Acute Respiratory Distress Syndrome Cases Volume and ICU Mortality in Medical Patients

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Dres received funding from Pulsion Medical System and Astra Zeneca. He was supported by The French Intensive Care Society (Société de Réanimation de Langue Française [SRLF] bourse de mobilité 2015), The 2015 Short Term Fellowship programme of the European Respiratory Society, The 2015 Bernhard Dräger Award for advanced treatment of acute respiratory failure of the European Society of Intensive Care Medicine, The Assistance Publique-Hôpitaux de Paris, The Fondation pour la Recherche Médicale (Fondation pour la Recherche Médicale 20150734498); and Mitacs Globalink Sorbonne Universités. Dr. Austin was supported by a Career Investigator Award from the Heart and Stroke Foundation (Ontario office). Dr. Demoule's institution received funding from Philips; he has signed research contracts with Covidien, Maquet, and Philips; he received funding from Medtronic, Hamilton, Covidien, Maquet, Resmed, Fisher & Paykel, and MSD; and he has also received personal fees from Covidien. Dr. Brochard's institution received funding from Air Liquide, Fisher Paykel, and Medtronic Covidien, and his research laboratory received research grants and/or equipment from Covidien, General Electric, Fisher Paykel, Maquet (with St Michael's Hospital), and Philips. Dr. Geri was supported by The French Intensive Care Society (SRLF bourse de mobilité 2015), by the Assistance Publique-Hopitaux de Paris and by the Bettencourt-Schueller Foundation. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Further members of the CUB-REA Group are listed in **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C974).

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DOI: 10.1097/CCM.0000000000002816

Objectives: To determine whether ICUs caring for higher volumes of acute respiratory distress syndrome patients would be associated with lower ICU mortality.

Design: A 9-year multicenter retrospective cohort study of prospectively collected data.

Setting: French medical ICUs.

Patients: From 2004 to 2012, acute respiratory distress syndrome cases were identified from a coding system through a regional database (Collège des Utilisateurs de Données en Réanimation).

Interventions: None.

Measurements and Main Results: Volume was calculated as the cumulative annual mean number of acute respiratory distress syndrome cases. Severity (Simplified Acute Physiology Score 2) and ICU mortality between categories (low, medium, and high) of acute respiratory distress syndrome cases volume were analyzed. Multivariable analysis using mixed effects models was performed to adjust for severity of illness and confounding factors. Over the study period, 8,383 acute respiratory distress syndrome patients among 31 ICUs met the study inclusion criteria. Overall, Simplified Acute Physiology Score 2 (median [interquartile]) was 58 (43–74), whereas ICU mortality was 53.7%. Severity as assessed by Simplified Acute Physiology Score 2 (median [interquartile]) was significantly higher in high-volume ICUs (> 65 acute respiratory distress syndrome per year) as compared to low (≤ 29 acute respiratory distress syndrome per year) and medium-volume ICUs (> 29–65 acute respiratory distress syndrome per year): 61 (46–77) versus 55 (41–72) and 55.0 (40–72), respectively ($p < 0.01$). ICU mortality was similar across the acute respiratory distress syndrome volume categories (53.6%, 54.1%, and 53.3% in low-, medium-, and high-volume categories ICUs, respectively).

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After adjustment for confounders, acute respiratory distress syndrome case volume was independently associated with ICU mortality (odds ratio for log-transformed volume: 0.77 [95% CI, 0.62–0.96]; $p = 0.02$).

Conclusions: ICUs caring for higher volumes of acute respiratory distress syndrome cases were associated with lower ICU mortality. (*Crit Care Med* 2017; XX:00–00)

Key Words: acute respiratory distress syndrome; case volume; intensive care unit; mortality; outcomes

The association between the number of patients treated in a center (center's volume) and patient outcomes is well established for numerous medical/surgical conditions (1–3) and notably in the ICUs (4–8). Reasons for the relationship between volume and outcomes are not fully elucidated but may stem from either increased provider experience and skills or selective referral to providers with better outcomes (9). Such a relationship has been established between hospital volume and the outcome of patients receiving mechanical ventilation in the United States (10). Whether such a relationship would exist in the specific setting of acute respiratory distress syndrome (ARDS), a common disease affecting up to 10% of patients admitted to ICUs has to date never been explored. In the last 20 years, survival among patients with ARDS has increased substantially. Nevertheless, ARDS still represents a high burden, both in terms of ICU/hospital mortality (11, 12) and long-term disability (13, 14). The outcome of patients with ARDS may have improved through the implementation of a broad range of better practices, including multidisciplinary care teams, lung protective ventilation strategies (15), and the use of adjunctive therapies, such as neuromuscular blocking agents (16), prone positioning (17), and/or protocols for sedation and weaning (18). Thus, we hypothesized that patients with ARDS admitted in ICUs with higher case volumes could have better outcomes than those admitted in ICUs with lower ARDS case volume. The purpose of the current study was to investigate the relationship between ARDS case volume and ICU mortality.

METHODS

We analyzed data prospectively collected in the Collège des Utilisateurs de Données en Réanimation (CUB-REA) database. Since 1992, the CUB-REA network has collected prospective data from 43 ICUs (including 22 academic centers) in the Greater Paris Area using a standardized web-based case report form. Admissions were identified over a 9-year period (2004–2012). This period was selected to optimize the number of ICUs that continuously participated in the collection of the data and to avoid using data after the most recent change in the ARDS definition. Recorded variables and coding methods were updated during annual meetings, and quality controls were performed regularly. The database quality has been assessed in previous studies (4, 6, 19). The CUB-REA project was approved by the Comité National Informatique et Liberté (French Data-Protection Watchdog agreement number 564407).

Selection of ICUs and Patients

ICUs were retained in the present analysis if they continuously participated in the CUB-REA database for at least six of the 9-year study period. Patients with ARDS were extracted from the database using the *International Classification of Diseases,* 10th Edition code J80 as primary or secondary diagnosis. Patients under the age of 18 years were excluded. For patients with multiple ICU admissions during one hospital stay, only the first admission was analyzed. Patients with ARDS who were mechanically ventilated for less than 48 hours were excluded. We hypothesized that these patients were either too sick to benefit from any intervention (patients died within the first 48 hr), would potentially be transferred to another center, or that ARDS was unlikely (see characteristics of these excluded patients in **Table SDC1**, Supplemental Digital Content 2, http://links.lww.com/CCM/C975).

Collected Data

For each patient, the following data were extracted: age, gender, comorbidities (Charlson Comorbidity Score) (20), ARDS risk factors (among bacterial pneumonia, viral pneumonia, other pneumonia, extrapulmonary sepsis, acute pancreatitis, transfusion > 10 units), organ failure during ICU stay (hemodynamic failure as defined as the need for vasopressor support or acute renal failure as the need for renal replacement therapy), and outcomes (duration of mechanical ventilation, hospital length of stay, ICU, and hospital mortality). Simplified Acute Physiology Score (SAPS2) was used to estimate patient's severity (21).

Case-Volume Calculation

Volumes of patients with ARDS were collected annually during the study period for each participating unit. Since annual admission volumes of patients with ARDS might vary from 1 year to the next, we calculated the cumulative annual mean of admissions of patients with ARDS during the study period, as previously described (19). As an example, the cumulative annual mean number of ARDS patients for 2005 was the total number of ARDS patients admitted to that unit before and in 2005 (i.e., 2004 and 2005) divided by two, and the 2006 ICU cumulative annual mean number of ARDS patients was the total number of patients with ARDS admitted in that unit before and in 2006 (i.e., 2004, 2005, and 2006) divided by three.

Running annual volumes were first categorized into quintiles for descriptive purposes at the ICU level. As the number of patients varies across ICUs, the number of patients in each quintile was not the same. ICUs within the fifth quintile were defined as high-volume category ICUs, ICUs of the third and fourth quintiles as medium-volume category ICUs, and ICUs of the first and second quintiles as low-volume category ICUs. The cutoffs defining the tertiles were determined arbitrarily since no previous data were available. They were chosen to obtain the best compromise between clinical meaning and the best balance of cases across tertiles.

As a sensitivity analysis, we also calculated ARDS case volume as a running mean according to the current year and

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the previous year (i.e., year *n* and *n*–1; for detailed description of calculation methods, see online supplement, Supplemental Digital Content 2, http://links.lww.com/CCM/C975) (4). Thus, depending on the considered year of admission, an ICU was not always classified within the same tertile.

To avoid endogeneity, we used the total number of ARDS cases before applying our exclusion criteria. The prevalence of patients with ARDS was computed by dividing the crude ARDS case volume by the number of total admissions. For regression analyses, ARDS case volume was used as a continuous predictor on the basis of 10-cases increment and was log transformed.

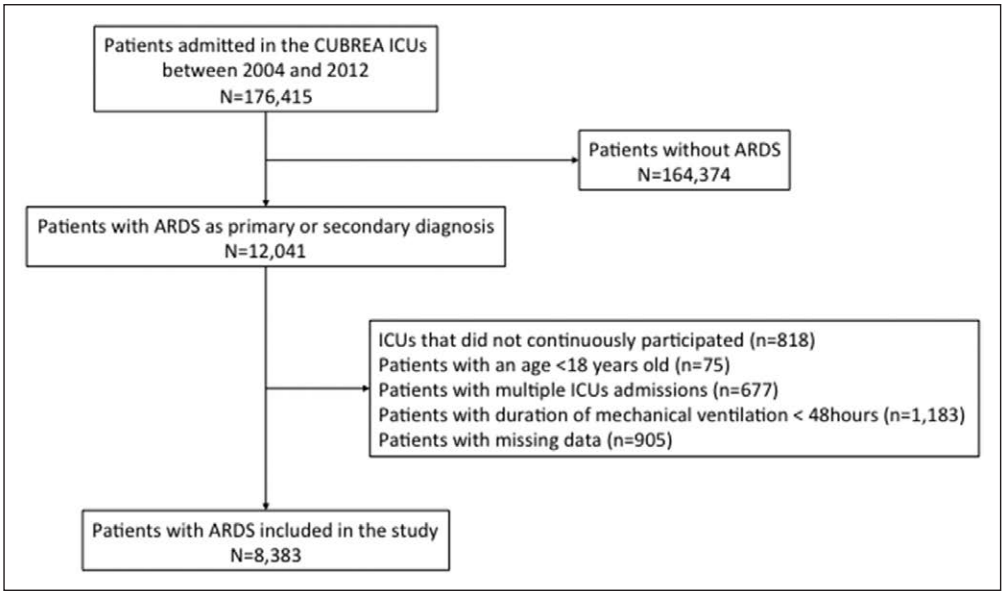

Figure 1. Flow chart of the study. ARDS = acute respiratory distress syndrome, CUBREA = Collège des Utilisateurs de Données en Réanimation.

Statistical Analysis

Data are presented as median (interquartile range [IQR], 25–75%) and *n* (%) for continuous and categorical variables, respectively. Comparisons between volume categories were performed using the Kruskall-Wallis test for continuous variables and the chi-square test for categorical variables. Tests for trends included the Cuzick test and the chi-square test for trend for continuous and categorical variables, respectively. Nonparametric tests were used as continuous variables were not normally distributed according to the Shapiro-Wilk test. The main outcome was ICU mortality. Association between variables and ARDS case-volume categories was evaluated in univariate analysis and then in multivariable hierarchical logistic regression, which allows the simultaneous assessment of patient-related risk factors and ICU characteristics, while controlling for center effect. Clinically relevant factors (age, gender, SAPS2, type of admission, Charlson Comorbidity Score, and organ failure) and ARDS case volume were included in the multivariable analysis based on the result of the univariate analysis (with $p < 0.05$) and on a strong scientific rationale supported by previous epidemiologic studies on ARDS (22). ARDS case volume was treated as a log-transformed continuous variable and forced into the model.

As a secondary analysis, generalized propensity score methods were used to estimate the effect of case volume on patient outcomes (see details in the supplemental data, Supplemental Digital Content 2, http://links.lww.com/CCM/C975). All statistical tests were two sided, and *p* values of 0.05 or less were considered statistically significant. All the statistical analysis was performed using Stata 14.1 software (Stata Corp, College Station, TX).

RESULTS

Patients

Between 2004 and 2012, 31 ICUs participated continuously in the CUB-REA database, from which 176,415 patients were admitted. Among them, 12,041 (6.8% of total ICU admissions) had ARDS. The proportions of ARDS cases among total ICU admissions and over mechanical ventilation cases were both significantly higher in high-volume category (**Fig. SDC1**, Supplemental Digital Content 2, http://links.lww.com/CCM/C975). Eventually, 8,383 patients met the inclusion criteria and were included into primary analysis (**Fig. 1**).

Characteristics and Management of Patients Across ARDS Case-Volume Categories

Overall patients' characteristics are presented in **Table 1**. Patients were severe as illustrated by a median (IQR) SAPS2 of 58 (43–74) at admission, but the majority had no comorbidity, 60% having a Charlson Comorbidity Score of 0. The main risk factor for ARDS was bacterial pneumonia (50%) followed by extrapulmonary sepsis (23%), whereas 13% of the patients had no risk factor identified. Hemodynamic failure was present in 73% of the patients and renal failure in 38%.

The distribution of cumulative annual volume of ARDS per ICU is shown in **Figure SDC2** (Supplemental Digital Content 2, http://links.lww.com/CCM/C975). ICU volume categories were distributed as follows: low-volume category: less than or equal to 29 ARDS per year, medium-volume category: greater than 29 and less than 65 ARDS per year, and high-volume category: greater than or equal to 65 ARDS per year. Table 1 shows the distribution of the patient's characteristics across the three case-volume categories (low, medium, and high). SAPS2 was higher in the high-volume category ICUs as compared with medium- and low-volume category ICUs: 61 (46–77) versus 55 (40–72) and 55 (41–72), respectively, $p < 0.01$. Hemodynamic

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TABLE 1. Patients' Characteristics, Management, and Outcomes According to the ICU's Cases Volume Category of Patients With Acute Respiratory Distress Syndrome

		ARDS Case-Volume Categories (Cases Per Year)				
Variables	**All Patients**	**Low**	**Medium**	**High**	***p*[a]**	***p* for Trend**
Patients, *n*	8,383	1,090	3,884	3,409		
Age (yr), median (IQR)	61 (48–73)	60 (49–70)	61 (49–74)	60 (47–73)	0.01	0.56
Male, *n* (%)	5,490 (66)	710 (65)	2,513 (65)	2,267 (67)	0.26	0.19
Medical admission, *n* (%)	8,063 (96)	1031 (95)	3,689 (95)	3,343 (98)	< 0.01	< 0.01
Simplified Acute Physiology Score 2, median (IQR)	58 (43–74)	55 (41–72)	55 (40–72)	61 (46–77)	< 0.01	< 0.01
Charlson Comorbidity Score, *n* (%)					< 0.01	< 0.01
0	5,030 (60)	574 (53)	2,212 (57)	2,244 (66)		
1	1,999 (24)	290 (27)	992 (25)	717 (21)		
≥ 2	1,354 (16)	226 (21)	680 (18)	448 (13)		
ARDS risk factors[b], n (%)						
Bacterial pneumonia	4,197 (50)	505 (46)	1,930 (49)	1,762 (52)	< 0.01	< 0.01
Viral pneumonia	222 (3)	25 (2)	108 (3)	89 (3)	0.66	0.79
Other pneumonia	635 (8)	107 (1)	207 (5)	321 (9)	< 0.01	0.02
Extrapulmonary sepsis	1,959 (23)	267 (24)	1,030 (27)	662 (19)	< 0.01	< 0.01
Acute pancreatitis	217 (3)	34 (3.1)	111 (3)	72 (2)	0.07	0.03
Transfusion (> 10 units)	467 (6)	62 (6)	224 (5)	181 (5)	0.68	0.47
No risk factor	1,082 (13)	168 (15)	471 (12)	443 (13)	0.02	0.24
Organ failure, *n* (%)						
Hemodynamic failure[c]	6,122 (73)	751 (69)	2,795 (72)	2,576 (76)	< 0.01	< 0.01
Renal failure[d]	3,193 (38)	404 (37)	1,260 (32)	1,529 (45)	< 0.01	< 0.01
Outcomes						
Mechanical ventilation duration (d), median (IQR)	9 (4–17)	9 (4–18)	9 (4–17)	8 (3–17)	< 0.01	< 0.01
Length of hospital stay (d), median (IQR)	19 (8–36)	21 (10–40)	18 (8–35)	18 (8–37)	< 0.01	0.18
ICU mortality, *n* (%)	4,502 (53.7)	584 (53.6)	2,101 (54.1)	1,817 (53.3)	0.79	0.69
Hospital mortality, *n* (%)	4,788 (57.2)	620 (57.3)	2,224 (57.3)	1,944 (57.0)	0.97	0.82

ARDS = acute respiratory distress syndrome, IQR = interquartile range.

[a]*p* value between low/medium and high.

[b]One patient could have one or more risk factors.

[c]Defined by the need of vasopressors.

[d]Defined by the need of renal replacement therapy.

Categorical variables are shown as *n* (%) and compared using a χ^2 test or a Fisher test as appropriate. Continuous variables are shown as median (IQR) and compared using a Kruskall-Wallis test. *p* value for trend has been calculated using a χ^2 trend test for binary variables and Cuzick test for ordinal and continuous variables.

failure and renal failure were more frequently observed in high-volume ICUs ($p < 0.01$). Global and ventilatory management of the patients is detailed in **Table SDC2** (Supplemental Digital Content 2, http://links.lww.com/CCM/C975). Of note, the use of neuromuscular blocking agents was similar across ICU case-volume categories, while prone positioning and inhaled nitric oxide were more frequently provided in low case-volume ICUs whereas veno-venous extracorporeal membrane oxygenation

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(ECMO) was more done in high case-volume ICUs. Changes in practice over the study period are presented in **Table SDC3** (Supplemental Digital Content 2, http://links.lww.com/CCM/C975). While use of prone positioning decreased over time, use of neuromuscular blockers, of ECMO, and rate of tracheostomy all increased.

ICU Mortality and Differences Across ARDS Volume Categories

Over the study period, ICU mortality was 53.7% (Table 1) and was similar across the three ARDS case-volume categories. After adjustment for confounders, higher ARDS case volume was independently associated with lower ICU mortality (odds ratio for log-transformed volume: 0.77 [95% CI, 0.62–0.96]; $p = 0.02$) (**Table 2** and **Fig. 2**). There was an interaction between SAPS2 and case volume on ICU mortality as the impact of case volume was more pronounced in the less severe patients (p for interaction < 0.11) (**Fig. 3**). We obtained the same results using the running mean calculation of case volume (**Table SDC4**, Supplemental Digital Content 2, http://links.lww.com/CCM/C975).

Propensity Score Analysis

Using propensity score weighting, low case volume and medium case volume were associated with an increased probability of ICU mortality compared with high case volumes (relative risk of 1.11 and 1.09, respectively; **Table SDC5**, Supplemental Digital Content 2, http://links.lww.com/CCM/C975). The number needed to harm were 19 and 24 in medium- and low-volume category ICUs as compared to high-volume category ICUs.

DISCUSSION

From a large regional cohort of medical critically ill patients, we reported the first investigation examining the effect of ARDS case volume on ICU mortality. Adjusting on confounders, we found that ICUs caring for higher numbers of patients with ARDS were associated with lower ICU mortality. Before interpreting the scope of our results, we rationalize below some aspects of our methods. The period of the study was restricted (from 2004 to 2012) to optimize the number of ICUs that continuously collected data and to homogeneously identify ARDS patients as per American–European Consensus Conference definition (23). After 2012, an international consensus panel of experts proposed a modified definition of ARDS, namely, Berlin definition, with three categories (mild, moderate, and severe) (24). Therefore, ARDS in the present study refers to the most severe forms of ARDS (moderate and severe ARDS) as per Berlin definition. This may explain the high mortality rate of our cohort which, of note, was also characterized by a high proportion of hemodynamic failure, a key prognostic factor of ARDS (25, 26).

Our predictive model shows that once the annual ARDS volume reached a certain threshold, the curve representing the association between volume and risk-adjusted ICU mortality became flat. Although the value of a "safe" threshold remains difficult to extrapolate, this finding may suggest that the benefit of increased patient volume in an ICU would be most pronounced at low-volume ICUs and would be attenuated as the ICU's case volume increased. Another important result is that the effect of case volume on ICU mortality was modulated by patient severity. This finding also suggests that for the sickest patients (i.e., SAPS2 > 80), there was no benefit to be treated in a high-volume center, likely because their prognosis was critical and mainly determined by their sole severity.

Although putative, we found some interesting results regarding the practices across ICUs. First, prone positioning was less frequently used in high-volume category ICUs, whereas paralyzing agents were similarly used across volume categories. This finding must be qualified insofar as the beneficial effects of early prone positioning on mortality in severe ARDS were reported

TABLE 2. Multivariable Hierarchical Logistic Regression of ICU Mortality Exploring Yearly Acute Respiratory Distress Syndrome Cases Volume

Variables	OR	95% CI	p
Male gender	1.04	0.94–1.15	0.44
Age			
< 50	1.00	1.00–1.00	
50–60	1.35	1.17–1.55	< 0.01
60–75	2.04	1.79–2.32	< 0.01
≥ 75	3.60	3.11–4.17	< 0.01
Simplified Acute Physiology Score 2[a]			
< 30	1.00	1.00–1.00	
30–50	1.20	1.04–1.38	< 0.01
50–65	1.63	1.40–1.90	< 0.01
≥ 65	3.64	3.10–4.28	< 0.01
Charlson Comorbidity Score			
0	1.00	1.00–1.00	
1	1.26	1.11–1.42	< 0.01
≥ 2	2.43	2.09–2.82	< 0.01
Medical admission	1.44	1.11–1.87	0.01
Hemodynamic failure	1.53	1.36–1.71	< 0.01
Renal replacement therapy	2.49	2.24–2.78	< 0.01
Volume of acute respiratory distress syndrome, log transformed	**0.77**	**0.62–0.95**	**0.02**
8,300 observations			

OR = odds ratio.

[a]Points related to age have been subtracted from Simplified Acute Physiology Score 2 before inclusion in the multivariable model.

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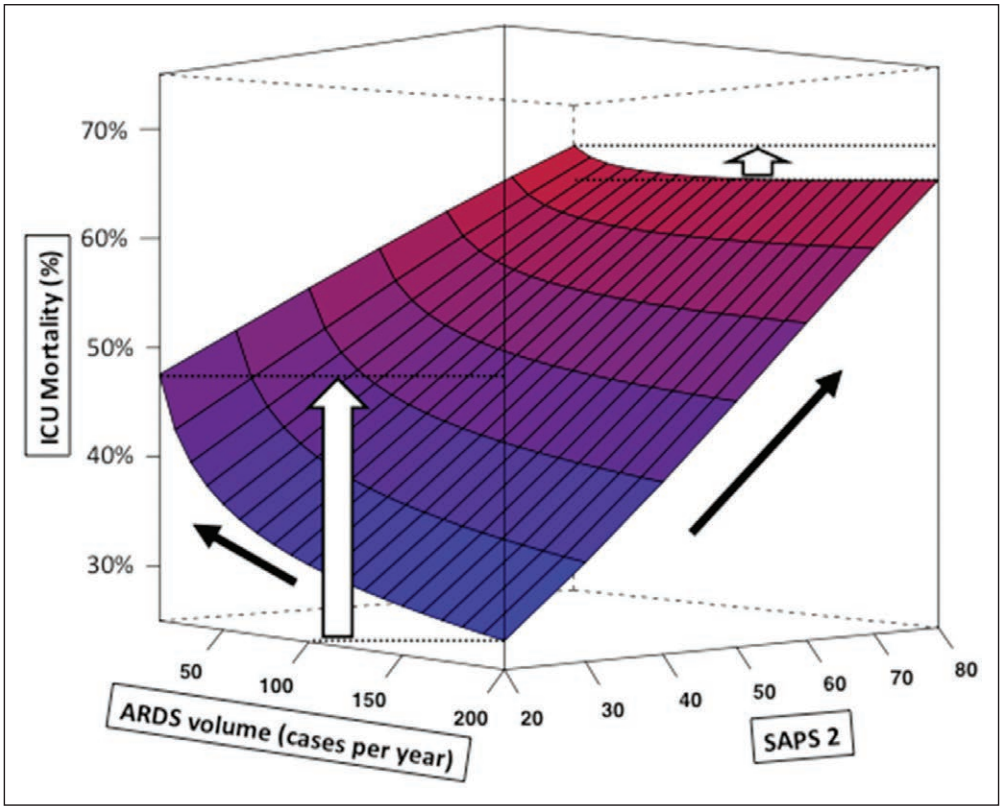

Figure 2. Predicted adjusted ICU mortality according to yearly acute respiratory distress syndrome (ARDS) volume and patient's severity (Simplified Acute Physiology Score [SAPS] 2 score). Confounders included age, gender, SAPS2, type of admission, Charlson Comorbidity Score, and organ failure (hemodynamic and renal). As shown by the white arrows, the relationship is modulated by the severity of the patients (p for interaction < 0.11). For the patients the most severe (higher SAPS2), the impact of ARDS case volume on ICU mortality is reduced (small white arrow), whereas for the patients the less severe (lower SAPS2), the impact of ARDS case volume on ICU mortality is accentuated (large white arrow).

after the end of our study period (17). The use of prone positioning has been popular in French ICUs since the early 2000s (27). Since our observation stopped in 2012, before the publication of the Prone Positioning in Severe Acute Respiratory Distress Syndrome study, it is possible that prone positioning was simply more selectively administered to the most severe patients in high-volume centers. Although disappointing, these findings confirm worldwide the low use of prone positioning as recently reported by the LungSafe investigators (11). Second, we observed a higher use of ECMO in the highest tertile of case volume. Last, we found that patients in the highest ARDS case volume came significantly more from home and emergency department, whereas patients in the lowest tertile came more likely from hospital ward. This may indicate that patients in low-volume ICUs had more often a late-onset ARDS, a condition recently demonstrated as being deleterious (28) and/or that the hospital policy for prevention of ARDS was better in high-volume centers leading to less referral from the ward (29).

Although observational, we believe that our findings will provoke further discussion in terms of global quality of care and management. As for many other settings in which this relationship has been established (5, 6, 8, 10, 19, 30), two hypotheses can be generated: 1) ICU interdisciplinary team develop more skills if they treat more patients ("practice makes perfect"), and 2) ICU interdisciplinary team achieving better outcomes receive more referrals and thus accrue larger volumes ("selective referral"). Evidence of the advantages of centralized organization in ARDS, in terms of patient outcome and cost-effectiveness ratio, is lacking in the literature. However, in the sickest patients requiring ECMO, some data suggest a benefit in survival for higher volume ECMO centers (30). This relationship has been established in other ICU settings, in particular, in the use of mechanical ventilation for which a beneficial association has been found between hospital case volume and patient's outcomes (10). Nevertheless, it is not always the case, for instance, for the management of out-of-hospital cardiac arrests (31). The lack of relationship between case volume and outcomes with these patients is actually not surprising because their poor outcome is likely foregone before ICU admission. In contrast, lung protective ventilation strategy has been shown to be beneficial for patients with ARDS (15, 32). In this regard, inclusion of patients in clinical trials (33) could explain, at least partially, the better prognosis observed in high-volume category ICUs, which are more likely to participate in research studies. This hypothesis is also supported by the higher proportion of ARDS among total cases of mechanical ventilation in high-volume category as compared to low and medium categories. This finding indicating higher exposure for each personnel may imply that high ARDS case-volume ICUs are more frequently caring a patient with ARDS, leading them to optimally endeavor protocols and adapt ventilation strategies. Likewise, other critical components of global management, such as infection control policies and separation from mechanical ventilation process, should significantly influence survival in these patients. Finally, the decisions of withdrawal and withholding of life support may also affect survival. Because of the observational design of the study, we could not capture these features and eventually investigate whether they could explain the findings. This should be addressed by further studies.

The main strength of our study is the inclusion of a large number of ARDS patients in several centers over a long period of time. To our knowledge, this is the first study investigating the relationship between case volume and ICU mortality in the

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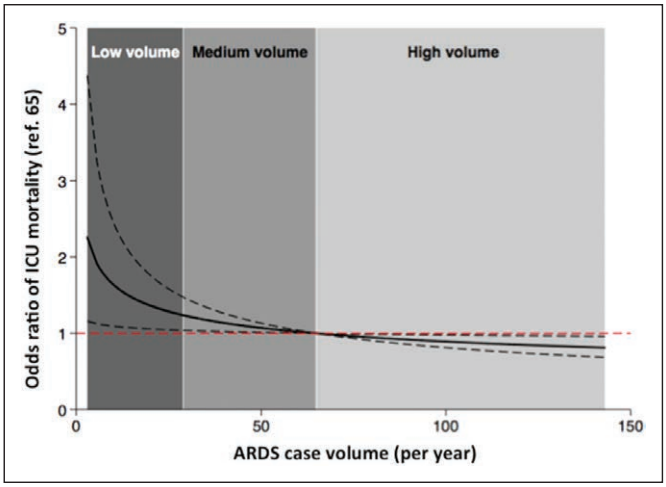

Figure 3. Adjusted relationship between case-volume of acute respiratory distress syndrome (ARDS) and ICU mortality. As case-volume has been included as a log-transformed continuous variable in the multivariable hierarchical logistic regression, we plotted the odds ratio for each case-volume (between 10 and 130) using 65 as a reference. The dashed red line is the identity line and dashed black lines 95% CIs.

specific setting of ARDS. Eventually, we used a variety of analytical approaches to rigorously address confounding factors. Despite our efforts, some potential confounders may not have been included; for instance, we could not adjust the findings on ARDS severity. Some limitations have to be addressed. First, the identification of patients with ARDS was based on hospital coding system. This method is prone to selection biases that may limit exhaustiveness of our results. Since our study is not a register study, our findings may not be considered as strict statements and warrant further confirmation. Second, there may be variations in the coding practices between ICUs in our sample and these may produce artifactual differences in ARDS outcomes. Third, although CUB-REA is a large database using prospectively collected data, the retrospective nature of our work prevented the opportunity to examine the role of important variables such as ventilator settings or arterial blood gases. Fourth, ICUs that reported cases for less than six consecutive years over the 9-year period of the study and patients mechanically ventilated for less than 48 hours were excluded. This may have introduced a selection bias in excluding potentially low-volume ICUs and patients with different outcomes. Last, with respect to the characteristics of the participating ICUs, we included patients mainly from medical admissions. Therefore, our findings may not be true in postsurgical and trauma ARDS patients.

CONCLUSION

In this multicenter cohort of critically ill patients, higher ARDS case volume was independently associated with lower ICU mortality. Although the specific reasons for this finding cannot be addressed by our data, it suggests that practice improves skills and experience with a beneficial effect on patient outcome. Further studies are warranted to delineate the underlying determinants and to confirm the generalization of this association. Quality and improvement programmes and global health policies may benefit from a better understanding of this relationship.

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