Management and outcomes of acute respiratory distress syndrome patients with and without comorbid conditions

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Abstract

Rationale: The standard of care for patients with acute respiratory distress syndrome (ARDS) has been developed based on studies that usually excluded patients with major comorbidities.

Objectives: To describe treatments and outcomes according to comorbidities in patients with ARDS admitted to 19 ICUs (1997–2014).

Methods: Patients were grouped based on comorbidities. Determinants of day-28 mortality were identified by multivariable Cox analysis stratified on center.

Measurements and main results: Among 4953 ARDS patients, 2545 (51.4%) had major comorbidities; the proportion with major comorbidities increased after 2008. Hematological malignancy was associated with severe ARDS and rescue therapies for refractory hypoxemia. COPD, HIV infection, and hematological malignancy were associated with a lower likelihood of invasive mechanical ventilation on the admission day. Admission-day SOFA score was higher in patients with major comorbidities, who more often received vasopressors, dialysis, or treatment-limitation decisions. Day-28 mortality was 33.7% overall, 27.2% in patients without major comorbidities, and 31.1% (COPD) to 56% (hematological malignancy) in patients with major comorbidities. By multivariable analysis, mortality was lower in patients with COPD and higher in those with chronic heart failure, solid tumors, or hematological malignancies. Mortality was independently associated with P02/FIO2 and PaCO2 on day 1, ARDS of pulmonary origin, worse SOFA score, and ICU-acquired events.

Conclusions: Half the patients with ARDS had major comorbidities, which were associated with severe ARDS, multiple organ dysfunction, and day-28 mortality. These findings do not support the exclusion of ARDS patients with severe comorbidities from randomized clinical trials. Trials in ARDS patients with whatever comorbidities are warranted.

Keywords: Acute respiratory failure, Cancer, Mortality, Leukemia, Ventilation

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Introduction

Research into acute respiratory distress syndrome (ARDS) has provided new pathophysiological insights that have major clinical implications [1, 2]. For instance, evidence that ventilator-induced lung injury is a major contributor to ARDS [3, 4] prompted the development of new protective ventilation strategies and of new mechanical ventilation (MV) guidelines [5–7]. To date, no pharmacological treatments have been proven effective in ARDS. However, in addition to MV for acute respiratory failure, treatments must be given not only for the condition associated with the acute or subacute, direct or indirect lung insult that caused ARDS to develop [8], but also for any preexisting comorbid conditions. In some cases, chronic comorbidities, such as malignancies, contribute to the development of ARDS, whereas in others they may increase the patient’s vulnerability to complications of ARDS or treatments [9]. In patients with ARDS, the presence of comorbidities is associated with increased mortality. A prospective study of 107 patients found that independent predictors of death included active malignancy, cirrhosis of the liver, HIV infection, and transplantation, in addition to age above 65 years [10]. However, since its publication in 1998, no other large study has investigated potential differences in ARDS outcomes according to the comorbidity profile. The findings from this study [10] led to the exclusion of patients with major comorbidities from subsequently performed clinical trials and epidemiological studies of mortality rates.

Excluding patients with major comorbidities from studies of ARDS leads to selection bias and limits the external validity of the findings. Another concern is that the sickest patients may be deprived of potentially beneficial treatments if they are not included in trials [11]. Moreover, knowledge about the predictors of mortality in patients with ARDS and major comorbidities may help to identify targets for improvement in other patients [12–15]. For instance, the cause of ARDS is closely associated with mortality in patients with cancer [16–20] but not in the overall population of patients with ARDS [1], hampering generalizability of the findings in unselected patients. For instance, the 12.5% unexpected rate of invasive aspergillosis in autopsy studies of non-immunocompromised patients with ARDS may be related to a lack of knowledge transfer from the immunocompromised literature [20]. Similarly, the deleterious effects of non-invasive ventilation followed by delayed invasive mechanical ventilation in patients with severe hypoxemia were first noticed in immunocompromised patients [18, 21] before being documented in unselected patients [15, 22].

Our primary objective here was to determine whether the prevalence of comorbidities in an unselected population with ARDS was sufficiently high to warrant concerns about the validity and acceptability of studies confined to patients without comorbidities. Our secondary objective was to determine whether the presentation, management, and outcomes of ARDS varied significantly according to the comorbidity profile; such differences would further support the need for studies in unselected patients and may identify new pathophysiological hypotheses and new areas for therapeutic improvements. To achieve these objectives, we retrospectively analyzed prospectively collected data. We estimated the adjusted impact of comorbidities on the characteristics and outcomes of ARDS.

Patients and methods

We conducted a retrospective analysis of the French multicenter prospective observational cohort in the OutcomeRea™ database [23]. The Clermont-Ferrand ethics committee approved the study. Adults admitted to the 19 participating ICUs were prospectively included from January 1, 1997, to July 9, 2014. Details of the database are provided in the online-only supplement.

Among patients receiving invasive MV within the first three ICU days, we identified those meeting the Berlin definition of ARDS [8]: respiratory symptoms with onset within the last 7 days and bilateral chest radiograph opacities not fully explained by heart failure or fluid overload and PaO2/FiO2 ratio ≤ 300 with PEEP ≥ 5 cm H2O. All the items from the Berlin definition have been collected in the database since its creation. Rescue strategies included nitric oxide, prone positioning and ECMO. The variables listed in the tables and figures were collected prospectively and audited. The main outcome was all-cause day-28 mortality. Additional details are available in the online-only supplement.

Major comorbidities were identified using the Knaus classification from the APACHEII [24], as described previously [25, 26], and categorized based on the list of exclusion criteria used in all clinical therapeutic trials in ARDS reported between 2005 and 2015 (Fig. 1). The categories were as follows: chronic respiratory diseases; chronic heart disease; solid tumors; liver cirrhosis; immunodeficiency induced by drugs (used in transplant recipients or to treat inflammatory diseases); hematological malignancies; and HIV infection. Other conditions
such as diabetes, hypertension, and chronic kidney disease were not classified as major comorbidities.

ICU-acquired events were defined as previously reported. A medical error as the failure of a planned action to be completed as intended (i.e., error of execution) or the use of a wrong plan to achieve an aim (i.e., error of planning), and an adverse event as an injury caused by a medical intervention that resulted in harm [27.]

Quality of the database
For most of the study variables, the data capture software immediately ran an automatic check for internal consistency, generating queries that were sent to the ICUs for resolution before incorporation of the new data into the database. In each participating ICU, data quality was checked by having a senior physician from another participating ICU review a 2% random sample of the study data from alternate years. A 1-day-long data capture training course held once annually was open to all OUTCOMEREA investigators and study monitors.

Statistical analysis
Quantitative variables are described as median and interquartile range and qualitative variables as n (%).

The primary objective of our study was to compare day-28 mortality in patients with versus without major comorbidities and across comorbidity groups. To identify variables associated with day-28 mortality, we built univariate Cox regression models stratified by center. Clinically relevant variables and variables significantly associated with day-28 mortality by univariate analysis were the lowest \( \text{PaO}_2/\text{FiO}_2 \) ratio categorized into categories adapted from the Berlin definition [6], pulmonary ARDS, SOFA score without respiratory points, use of inotropic drugs, hemodialysis, ICU-acquired events, ECMO, and \( \text{PCO}_2 > 50 \text{ mmHg} \). These variables were entered into multivariable models. Five missing values were imputed for \( \text{PCO}_2 \) [28]. All variables entered in multivariate models were collected at ICU admission. Colinearity between variables and pairwise interactions were tested. Multivariate Cox regression was performed with stepwise selection. Each comorbidity category was forced into the model. Age was analyzed as a covariate and not a comorbidity. Survival models were censored at day 28. Patients who were lost to follow-up before day 28 were censored at hospital discharge.

Time trends in day-28 mortality in patients without comorbidities and in those with at least one comorbidity were evaluated with the Cochran–Armitage test. To evaluate the effect of \( \text{PaO}_2/\text{FiO}_2 \) ratio on day-28 mortality, we built a multivariate Cox regression model stratified by center and adjusted on comorbidities, extra-respiratory SOFA score items, and worst \( \text{PCO}_2 \) on day 1. The Cox model was selected as it included time-dependent variables. A spline term on the \( \text{PaO}_2/\text{FiO}_2 \) ratio was used. ROC curve analysis was performed to assess how well the Berlin severity category on day 1 predicted day-28 mortality.
All statistical analyses were conducted with SAS 9.3 (SAS Institute, Cary, NC, USA). P values < 0.05 were considered statistically significant.

Results
Patients
Among the 19,019 adults admitted to the 19 participating ICUs throughout the 17.5-year recruitment period, 9804 (51.6%) received MV within 3 days after ICU admission and, among these, 5465 (55.7%) had \( \text{PaO}_2/\text{FiO}_2 \leq 300 \) (Fig. 2), including 4953 who met criteria for ARDS and were included in the study. Of these 4953 patients, 2408 (48.6%) had no major comorbidities, 1942 (39.2%) had one major comorbidity, and 603 (12.2%) had two or more major comorbidities. The most common comorbid conditions were chronic respiratory diseases \( (n=948) \), followed by chronic heart failure \( (n=673) \), solid tumors \( (n=628) \), liver cirrhosis \( (n=357) \), drug-related immunodeficiency \( (n=256) \), hematological malignancies \( (n=248) \), and HIV infection \( (n=104) \). Table 1 reports the patient characteristics in the comorbidity groups.

Day-28 mortality
Day-28 mortality was 33.7% (1667 deaths) overall, 27.2% in patients with no comorbidities, and 31.1% (COPD group) to 56% (hematological malignancies group) in patients with at least one comorbidity (Table 1; Fig. 2). By multivariable analysis (Table 2), chronic heart failure, solid tumors, and hematological malignancies were independently associated with higher day-28 mortality, whereas COPD was associated with lower day-28 mortality. A worse SOFA score and the occurrence of ICU-acquired events were associated with higher day-28 mortality. Pulmonary ARDS was associated with lower day-28 mortality compared to extra-pulmonary ARDS. Finally, highest \( \text{PaCO}_2 \) on day 1 independently predicted day-28 mortality.

According to the Berlin definition, 1864 (37.6%) patients had mild, 2034 (41.1%) moderate, and 1055 (21.3%) severe ARDS. Day-28 mortality differed significantly across these three groups (26.5, 35.5, and 46.6%, respectively, \( P < 0.0001 \)). However, the ability of the Berlin severity definition to predict day-28 mortality was only fair on day 1 [area under the curve (AUC), 0.59] and day 2 (AUC, 0.61). \( \text{PaO}_2/\text{FiO}_2 < 100 \) was significantly associated with day-28 mortality (Fig. 3). \( \text{PaCO}_2 > 50 \text{ mmHg} \) on day 1 was also significantly associated with day-28 mortality [hazard ratio, 1.005/point; 95% confidence interval (CI), 1.002–1.009; \( P = 0.003 \)].

ARDS features according to comorbidities
Of the 4953 patients, 1217 (24.6%) had pulmonary ARDS (Table 1). Pulmonary ARDS was more common among patients with liver cirrhosis or immunodeficiency compared to patients without comorbidities. Invasive MV on day 1 was less common among patients with COPD, HIV infection, or hematological malignancies compared to patients without comorbidities. Patients with hematological malignancies more often had severe ARDS, and more often received rescue therapies for refractory hypoxemia (OR, 1.79; 95% CI, 1.22–2.61; \( P < 0.01 \)). Finally, except in the group with respiratory diseases, the SOFA score at admission was higher in the groups with comorbidities, which also had greater use of vasopressors and renal replacement therapy, compared to the group without comorbidities.

Treatment-limitation decisions
Figure 4 displays the odds ratios (OR) for treatment-limitation decisions according to the comorbidity groups. Overall, treatment-limitation decisions taken within 2 days after ICU admission were significantly more common in patients with liver cirrhosis (OR, 1.94; 95% CI, 1.26–3.00; \( P < 0.01 \)), solid tumors (OR, 1.93; 95% CI, 1.36–2.75; \( P < 0.01 \)), or hematological malignancies (OR, 1.79; 95% CI, 1.06–3.01; \( P = 0.03 \)). As the ICU stay length increased, compared to patients without comorbidities, those with comorbidities other than HIV infection or drug-related immunodeficiency increasingly received
treatment-limitation decisions. Last, among patients who died, those with COPD or solid tumors were significantly more likely to have treatment-limitation decisions.

**Time trends**

As compared to ICU admission between 1997 and 2007, ICU admission after 2008 was more common in patients with drug-related immunodeficiency (OR, 1.71; 95% CI, 1.32–2.22; \( P < 0.01 \)), hematological malignancies (OR, 1.65; 95% CI, 1.27–2.15; \( P < 0.01 \)), liver cirrhosis (OR, 1.36; 95% CI, 1.09–1.70; \( P < 0.01 \)), or solid tumors (OR, 1.22; 95% CI, 1.02–1.46; \( P = 0.03 \)), compared to patients with no comorbidities. Age was not different between the two time periods. In patients

### Table 1 Patient characteristics in the groups with and without comorbidities

|                      | No comorbidity (n = 2408) | COPD (n = 948) | CHF (n = 673) | Solid Tumor (n = 628) | Cirrhosis (n = 357) | Drug-related immunodeficiency (n = 256) | Hematological malignancy (n = 248) | HIV infection (n = 104) |
|----------------------|---------------------------|---------------|--------------|----------------------|-------------------|--------------------------------------|----------------------------------|-----------------------|
| ICU admission after 2008 | 862 (35.8) | 353 (37.2) | 265 (39.4) | 254 (40.4) | 154 (43.1) | 125 (48.8) | 119 (48) | 31 (29.8) |
| SOFA score on day 1  | 7 [5; 10] | 7 [5; 10] | 8 [6; 11] | 8 [5; 10] | 10 [7; 14] | 8 [6; 11] | 10 [7; 13] | 9 [6; 11] |
| Pulmonary ARDS       | 1669 (69.3) | 723 (76.3) | 438 (65.1) | 373 (59.4) | 250 (70) | 179 (69.9) | 219 (88.3) | 91 (87.5) |
| Invasive MV on day 1  | 2036 (84.6) | 740 (78.1) | 554 (82.3) | 495 (78.8) | 271 (75.9) | 193 (75.4) | 156 (62.9) | 66 (63.5) |
| Severe ARDS          | 491 (20.4) | 201 (21.2) | 129 (19.2) | 139 (22.1) | 75 (21) | 63 (24.6) | 63 (25.4) | 28 (26.9) |
| Highest PaCO2 at day 1 | 39 (34–46) | 47 (38–62) | 40 (32–48) | 40 (34–47) | 37 (0–44) | 39 (33–47) | 38 (32–47) | 42 (34–50) |

**Treatments during the ICU stay**

|                      | No comorbidity (n = 2408) | COPD (n = 948) | CHF (n = 673) | Solid Tumor (n = 628) | Cirrhosis (n = 357) | Drug-related immunodeficiency (n = 256) | Hematological malignancy (n = 248) | HIV infection (n = 104) |
|----------------------|---------------------------|---------------|--------------|----------------------|-------------------|--------------------------------------|----------------------------------|-----------------------|
| Vasopressors         | 1545 (64.2) | 678 (71.5) | 544 (80.8) | 479 (76.3) | 284 (79.6) | 189 (73.8) | 216 (87.1) | 76 (73.1) |
| Renal replacement therapy | 429 (17.8) | 164 (17.3) | 198 (29.4) | 134 (21.3) | 110 (30.8) | 84 (32.8) | 98 (39.5) | 34 (32.7) |
| Rescue strategies     | 209 (8.7) | 91 (9.6) | 45 (6.7) | 58 (9.2) | 31 (8.7) | 27 (10.5) | 36 (14.5) | 18 (17.3) |
| Nitric oxide          | 131 (5.4) | 69 (7.3) | 35 (5.2) | 44 (7) | 18 (5) | 16 (6.3) | 24 (9.7) | 14 (13.5) |
| Prone positioning     | 111 (4.6) | 41 (4.3) | 13 (1.9) | 26 (4.1) | 15 (4.2) | 15 (5.9) | 18 (7.3) | 8 (7.7) |
| ECMO                 | 32 (1.3) | 3 (0.3) | 4 (0.6) | 3 (0.5) | 3 (0.8) | 2 (0.8) | 1 (0.4) | 2 (1.9) |
| Treatment-limitation decisions | 3 (0.3)c | 4 (0.6) | 3 (0.5) | 3 (0.8) | 2 (0.8) | 1 (0.4) | 2 (1.9) |

**Note:** 603 patients had more than one comorbidity

COPD chronic obstructive pulmonary disease, CHF chronic heart failure, HIV human immunodeficiency virus, ICU intensive care unit, SOFA sequential organ function assessment, MV mechanical ventilation, ARDS acute respiratory distress syndrome, PaCO2 partial pressure of carbon dioxide in arterial blood, ECMO extracorporeal membrane oxygenation, VAP ventilator-associated pneumonia

\( a \) Defined as decisions to withhold or withdraw life-supportive treatments

\( b \) Defined as events that were not expected at ICU admission but may affect outcomes, i.e., bleeding, myocardial or mesenteric infarction, atelectasis, cardiac arrest, arrhythmia requiring cardioversion, pulmonary embolism, drug allergy, seizures, medical error, hypoglycemia, and pericarditis requiring drainage

\( c \) \( P < 0.05 \) compared to patients with no major comorbidities
Table 2 Multivariate analysis of factors independently associated with day-28 mortality in patients with ARDS (Cox model stratified on center)

| Variable                              | Hazard ratio (95% confidence interval) | P value |
|---------------------------------------|----------------------------------------|---------|
| Comorbid conditions                   |                                        |         |
| Chronic respiratory disease           | 0.824 (0.721–0.942)                    | 0.004   |
| Chronic heart failure                 | 1.492 (1.308–1.701)                    | < 0.0001|
| Liver cirrhosis                       | 1.124 (0.951–1.329)                    | 0.171   |
| Solid tumor                           | 1.544 (1.350–1.765)                    | < 0.0001|
| Drug-related immunodeficiency         | 1.058 (0.850–1.317)                    | 0.613   |
| Hematological malignancy              | 1.514 (1.243–1.844)                    | 0.0001  |
| HIV infection                         | 0.767 (0.539–1.091)                    | 0.139   |
| Lowest PaO2/FiO2 ratio                |                                        |         |
| 200–300 (mild ARDS)                   | Reference                              |         |
| 100–299 (moderate ARDS)               | 1.229 (1.094–1.381)                    | 0.0005  |
| < 100 (severe ARDS)                   | 1.692 (1.489–1.923)                    | < 0.0001|
| Highest PaCO2 on day 1 > 50 mmHg      | 1.411 (1.252–1.589)                    | < 0.0001|
| Pulmonary ARDS                        | 0.680 (0.595–0.775)                    | < 0.0001|
| SOFA score without respiratory points |                                        |         |
| on day 1                               |                                        |         |
| < 4                                   | Reference                              |         |
| 4–5                                   | 1.526 (1.268–1.835)                    | < 0.0001|
| 5–8                                   | 2.329 (1.961–2.766)                    | < 0.0001|
| > 8                                   | 5.033 (4.254–5.955)                    | < 0.0001|
| ICU–acquired events<sup>a</sup>       | 1.411 (1.252–1.589)                    | < 0.0001|

ARDS acute respiratory distress syndrome, HIV human immunodeficiency virus, PaO2/FiO2 ratio of partial pressure of oxygen in arterial blood over fraction of inspired oxygen, PaCO2 partial pressure of carbon dioxide in arterial blood, SOFA Sequential Organ Function Assessment, ICU intensive care unit.

<sup>a</sup> Defined as events that were not expected at ICU admission but may affect outcomes, i.e., bleeding, myocardial or mesenteric infarction, atelectasis, cardiac arrest, arrhythmia requiring cardioversion, pulmonary embolism, drug allergy, seizures, medical error, hypoglycemia, and pericarditis requiring drainage.

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**Fig. 3** Hazard ratio for day-28 mortality according to PaO2/FiO2 on day 1. The depicted spline is adjusted on comorbidities, SOFA score on day 1 without the respiratory subscore, and worst PaCO2 on day 1.
without comorbidities, mortality rate remained unchanged between the two time periods. However, in patients with major comorbidities, mortality non-significantly decreased (Fig. 5). The number of patients on dialysis for end-stage renal failure was too small for a separate analysis.

Discussion
In an unselected population with ARDS in 1997-2014, half had major comorbidities and this proportion increased over time. In the group with major comorbidities, hypoxemia was more severe, extrapulmonary organ dysfunction more common, and ICU resource consumption greater. Presence of at least one major comorbidity was independently associated with higher day-28 mortality. These findings suggest that ARDS trials excluding patients with major comorbidities actually hamper the generalizability of study findings that may not be generalizable to the whole ARDS population.

Patients admitted to the ICU today are older, more severely ill, and more likely to have chronic comorbidities compared to 20 years ago [26, 29]. Several factors may explain these changes, including the aging of the population [30] and the better survival among patients with cancer [31], cardiovascular disease [32], and chronic inflammatory disorders [33]. Due to therapeutic advances, many patients now live with chronic medications that impair their immune defenses [34]. A role for

**Fig. 4** Odds ratio for treatment-limitation decisions according to the comorbidity group. a Shows decisions made within 2 days after ICU admission and b decisions made at any time during the ICU stay. The reference group is the group without comorbidities. COPD chronic obstructive pulmonary disease, CHF chronic heart failure, HIV human immunodeficiency virus.
these factors is supported by our finding that half the patients with ARDS had major comorbidities and that this proportion increased over time. At present, these patients are denied enrolment into studies of treatments that may improve their short- and long-term survival, as well as their health-related quality of life [30], raising concerns and questions about the main goals of clinical research [35], which should be to improve patient survival and wellbeing [36].

Studies that exclude half the potentially eligible patients also raise methodological concerns about external validity. Most of the advances in ARDS management have stemmed from improvements in our understanding of pathophysiological mechanisms. There is no evidence that these mechanisms differ between patients with versus without comorbidities, and therefore no reason not to apply and to study the new treatments in patients with comorbidities. Moreover, the types of comorbidities used as exclusion criteria varied across studies, further aggravating concerns about external validity. Thus, only half the studies excluded patients with chronic respiratory failure. Finally, some patients with undiagnosed cancer, COPD, or liver disease may have been included in studies of ARDS.

Our findings indicate that including unselected ARDS patients may decrease the sample size needed to obtain the required number of events. Major clinical endpoints in ARDS research are respiratory and global severity, need for rescue strategies, ICU-acquired infectious or non-infectious events, and mortality [36]. All these endpoints were significantly more common in our patients with major comorbidities. The frequency differences suggest that sample sizes could be reduced by up to 30% if unselected patients were included. Smaller sample sizes improve the feasibility and decrease the costs of randomized controlled trials while also decreasing the risk of harm to patients [37].

Taken together, these arguments support the inclusion of patients with comorbidities in physiological and clinical studies of ARDS. Also, including unselected patients may allow to refine the clinical phenotypes of ARDS in terms of lung and systemic inflammatory patterns, pulmonary involvement (focal vs. diffuse or pulmonary vs. extrapulmonary), risk-stratification biomarkers, and response to treatments [38]. An alternative to apply strict exclusion criteria that hamper generalizability of the findings would be to use stratification. This method can be used to ensure equal allocation of subgroups of participants to each treatment group. This may be done for any comorbidity.

This study has several limitations. First, we neither assessed the treatment responses nor refined the clinical phenotypes. However, the large number of patients suggests hypotheses of potential usefulness for future ARDS research. Second, most of the recent advances in ARDS were provided by new insights into the mechanical,
pathological, inflammatory, and immune–biological properties of the affected lungs. However, we did not have the data needed for comparisons of plateau, driving, or transpulmonary pressures across comorbidity groups. Neither could we compare lung morphology and pathology or ARDS biomarkers between patients with and without major comorbidities. Last, the exclusion criteria used in clinical trials are intended in part to maximize patient safety and to obtain uniform patient populations, although they also increase the chances of achieving efficacy endpoints. Nevertheless, using exclusion criteria that are highly prevalent is open to criticism. Other methodological tools are available, such as stratification on factors other than the study intervention, which facilitates the control of confounding factors and the detection and interpretation of relationships among variables.

In summary, our findings strongly suggest that including unselected patients in studies of ARDS would provide new information of greater relevance to clinical practice compared to studies done in the past, and give the most vulnerable patients access to potential benefits from experimental treatment strategies. Also, applying the available evidence to patients with comorbidities may show differences in responses to therapy and determinants of survival, thereby identifying new targets for improvement.

Electronic supplementary material
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In summary, our findings strongly suggest that including unselected patients in studies of ARDS would provide new information of greater relevance to clinical practice compared to studies done in the past, and give the most vulnerable patients access to potential benefits from experimental treatment strategies. Also, applying the available evidence to patients with comorbidities may show differences in responses to therapy and determinants of survival, thereby identifying new targets for improvement.

Electronic supplementary material
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References

1. Papazian L, Calfee CS, Chiurullo D, Luyt C-E, Meyer NJ, Sekiguchi H, Matthay MA, Meduri GU (2016) Diagnostic workup for ARDS patients. Intensive Care Med 42:674–685

2. Slutsky AS, Villar J, Pesenti A (2016) Happy 50th birthday ARDS! Intensive Care Med 42:657–659

3. Dreyfuss D, Soler P, Basset G, Saumon G (1988) High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159–1164

4. Slutsky AS, Ranieri VM (2013) Ventilator-induced lung injury. N Engl J Med 369:2126–2136

5. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munsidi L, Walkley AJ, Adhikari NKJ, Amato MBP, Branson R, Brower RG, Ferguson ND, Gattinoni L, Gattinoni L, Hess D, Mancebo J, Meade MO, McAuley DF, Ranieri M, Sobrero F, Talmor D, Ware LB, Matthay MA, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) Score: A practical tool for organ dysfunction/l dd. Crit Care Med 24:707–710

6. Claesson J, Freundlich M, Gunnarsson I, Laake JH, Møller MH, Vandvik PO, Varpula T, Wramminger N, Zambon O (2013) Scandinavian clinical practice guideline on ventilation in adults with acute respiratory distress syndrome. Acta Anaesthesiol Scand 59:286–297

7. Claesson J, Freundlich M, Gunnarsson I, Laake JH, Møller MH, Vandvik PO, Varpula T, Wramminger N, Zambon O (2013) Scandinavian clinical practice guideline on ventilation in adults with acute respiratory distress syndrome. Acta Anaesthesiol Scand 59:286–297

8. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Gattinoni L, Gattinoni L, Hess D, Mancebo J, Meade MO, McAuley DF, Ranieri M, Sobrero F, Talmor D, Ware LB, Matthay MA, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) Score: A practical tool for organ dysfunction/l dd. Crit Care Med 24:707–710

9. Pola MD, Navarrete-Mondejar E, Hurtado B, Vázquez-Mata G (2000) Acute respiratory distress syndrome: resource use and outcomes in 1985 and 1995, trends in mortality and comorbidities. J Crit Care Med 15:91–96

10. Zilberberg MD, Epstein SK (1998) Acute lung injury in the medical ICU: comorbid conditions, age, etiology, and hospital outcome. Am J Respir Crit Care Med 157:1159–1164

11. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA, NHLBI ARDS Network. (2014) Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2:61–620

12. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, LUNG SAFE Investigators, ESMIC Trials Group (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 Countries. JAMA 315:788–800

13. Laffey JG, Madotto F, Bellani G, Pham T, Fan E, Brochard L, Amin P, Arabi Y, Bajwa DK, Bruhn A, Ceryn V, Clarkson K, Heunks L, Kurashahi K, Laake JH, Lorénte JA, Mcelain M, Nin N, Polo JE, Piloulllou L, Qiu H, Jiménez JGS, Esteban A, McAuley DF, van Haren F, Ranieri M, Rubenfeld G, Wrigge H, Slutsky AS et al (2017) Geo-economic variations in epidemiology, patterns of care, and outcomes in patients with acute respiratory distress syndrome: insights from the LUNG SAFE prospective cohort study. Lancet Respir Med 5:627–638

14. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Amin P, Arabi Y, Bajwa DK, Bruhn A, Ceryn V, Clarkson K, Heunks L, Kurashahi K, Laake JH, Larsson A, McAuley DF, Mcelain M, Nin N, Qiu H, Ranieri M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, LUNG SAFE Investigators, and the ESMIC Trials Group (2016) Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med 42:1860–1876

15. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, Esteban A, Gattinoni L, Lumbasibirevic P, Piloulllou L, van Haren F, Larsson A, McAuley DF, Bauer PR, Arabi YM, Ranieri M, Antonelli M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, LUNG SAFE Investigators, ESMIC Trials Group (2017) Noninvasive ventilation of patients with acute respiratory distress syndrome: insights from the LUNG SAFE Study. Am J Respir Crit Care Med 195:67–77

16. Azoulay E, Pickkers P, Soares M, Perrier A, Rello J, Bauer PR, van de Louw A, Hermal a P, Masic V, Taconne FS, Martin Loeches I, Meyhoff TS, Salluh J, Schellongowski P, Rusinova K, Terzi N, Mehta S, Antonelli M, Koutachtet A, Barratt-Due A, Valkonen M, Landburg PP, Brunef F, Bukan RB, Pène F, Metaxa V, Moreau AS, Souppart V, Buirghi G et al (2017) Acute hypoxemic respiratory failure in immunocompromised patients: the Efrain multination prospective cohort study. Intensive Care Med. https://doi.org/10.1007/s00134-017-4947-1

17. Azoulay E, Lammle MT, Pekurci D, Pène F, Koutachtet A, Perez P, Vincent F, Mayaux J, Benoit D, Brunf E, Meert A-P, Nyungu M, Rabitat A, Darmon M (2014) Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med 40:1106–1114

18. Adda M, Coquet I, Darmon M, Thierry G, Schlemmer B, Azoulay E (2008) Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. Crit Care Med 36:2766–2772

19. Azoulay E, Schlemmer B (2006) Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med 32:808–822

20. de Hemptinne Q, Remmelink M, Brimioulle S, Salmon I, Vincent JL (2009) ARDS: a clinicopathological confrontation. Chest 135:946–949

21. Depuydt PO, Benoit DD, Vandevoorde KH, Decruyenaere JM, Colardyn FA (2004) Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. Chest 126:1299–1306

22. Frat J-P, Thille AW, Mercai C, Girault C, Ragot S, Perbet S, Prat G, Boultain T, Morawiec E, Cottereau A, Da vequart J, Neer S, Razai K, Mira J-P, Argaud L, Chakarian J-C, Ricard J-D, Wittebole X, Chevalier S, Herbrand A, Fartoukh M, Constantin J-M, Tonnelier J-M, Pierrot J, Mathonnet A, Béduneau G, Deletage-Metereau C, Richard J-C, Brochard CM, Laraison T et al (2015) High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 372:2185–2196

23. Truche A-S, Darmon M, Bally S, Clech C, Dupuis C, Missot B, Azoulay E, Schwebel C, Boudauma L, Kelle H, Adrie C, Dumenil A-S, Argual L, Marcotte G, Jamali S, Zaoui P, Laurent V, Goldgran-Toledano D, Sonneville E, Schwebel C, Bouadma L, Kallel H, Adrie C, Dumenil A-S, Argaud L, Engl J Med 372:2185–2196

24. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829

25. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhard C, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ

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