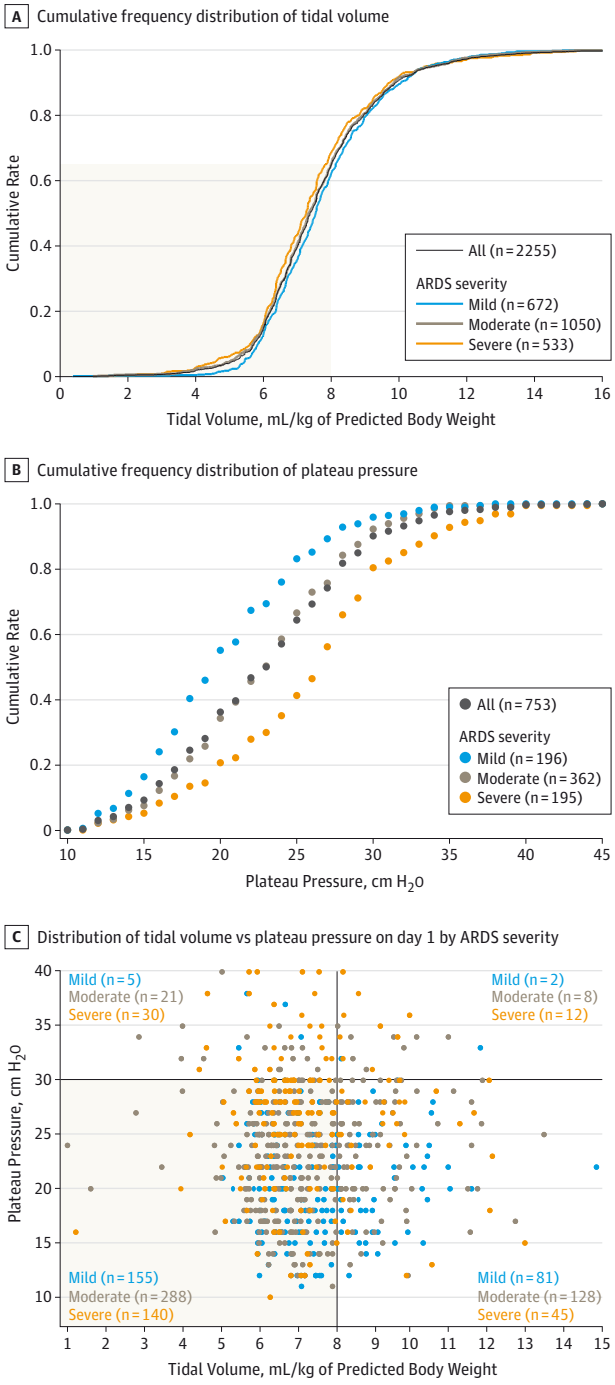
A total of 2377 patients developed ARDS in the first 48 hours of acute hypoxemic respiratory failure and received invasive mechanical ventilation. The period prevalence of mild ARDS was 30.0% (95% CI, 28.2%-31.9%); moderate, 46.6% (95% CI, 44.5%-48.6%); and severe, 23.4% (95% CI, 21.7%-25.2%) (Figure 1). Ventilator management differed among the ARDS severity groups, while the use of adjunctive measures increased and mortality was higher with greater ARDS severity (**Table 3**, **Table 4**, and **Table 5**). At diagnosis, increasing ARDS severity was paralleled by worsening Sequential Organ Failure Assessment (SOFA) scores, which was largely accounted for by the pulmonary component. The nonpulmonary component of the SOFA score was higher in patients with an increased ARDS severity category (Table 3). The $Paco_2$ increased and pH decreased in patients with increased ARDS severity category (Table 3, eFigure 1A-B in the Supplement). Three hundred sixteen patients (13.3%) with ARDS had a $Paco_2$ of 60 mm Hg or higher. However, the extent and severity of hypercapnia was relatively modest, even in severe ARDS.

Mechanical Ventilation in ARDS

Ventilator management varied with ARDS severity (Table 3). However, the decrease in tidal volume and increase in PEEP, from mild to moderate to severe ARDS, while statistically significant, was clinically modest (Table 3). In patients with ARDS 35.1% (95% CI, 33.1%-37.1%) received a tidal volume of more than 8 mL/kg PBW (**Figure 2**A and eFigure 1C in the Supplement), while 82.6% (95% CI, 81.0%-84.1%) received a PEEP of less than 12 cm H_2O.

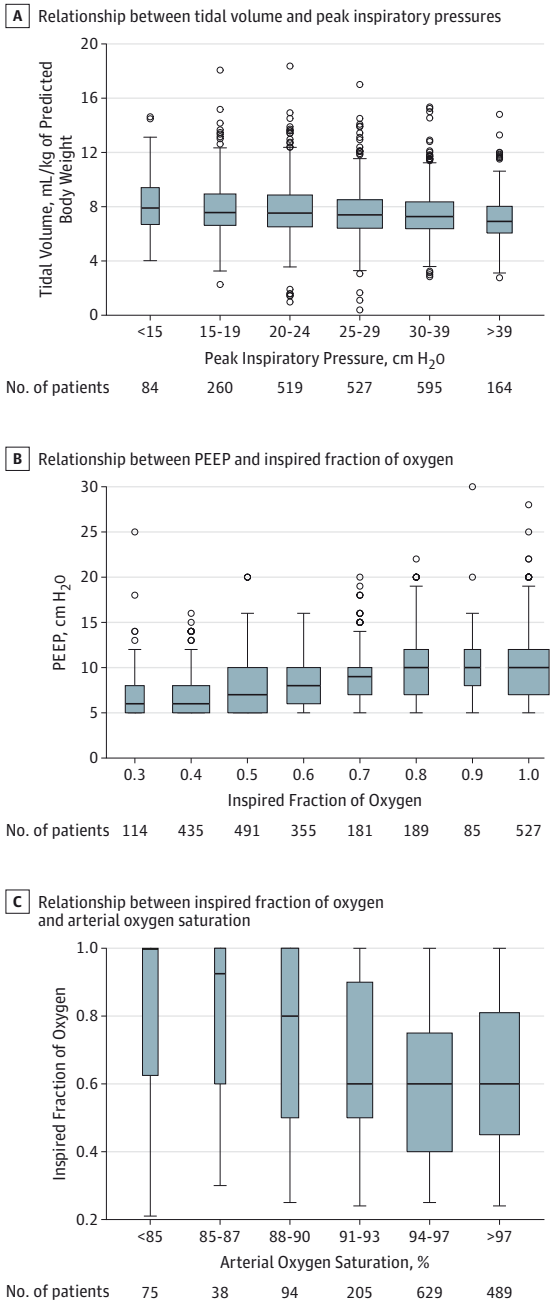
The distribution of P_{plat} differed significantly with ARDS severity (Figures 2B and eFigure 1D in the Supplement). P_{plat} was measured in 40.1% (95% CI, 46.0%-51.0%) of patients, irrespective of ARDS severity. This rose to 48.5% (95% CI, 46.0%-51.0%) of patients in whom there was no evidence for

Figure 2. Ventilation Parameters in Patients With ARDS



A, Cumulative frequency distribution of tidal volume was similar in patients in each severity category, with 65% of patients with acute respiratory distress syndrome (ARDS) receiving a tidal volume of 8 mL/kg of predicted body weight or less. B, In contrast, a right shift of the cumulative frequency distribution curves of plateau pressures was seen for increasing ARDS severity category, with plateau pressure of more than 30 cm H_2O in 8.5% of patients for which these data are available. C, Represents the distribution of day-1 tidal volume vs plateau pressure for each patient for which these data are available. Two-thirds of the patients fell within the limits for *protective ventilation*, defined as plateau pressure less than or equal to 30 cm H_2O and tidal volume of less than or equal to 8 mL/kg of predicted body weight. Data refer to the first day of ARDS.

Figure 3. Mechanical Ventilation Settings in Early Acute Respiratory Distress Syndrome



A, Tidal volume remained relatively constant across the range of peak inspiratory pressures. B, Positive end-expiratory pressure (PEEP) progressively increased in patients requiring higher inspired fraction of oxygen (F_{IO_2}). C, There was a stepwise increase in F_{IO_2} at lower arterial oxygen saturations, with F_{IO_2} steeply increasing at atrial oxygen saturation (Sa_{O_2}) values lower than 91%. Data refer to the first day of ARDS.

For each box plot, the middle line represents the median, the lower hinge represents the first quartile, the upper hinge represents the third quartile, the whiskers extend to 1.5 times interquartile range, and the outliers are values outside the whiskers' range. The boxes are drawn with widths proportional to the square root of the number of observations in the groups. The numbers below each box plot represent the total number of patients in each group.

spontaneous ventilation. Two-thirds of patients in whom P_{plat} was reported received *protective mechanical ventilation* as defined by a tidal volume of 8 mL/kg of PBW or less and a P_{plat} of 30 cm H_2O or less (Figure 2C). In patients in whom P_{plat} was measured, 91.9% (95% CI, 88.1%-94.9%) of those receiving a tidal volume of more than 8 mL/kg PBW had a P_{plat} of 30 cm H_2O or less (Figure 2C). Less than 3% of patients received a tidal volume of more than 8 mL/kg and had a P_{plat} pressure of more than 30 cm H_2O (Figure 2C).

There was no relationship between tidal volume and either peak inspiratory pressure, P_{plat} or lung compliance (**Figure 3**A and eFigure 2 in the Supplement). Tidal volume was significantly higher in patients in a spontaneous breathing mode (7.5; 95% CI, 7.4-7.6 vs 7.9; 95% CI, 7.8-8.1 mL/kg PBW, $P < .001$; Table 3).

Positive end-expiratory pressure levels were relatively low (Table 3) and were higher in patients with higher peak inspiratory pressure and higher P_{plat}. In addition, no relationship was found between PEEP and the Pa_{O_2}/F_{IO_2} ratio, F_{IO_2} (Figure 3B) or lung compliance (eFigure 2 in the Supplement). In contrast, there was an inverse relationship between F_{IO_2} and Sp_{O_2}, suggesting that clinicians used F_{IO_2} to treat hypoxemia (Figure 3C).

Use of Adjunctive Measures

The use of adjunctive treatments in patients with ARDS on day 1 or 2 was relatively low but increased with ARDS severity (Table 4). Continuous neuromuscular blocking agents, high-dose steroids, and recruitment maneuvers were the most frequently used adjuncts. In patients with severe ARDS, continuous neuromuscular blockade was used in 37.8% (95% CI, 34.1%-41.2%), prone position in 16.3% (95% CI, 13.7%-19.2%), and recruitment maneuvers in 32.7% (95% CI, 29.3%-36.2%).

ARDS Outcomes

Severity of ARDS worsened in 356 (19.6%, 95% CI, 17.8%-21.5%) patients with mild or moderate ARDS (Table 5). There was a decreased likelihood of unassisted breathing (**Figure 4**A) and survival (Figure 4B) at day 28 with increasing severity. Overall, unadjusted ICU and hospital mortality from ARDS were 35.3% (95% CI, 33.3%-37.2%) and 40.0% (95% CI, 38.1%-42.1%), respectively (Figure 4 and Table 5). The number of ventilator-free days decreased (eFigure 3 in the Supplement), and the length of ICU—but not hospital—stay, increased with greater ARDS severity category. Both ICU and hospital survival decreased with increased ARDS severity (Table 5). Patients with a driving pressure (ie, P_{plat}-PEEP) of more than 14 cm H_2O on day 1 had a worse outcome (Figure 4C). There was a direct relationship between both plateau and driving pressure quintile and mortality rate (**Figure 5**).

Discussion

In this prospective study carried out in 459 ICUs in 50 countries in 5 continents, ARDS appeared to represent an impor-

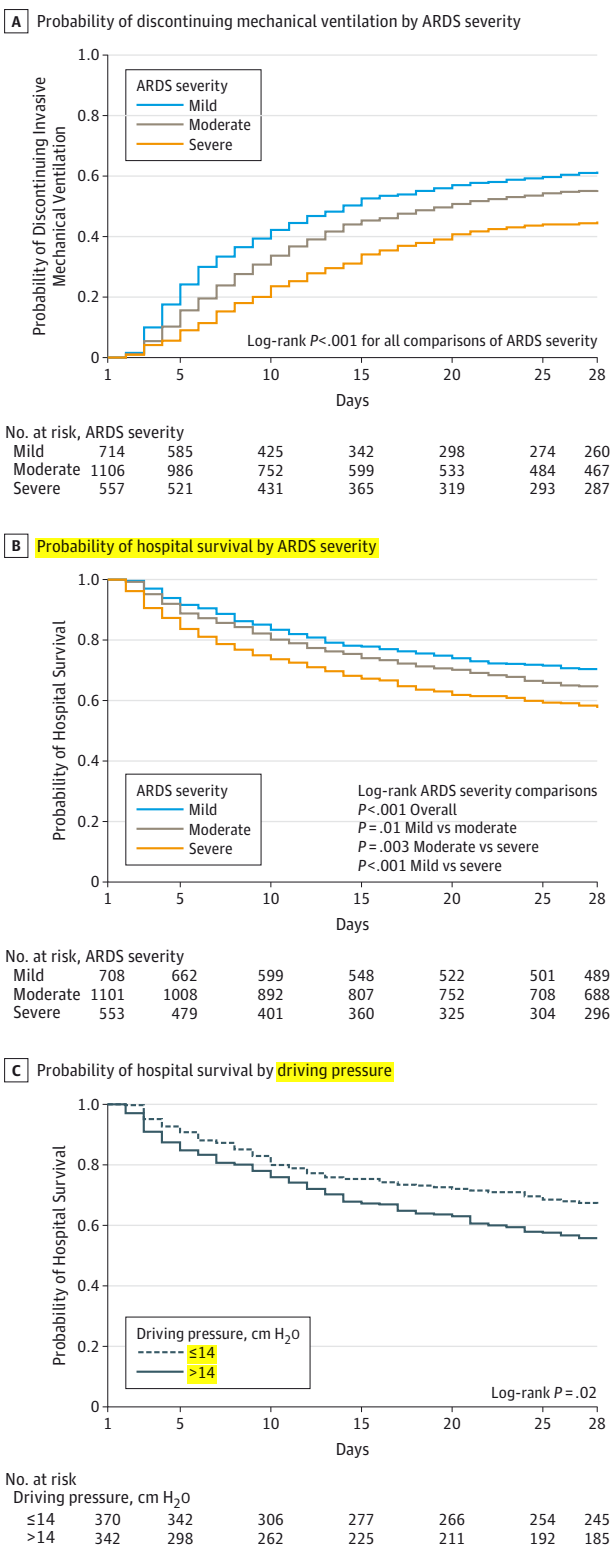
tant public health problem globally, with some geographic variation and with a very high mortality of approximately 40%. A major finding was the underrecognition of ARDS by clinicians, the low use of contemporary ventilatory strategies and adjuncts, and the limited effect of physician diagnosis of ARDS on treatment decisions. These findings indicate the potential for improvement in management of patients with ARDS.

In this study, the geographic variation in ARDS incidence ranged from 0.27 to 0.57 cases per ICU bed per 4 weeks and prcentage of ICU admissions. Because we could not estimate the population served by the ICUs in this study, we could not calculate population incidence for ARDS; therefore, relatively little can be inferred about the burden of ARDS in participating countries. The nearly 2-fold variation in ICU incidence in this study and the known variation in ICU resources internationally may well explain the variability in ARDS studies that involved specific geographic populations,[5] with the highest estimates in the United States[4,17] and Australia.[18,19] Our ICU incidence data are concordant with other estimates using similar approaches that have generated reliable population incidence data.[20]

These results suggest that ARDS continues to be underrecognized by clinicians in the era of the Berlin Definition, similar to previous findings using the American-European consensus conference (AECC) definition.[14,21-23] A key feature of our study design was that data were collected for each component of the Berlin Definition in all patients with hypoxemia breathing with the aid of a ventilator, which allowed us to identify patients with ARDS from the raw data. We chose this approach to enable a more robust evaluation of the incidence, as well to assess clinician recognition of ARDS. The rate of clinician recognition of ARDS was low, with 40% of all cases not being diagnosed. Clinician recognition rates increased with increasing disease severity but was still less than 80% in severe ARDS. Independent factors contributing to clinician recognition were younger patient age, lower predicted body weight, the presence of extrapulmonary sepsis or pancreatitis, and greater disease severity. Conversely, the absence of a risk factor for ARDS was associated with underrecognition of ARDS. Lower numbers of nurses and physicians per ICU patient were both associated with reduced clinician recognition of ARDS. It is possible that the way in which the data were collected contributed, in part, to clinician underrecognition of ARDS. Specifically, it is possible that the ICU clinician knew that the patient had ARDS, but this was not made known to the site investigators or reported in the patient chart. However, not indicating the diagnosis of ARDS in the chart constitutes a form of underrecognition. In addition, that the study had an explicit focus on ARDS, that all participants were offered online training on ARDS diagnosis, and that the case report form asked at 2 separate points in the study if the patient had ARDS, make this possibility less likely.

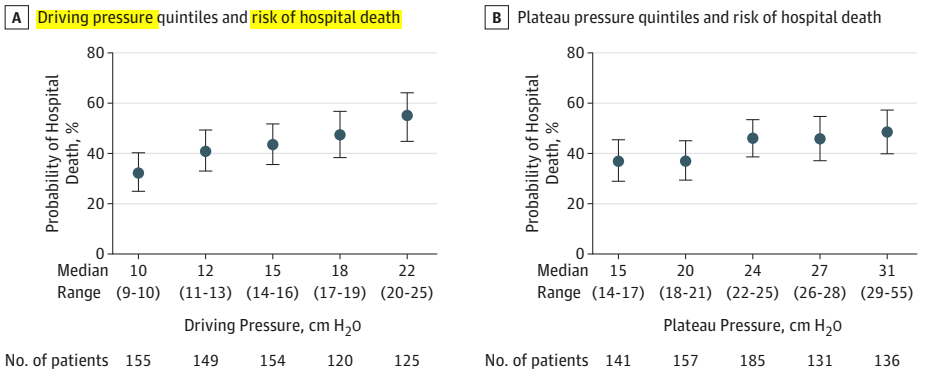
It is unclear whether clinician recognition of ARDS affects outcome because recognition may be only one of a number of barriers to the use of ventilatory and adjunctive

Figure 4. Outcome From Acute Respiratory Distress Syndrome



A, There was a lower likelihood of unassisted breathing with increasing severity of acute respiratory distress syndrome. B, There was a lower likelihood of survival to day 28 with increasing severity of acute respiratory distress syndrome (ARDS) at day 1. C, Patients with a driving pressure of greater than 14 cm H_2O on day 1 of ARDS criteria had a higher mortality.

Figure 5. Driving Pressure and Plateau Pressure and Outcome From ARDS



A, Mortality increased with increasing quintiles of driving pressure on first day of ARDS. B, The relationship between mortality and quintiles of plateau pressure is provided for comparison. Error bars indicate 95% confidence interval.

treatment strategies, while the sickest patients are more frequently diagnosed.[14,24] After adjusting for potential confounders, clinician diagnosis of ARDS was not independently associated with the use of lower tidal volume. Conversely, clinician diagnosis of ARDS was significantly associated with the use of higher PEEP, prone positioning, and neuromuscular blockade. Although the reasons for this are unclear, clinicians do not appear influenced by the presence or absence of ARDS for setting tidal volume and may be motivated by other factors (eg, perceived comfort, pH, $Paco_2$, etc).

Our data appear to demonstrate the predictive validity of the Berlin Definition, and are consistent with a recent observational study.[7] Increasing ARDS severity was associated with longer ICU stay, fewer days of invasive ventilation, longer hospital stays, and higher mortality. Patients with severe ARDS were younger, had fewer comorbidities but had a significantly worse outcome. The proportion of patients in each severity category was similar to that determined in retrospective analyses.[1]

ARDS appears to be undertreated in terms of the use of optimal, proven, or recommended approaches to mechanical ventilation and regarding the use of some adjunctive measures. Plateau pressure was reported in only 40.1% of all patients with ARDS, which increased to 48.5% of patients in whom there was no evidence for spontaneous ventilation. Although it is possible that patients in whom plateau pressure was measured were ventilated differently, this did not appear to be the case, at least in terms of tidal volume. We found no evidence to suggest that lower tidal volumes or higher PEEP were used in patients with a less compliant respiratory system or greater ARDS severity as reported in prior studies.[22] Low tidal volume ventilation was the most frequently used intervention, but more than one-third of all patients with ARDS received a tidal volume of more than 8 mL/kg of PBW, and approximately 60% received a tidal volume of more than 7 mL/kg of PBW. This finding is consistent with recent nonprotocolized RCTs in which patients received larger tidal volumes than expected.[12,25] In our study, PEEP was relatively low and constant across the spectrum of ARDS severity, with more than 80% of patients with ARDS receiving PEEP of 12 cm H_2O or less. Hypoxemia appeared to be treated predominantly by increasing Fio_2. High levels of permissive hypercapnia were infrequent. Adjunctive measures were used infrequently; this appeared to be the case for less expensive interventions such as prone positioning and neuromuscular blockade, as well as for expensive and invasive technologies such as extracorporeal membrane oxygenation. It is possible that the relatively low use of adjunctive measures such as neuromuscular blockade or prone positioning reflects ongoing uncertainty about the quality of evidence supporting these interventions.

ARDS continues to have a high mortality, despite advances in supportive care. There was a significant increase in mortality with each increase in ARDS severity category. Overall, 40% of patients with ARDS died in the hospital. Although detailed analyses of the factors contributing to outcome are beyond the scope of this article, we also confirmed a recent report[26] suggesting that higher driving pressure is associated with increased risk of death; albeit, our data should be interpreted cautiously as P_{plat} was available in a minority of patients.

This study has a number of limitations. Our focus on winter months, while allowing us to examine the burden of ARDS during the same season across the globe, may overstate ICU incidence figures for ARDS, due to specific diseases such as influenza.[27] In addition, despite enrolling a large number of ICUs from around the world, our convenience sample may be prone to selection biases that may limit generalizability; therefore, we are unable to calculate population-based incidence figures for ARDS. Similar to other epidemiological studies, we did not have access to the source data for the patients in the enrolling ICUs, so it is possible that not all patients with ARDS in participating centers were enrolled. However, enrollment of patients with ARDS from participating ICUs met expectations based on their recorded 2013 admission rates, while data from lower

recruiting ICUs was not different from that from higher enrolling ICUs, suggesting the absence of reporting biases. To ensure data quality, we instituted a robust data quality-control program in which all centers were requested to verify data that appeared inconsistent or erroneous. Although chest x-ray interpretation was performed by on-site clinicians, which potentially increased variability, we attempted to standardize interpretation by offering all the investigators web-based training. Another limitation is the lack of data collection concerning the use of conservative fluid strategy. Lastly, our assumption that patients discharged from the hospital before day 28 were alive at that time point is a further limitation.

Conclusions

Among ICUs in 50 countries, the period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be underrecognized, undertreated, and associated with a high mortality rate. These findings indicate the potential for improvement in management of patients with ARDS.

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Critical Care

VIEWPOINT Open Access

The LUNG SAFE: a biased presentation of the prevalence of ARDS!

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Abstract

The recent Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) challenges current data on the prevalence of acute respiratory distress syndrome (ARDS). The LUNG SAFE investigators claimed that their data demonstrated the predictive validity of the Berlin criteria. Also, the LUNG SAFE showed a disturbingly large gap between scientific evidence and medical practice. All of these statements demand that we question the interpretations of the study's findings.

The fundamental feature of a scientific system is not that its propositions are verifiable, but that its propositions are falsifiable.

Karl Popper

Acute respiratory distress syndrome (ARDS) is an acute and intense inflammatory response of the lungs that occurs as a result of either a direct or an indirect insult to the alveolar capillary membrane, causing increased permeability and subsequent interstitial and alveolar pulmonary edema. Characterized clinically by severe hypoxemia and bilateral radiographic infiltrates, ARDS usually occurs in previously healthy people. Usually, there is a latent period of 18–24 h between the insult and the development of the full-blown clinical syndrome. After this period, tachypnea, labored breathing, and cyanosis are observed. ARDS is generally confirmed by arterial hypoxemia and generalized infiltrates on chest radiograph, and the abnormalities in lung mechanics and oxygenation are better assessed once the patient is intubated and receiving mechanical ventilation (MV). Since 1967, little change in ventilator practice occurred until the publication of the pivotal ARMA trial [1] demonstrated that a lung-protective strategy using a tidal volume (V_T) of 4–8 ml/kg of predicted body weight (PBW) and moderate levels of positive end-expiratory pressure (PEEP) improved survival. Since then, limitation of V_T to 6–8 ml/kg PBW and plateau pressure to a maximum of 30 cmH_2O, and application of PEEP between 10 and 16 cmH_2O represents the standard for MV in ARDS patients.

To date, efforts to diagnose or describe ARDS by one or more laboratory tests have failed. When defining ARDS, the specific ranges and conditions under which to evaluate the hypoxemia (most frequently assessed by the partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio) have varied considerably. The original description [2], the American–European Consensus Committee [3], and the Berlin criteria [4] proved to be incapable of identifying uniform groups of patients in terms of severity and outcome [5–8] since none of them consider the sensitivity of PaO_2/FiO_2 to ventilator settings and the effects of routine care during the first 24 h for appropriate stratification, categorization, and prognostication [8]. There are no data that link a particular baseline PaO_2/FiO_2 to predictable structural changes in the alveolar capillary membrane. In addition, no biomarker has been described that is specific for ARDS, so it is plausible that ARDS prevalence is overestimated because many patients with acute hypoxemic respiratory failure from other diseases with bilateral pulmonary opacities and infiltrates [9] or patients with atelectasis, cardiogenic pulmonary edema, fluid overload, and obesity could be incorrectly diagnosed as having ARDS. Misdiagnosis can also occur if clinicians consider qualifying PaO_2 values resulting from acute events unrelated to the disease process instead of

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considering only PaO_2 values while patients are clinically stable [10].

The recent Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) [11] challenges all of these statements and demands that we question the interpretations of its findings. The LUNG SAFE investigators reported an ARDS prevalence of 10.4 % of all ICU admissions and of 23.4 % of all patients receiving MV, a huge figure exceeding by an order of magnitude that expected from current clinical experience in Europe [12–15]. At least four sources of bias could explain this surprisingly epidemic figure.

First, 40 % of ARDS cases were included using an algorithm-recognition ARDS tool while participating clinicians did not diagnose them as ARDS. Considering all of the alternate causes of hypoxemia already listed that present as bilateral infiltrates on chest radiograph, it is quite challenging to disregard the clinician's bedside interpretation that ARDS was not present for that of a computer algorithm which does not take into consideration these issues. How was the algorithm validated?

Second, more than 17 % of patients diagnosed with ARDS based on the Berlin criteria did not fulfill the criteria 24 h after routine care. Actual ARDS does not resolve in 24 h. Those patients who did not continue to meet criteria after 24 h most likely did not have ARDS and most likely had an alternate cause of hypoxemia and bilateral infiltrates that could be rapidly reversed [8–10].

Third, the study was performed in a short 4-week period during the winter of 2014, when prevalence of pulmonary infections, including H1N1 infection, had a seasonal peak [16] (pneumonia was reported to be almost 4-fold that of sepsis, a figure not supported by previous incidence studies) [12–15]. It is inappropriate to extrapolate data derived during a known worst seasonal period of a condition to represent the prevalence of the condition year around.

Finally, ICUs that did not enroll at least one ARDS patient during those 4 weeks were excluded from the analysis. This may be the most biasing problem of all. How can it be justified to eliminate data from groups originally designed to be part of the study of prevalence simply because they did not have a patient who met the criteria during the study period? The distribution of ARDS patients differs from institution to institution. Referral centers can be expected to have a higher prevalence than the average ICU, which may have periods without any ARDS patients. All should be considered in determining global prevalence.

Overall until now, the hospital mortality rate of patients with ARDS has remained >40 % in major observational studies [15]. Based on the p value for the 5 % absolute differences between the reported mortality rate of mild vs moderate ARDS and moderate vs severe ARDS, the LUNG SAFE investigators claimed that their data demonstrated the predictive validity of the Berlin criteria. What matters, however, is the probability that when you find that a result is "statistically significant" there is actually a real effect [17]. The Berlin definition does not help in segmenting patients into homogeneous subgroups with similar lung injury and outcome at its onset [8, 18]. Notably, there were no standard rules for measuring the PaO_2/FiO_2 at any time during the LUNG SAFE, and it was not reported how many patients within each category remained in the same category after the first 24 h of routine care. From this point of view, hospital mortality differences (calculated by us) between mild and moderate ARDS ($p = 0.022$) and between moderate and severe ARDS ($p = 0.03$) are meaningless since the use of nonstandardized PaO_2/FiO_2 measurement makes it difficult, if not impossible, to interpret the degrees of lung injury [18]. Of note, patients categorized as having severe ARDS, based on the Berlin definition, were younger and had fewer comorbidities and a worse outcome, a finding that contradicts previous knowledge [19]. There is still a need for a better ARDS definition—one that takes into consideration the patient's actual ventilator settings and the fact that over the first 24 h of presumed ARDS, as the patient is stabilized, the true severity of the syndrome is identified and the status of many patients dramatically improves during this period.

Also, the LUNG SAFE investigators constructed 28-day survival curves for every ARDS category with missing patients in each category and assumed that patients discharged from the hospital before day 28 were alive. Mortality is a crucial outcome that should be measured very precisely. Causes of mortality were not reported. Patients with mild forms of ARDS do not die from ARDS but from the underlying disease (cancer, acquired immunodeficiency syndromes, stroke, advanced age), usually once discharged from the ICU [10]. Finally, surprisingly, the use of adjunctive therapies was analyzed after reclassifying patients using selectively the worst value of PaO_2/FiO_2 over the course of ICU stay instead of using the initial categorization, as the Berlin criteria mandate.

Besides all of these methodological sources of bias, a very relevant contribution of the LUNG SAFE is that it shows a disturbingly large gap between scientific evidence and medical practice. Most patients enrolled in this study were ventilated with $V_T > 7$ ml/kg PBW, PEEP < 10 cmH_2O, and $FiO_2 > 0.6$ and did not have their plateau pressure measured. A significant proportion of patients were ventilated with $V_T > 9$ ml/kg and less than 18 % of patients received PEEP > 11 cmH_2O. It would be interesting to see whether there was a correlation between applied V_T and PEEP with worsening lung damage or with mortality. Why were proven therapies such as low-V_T MV, moderate to high levels of PEEP, and limitation of plateau pressure indeed

ignored? Thus, it can only be assumed that there is still a huge need to assist the medical community in understanding the importance of lung-protective ventilation in all patients we mechanically ventilate.

Ethics statement
Not applicable.

Consent statement
Not applicable.

Abbreviations
ARDS: acute respiratory distress syndrome; ARMA: A Respiratory Management in Acute Lung Injury/ARDS trial; LUNG SAFE: Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure; MV: mechanical ventilation; PaO_2/FiO_2: partial pressure of oxygen in arterial blood/fraction of inspired oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure; V_T: tidal volume.

Competing interests
JV has received research grants from Maquet. RMK has received research grants from Venner Medical and Covidien, and is a consultant for Covidien and Orange Med Inc. MJS has no competing interests.

Authors' contributions
JV conceived the manuscript, participated in its design and coordination, and helped to draft the manuscript. MJS conceived the manuscript, participated in its design and coordination, and helped to draft the manuscript. RMK conceived the manuscript, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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CORRESPONDENCE

You neglected a few

Jason Chertoff*

Dear Editor,

In their article in the May 2016 issue of *Intensive Care Medicine*, Dr. Bihari et al. propose ten hypothetical studies that may have the potential to improve management of acute respiratory distress syndrome (ARDS) in the future [1]. Although well articulated and accurately presented, my main contention is that in their ten studies the authors focused on topics that have already been investigated and addressed in prior trials, studies, reviews, and meta-analyses [2, 3]. Instead of fixating on the pathophysiology of ARDS, which so many investigators have already done, I wish that the authors had used their forum to discuss what I believe to be most intriguing about ARDS: the barriers to prone positioning's widespread adoption in everyday clinical practice. As the authors mention, PROSEVA definitively showed a significant survival benefit from prone positioning in a select subgroup of patients with severe ARDS [4]. In fact, with a 50 % reduction in mortality and a hazard ratio of 0.39, prone positioning for patients with severe ARDS may be more beneficial than any other previously studied intervention for this subgroup of patients [4]. Unfortunately, as seen in the LUNG-SAFE trial, which demonstrated that only 16.4 % of severe ARDS patients are actually proned, prone positioning is presumably vastly underutilized [5]. To my disappointment, instead of addressing this perplexing underutilization phenomenon with potential studies, the authors provided its readers with ten studies that ignore LUNG-SAFE's disconcerting results [1]. As an exercise to highlight my point, try to imagine the uproar if only 16.4 % of patients with hyperlipidemia refractory to lifestyle changes were prescribed statin therapy, or 16.4 % of patients with diabetes and chronic kidney disease were prescribed angiotensin converting enzyme inhibitors (ACE inhibitors); my guess is that these dismal rates would quickly be addressed. So, some paramount questions continue to remain after reading the authors' ideas for future ARDS studies and they are: (1) In the appropriate patient, why is prone positioning so underutilized in ARDS management? (2) What studies can we as clinician researchers and educators perform to address this underutilization? (3) What interventions can be performed that address the barriers to widespread adoption and improve the utilization rate of prone positioning? (4) What studies can we perform to test the efficacy of these interventions? Needless to say, there exists an understudied and poorly elucidated discrepancy between prone positioning's effectiveness and utilization. In addition to the ten studies proposed by Bihari et al., it is also imperative to include researching and addressing the reasons why prone positioning is so unpopular. Perhaps follow-up confirmatory studies to PROSEVA and LUNG-SAFE are required to promote prone positioning's popularity in severe ARDS management.

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