ORIGINAL

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 P_aO_2/F_iO_2 and $PaCO_2$ 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

Take home message

Half the ARDS patients have major comorbidities and this proportion increased over time. The differences in presentation and outcome of ARDS between patients with and without major comorbidities challenge the acceptability of confining studies to relatively healthy patients.

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 PaO_2/FiO_2 ratio ≤ 300 with $PEEP \geq 5$ cm H_2O. 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

Intervention	Journal	First Author	Cancer, Transplants Immunocompromised	Cirrhosis	Neuromuscular disease	Age	COPD	Heart Failure	Limited life expectancy	Burns	DNR
Rosuvastatin	NEJM 2014	Truwit									
Recombinant human activated protein C	PLOS 1 2014	Cornet									
Adaptive support ventilation	Respirology 2013	Agarwal									
Prone positioning	NEJM 2013	Guérin									
HFO	NEJM 2013	Ferguson				85yo					
HFO	NEJM 2013	Young									
Full Enteral	JAMA 2012	Rice									
β-2 agonist	Lancet 2012	Gao Smith									
Open lung strategy	Crit Care 2011	Hodgson									
Omega-3 + antioxidant	JAMA 2011	Rice									
β-2 agonist	AJRCCM 2011	Matthay									
NMBAs	NEJM 2010	Papazian									
Prone positioning	JAMA 2009	Taccone									
Esophageal pressure	NEJM 20008	Talmor									
Prone positioning	ICM 2008	Fernandez									
PEEP setting	JAMA 2008	Mercat									
Protocolized ventilation strategy	JAMA 2008	Meade						left atrial hypertension			
Ventilation strategy	CCM 2006	Villar									
PAC	NEJM 2005	Wheeler									

HFO, high-flow oxygen therapy; NMBAs, neuromuscular blocking agents; PAC, pulmonary artery catheter

Fig. 1 Systematic review of all therapeutic trials in ARDS published between 2005 and 2015. Comorbid conditions are displayed in red if they were exclusion criteria in the trial and in green if they were not [39–57]

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 OUT-COMEREATM 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 P_aO_2/F_iO_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 $PCO_2 > 50$ mmHg. These variables were entered into multivariable models. Five missing values were imputed for 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 P_aO_2/F_iO_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 P_aCO_2 on day 1. The Cox model was selected as it included time-dependent variables. A spline term on the P_aO_2/F_iO_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 $PaO_2/FiO_2 \leq 300$ (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 $PaCO_2$ 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). $PaO_2/F_iO_2 < 100$ was significantly associated with day-28 mortality (Fig. 3). $PaCO_2 > 50$ 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
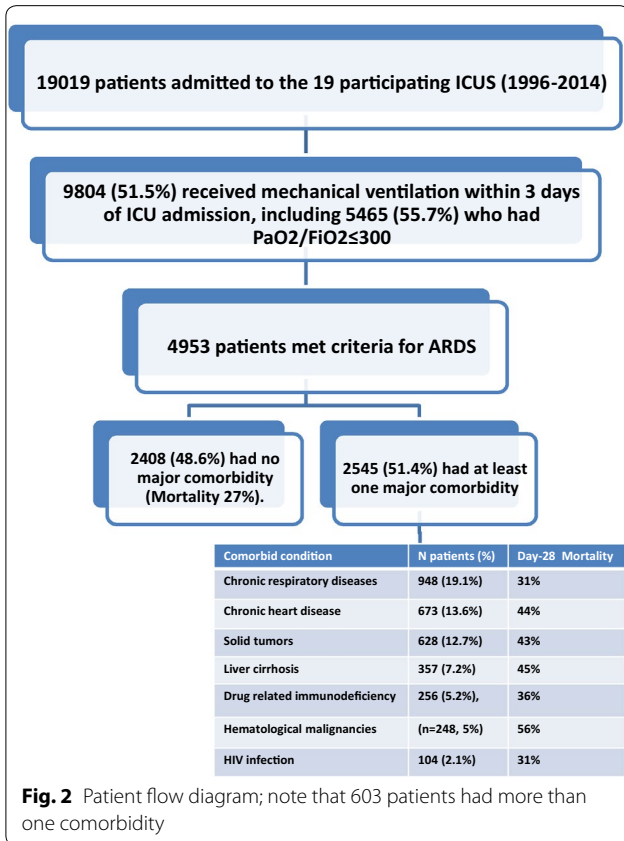

19019 patients admitted to the 19 participating ICUS (1996-2014)

9804 (51.5%) received mechanical ventilation within 3 days of ICU admission, including 5465 (55.7%) who had PaO2/FiO2≤300

4953 patients met criteria for ARDS

2408 (48.6%) had no major comorbidity (Mortality 27%).

2545 (51.4%) had at least one major comorbidity

Comorbid condition	N patients (%)	Day-28 Mortality
Chronic respiratory diseases	948 (19.1%)	31%
Chronic heart disease	673 (13.6%)	44%
Solid tumors	628 (12.7%)	43%
Liver cirrhosis	357 (7.2%)	45%
Drug related immunodeficiency	256 (5.2%),	36%
Hematological malignancies	(n=248, 5%)	56%
HIV infection	104 (2.1%)	31%

Fig. 2 Patient flow diagram; note that 603 patients had more than one comorbidity

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)[c]	154 (43.1)[c]	125 (48.8)[c]	119 (48)[c]	31 (29.8)
SOFA score on day 1	7 [5; 10]	7 [5; 10]	8 [6; 11][c]	8 [5; 10]	10 [7; 14][c]	8 [6; 11][c]	10 [7; 13][c]	9 [6; 11][c]
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)[c]	554 (82.3)	495 (78.8)	271 (75.9)	193 (75.4)	156 (62.9)[c]	66 (63.5)[c]
Severe ARDS	491 (20.4)	201 (21.2)	129 (19.2)	139 (22.1)	75 (21)	63 (24.6)	63 (25.4)[c]	28 (26.9)
Highest PaCO2 at day 1	39 (34–46)	47 (38–62)[c]	40 (32–48)	40 (34–47)	37 (0–44)[c]	39 (33–47)	38 (32–47)	42 (34–50)
Treatments during the ICU stay								
Vasopressors	1545 (64.2)	678 (71.5)[c]	544 (80.8)[c]	479 (76.3)[c]	284 (79.6)[c]	189 (73.8)[c]	216 (87.1)[c]	76 (73.1)[c]
Renal replacement therapy	429 (17.8)	164 (17.3)	198 (29.4)[c]	134 (21.3)[c]	110 (30.8)[c]	84 (32.8)[c]	98 (39.5)[c]	34 (32.7)[c]
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)[c]	35 (5.2)	44 (7)	18 (5)	16 (6.3)	24 (9.7)[c]	14 (13.5)[c]
Prone positioning	111 (4.6)	41 (4.3)	13 (1.9)[c]	26 (4.1)	15 (4.2)	15 (5.9)	18 (7.3)	8 (7.7)
ECMO	32 (1.3)	3 (0.3)c	4 (0.6)	3 (0.5)	3 (0.8)	2 (0.8)	1 (0.4)	2 (1.9)
Treatment-limitation decisions[a]								
On day 1 or day 2	101 (4.2)	39 (4.1)	36 (5.3)	49 (7.8)[c]	28 (7.8)[c]	12 (4.7)	18 (7.3)[c]	2 (1.9)
At any time during the ICU stay	335 (13.9)	187 (19.7)[c]	136 (20.2)[c]	164 (26.1)[c]	84 (23.5)[c]	45 (17.6)	59 (23.8)	14 (13.5)
Reintubation	464 (19.3)	217 (22.9)[c]	133 (19.8)	108 (17.2)	57 (16)	44 (17.2)	31 (12.5)[c]	21 (20.2)
ICU-acquired events[b]	1136 (47.2)	525 (55.4)[c]	391 (58.1)[c]	345 (54.9)[c]	213 (59.7)[c]	163 (63.7)[c]	141 (56.9)[c]	49 (47.1)
VAP	277 (11.5)	161 (17)	78 (11.6)	87 (13.9)	49 (13.7)	37 (14.5)	44 (17.7)	17 (16.3)
Day-28 mortality	655 (27.2)	295 (31.1)[c]	293 (43.5)[c]	271 (43.2)[c]	162 (45.4)[c]	91 (35.5)[c]	139 (56)[c]	33 (31.7)

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, $PaCO_2$ 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
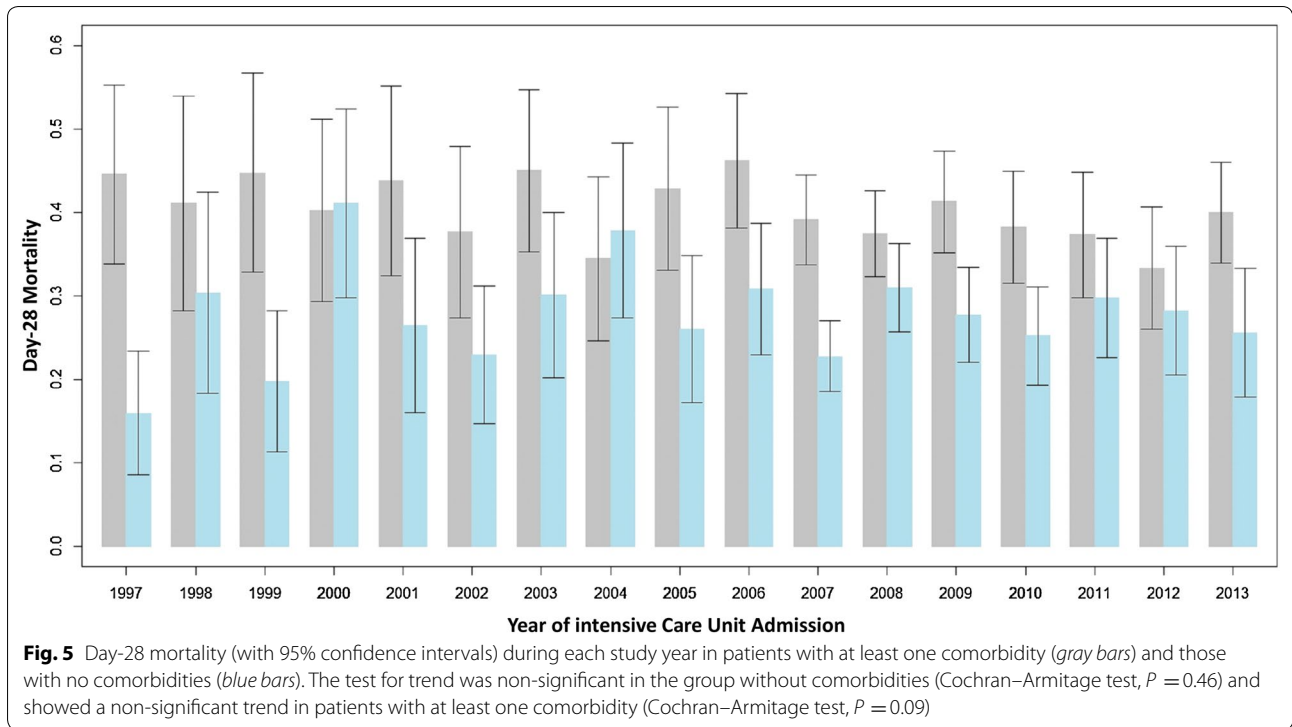
[c] $P < 0.05$ compared to patients with no major comorbidities

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 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 P_aO_2/F_iO_2 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 P_aCO_2 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[a]	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

[a] 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
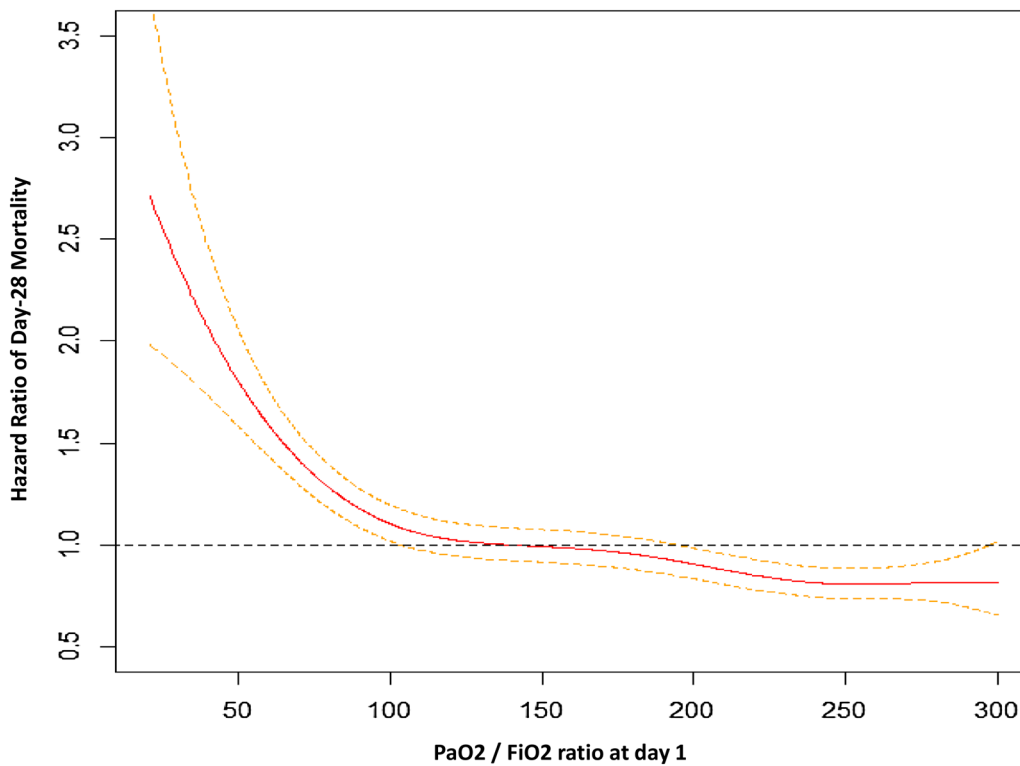
Fig. 3 Hazard ratio for day-28 mortality according to P_aO_2/F_iO_2 on day 1. The depicted spline is adjusted on comorbidities, SOFA score on day 1 without the respiratory subscore, and worst $PaCO_2$ on day 1
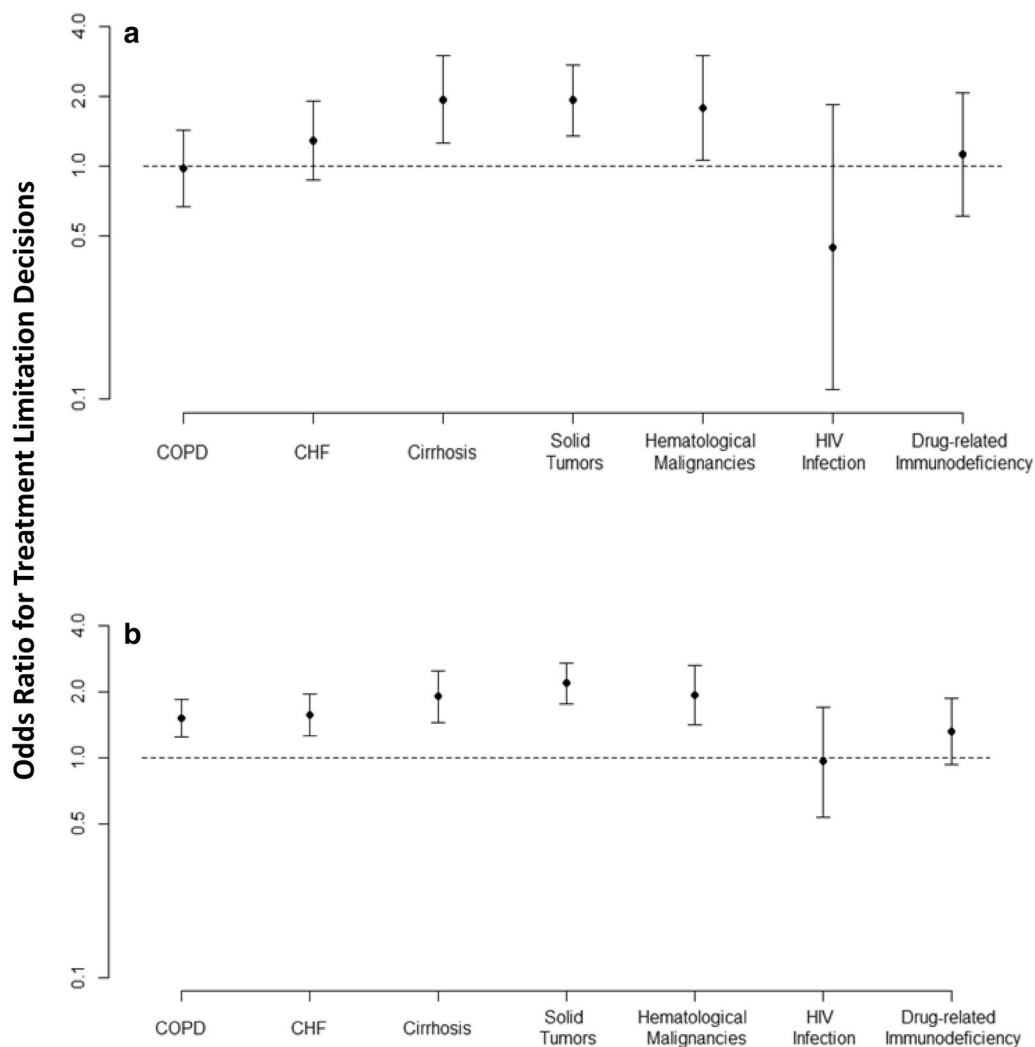
Fig. 4 Odds ratio for treatment-limitation decisions according to the comorbidity group. **a** Shows decisions made within 2 days after ICU admission and **b** decisions made at any time during the ICU stay. The reference group is the group without comorbidities. *COPD* chronic obstructive pulmonary disease, *CHF* chronic heart failure, *HIV* human immunodeficiency virus

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. 5 Day-28 mortality (with 95% confidence intervals) during each study year in patients with at least one comorbidity (*gray bars*) and those with no comorbidities (*blue bars*). The test for trend was non-significant in the group without comorbidities (Cochran–Armitage test, $P = 0.46$) and showed a non-significant trend in patients with at least one comorbidity (Cochran–Armitage test, $P = 0.09$)

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.

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