Title

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Journal

Intensive Care Medicine, 46(6)

ISSN

0342-4642

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Publication Date

2020-06-01

DOI

10.1007/s00134-020-06010-9

Peer reviewed

Intensive Care Med
https://doi.org/10.1007/s00134-020-06010-9

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Acute respiratory distress syndrome-attributable mortality in critically ill patients with sepsis

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Abstract

Purpose: Previous studies assessing impact of acute respiratory distress syndrome (ARDS) on mortality have shown conflicting results. We sought to assess the independent association of ARDS with in-hospital mortality among intensive care unit (ICU) patients with sepsis.

Methods: We studied two prospective sepsis cohorts drawn from the Early Assessment of Renal and Lung Injury (EARLI; $n = 474$) and Validating Acute Lung Injury markers for Diagnosis (VALID; $n = 337$) cohorts. ARDS was defined by Berlin criteria. We used logistic regression to compare in-hospital mortality in patients with and without ARDS, controlling for baseline severity of illness. We also estimated attributable mortality, adjusted for illness severity by stratification.

Results: ARDS occurred in 195 EARLI patients (41%) and 99 VALID patients (29%). ARDS was independently associated with risk of hospital death in multivariate analysis, even after controlling for severity of illness, as measured by APACHE II (odds ratio [OR] 1.65 (95% confidence interval [CI] 1.02, 2.67), $p = 0.04$ in EARLI; OR 2.12 (CI 1.16, 3.92), $p = 0.02$ in VALID). Patients with severe ARDS ($P/F < 100$) primarily drove this relationship. The attributable mortality of ARDS was 27% (CI 14%, 37%) in EARLI and 37% (CI 10%, 51%) in VALID. ARDS was independently associated with ICU mortality, hospital length of stay (LOS), ICU LOS, and ventilator-free days.

Conclusions: Development of ARDS among ICU patients with sepsis confers increased risk of ICU and in-hospital mortality in addition to other important outcomes. Clinical trials targeting patients with severe ARDS will be best poised to detect measurable differences in these outcomes.

Keywords: Acute respiratory distress syndrome, Acute lung injury, Sepsis, Mortality

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Introduction

Acute respiratory distress syndrome (ARDS) is a clinical syndrome in critically ill patients involving acute respiratory failure, hypoxemia, and non-cardiogenic pulmonary edema [1, 2]. To date, there are no effective pharmacotherapies for ARDS. The attributable mortality for ARDS among patients with sepsis, the most common ARDS risk factor, has not been previously estimated. Empiric estimation of the effect of ARDS on mortality is crucial in this population for the design of future clinical trials.

Proximal causes of death are notoriously difficult to identify in critically ill patients, particularly since most ICU patients die after withdrawal of life-sustaining measures [3, 4]. Given that the supportive therapies shown to reduce mortality in ARDS include primarily a ventilator strategy and prone positioning, it may seem implicit that there exists some modifiable mortality attributable to ARDS related to oxygenation [5, 6]. However, for decades, it has been clear that refractory hypoxemia accounts for only a small fraction of deaths in ARDS [7, 8]. A recent study showed the majority of deaths of ICU patients with ARDS were not directly related to lung damage [9]. Thus, it has been challenging to determine what proportion of mortality is attributable to ARDS itself (and therefore a potential target for ARDS-focused clinical trials), and what proportion is driven by the underlying ARDS risk factor, comorbidities, or a combination of the two. Quantifying the ARDS-attributable mortality—the excess mortality among patients with ARDS that can be attributed to ARDS—would help inform design of future ARDS clinical trials.

Previous studies examining the impact of ARDS on mortality have shown conflicting results [10–17]. In a large retrospective study of ventilated ICU patients, development of early or late ARDS was not associated with an increase in mortality at 28 days [17]. However, severe ARDS was associated with increased mortality at 2 years. These studies have varied tremendously with regard to patient population and controlling for baseline severity of illness. Notably, many studies focused on trauma populations, a subgroup which may not be representative of patients with other ARDS risk factors [18]. The relevance of older studies to current practice is also unclear, given most were performed before the era of low tidal volume ventilation and modern resuscitation practices. Recent studies have not focused on sepsis, the most common ARDS risk factor.

Using two prospective ICU cohorts, we assessed whether development of ARDS in the current era is independently associated with mortality among medical and surgical ICU patients with sepsis. Limited results from this study were reported in abstract [19].

Take-home message

In two prospective cohorts of critically ill patients with sepsis, development of ARDS conferred increased risk for hospital mortality, independent of overall severity of illness. This association was driven almost entirely by those patients with severe ARDS. Development of ARDS was also associated with increased intensive care (ICU) mortality, hospital length-of-stay, and ICU length-of-stay.

Methods

Participants

We studied patients from two prospectively enrolled critically ill adult cohorts: (1) Early Assessment of Renal and Lung Injury (EARLI) study and (2) Validating Acute Lung Injury markers for Diagnosis (VALID) study [20–23]. The EARLI cohort includes adult patients admitted from the emergency department to an ICU at either an academic medical center or county hospital in San Francisco, California [20, 22]. The VALID cohort includes adult patients from an academic medical center in Nashville, Tennessee [21, 23]. EARLI was approved by the University of California, San Francisco Institutional Review Board (IRB). VALID was approved by the Vanderbilt IRB. In both cohorts, consent was obtained from patients or their surrogates when possible. Further details about enrollment and consent have been reported and are provided in the online data supplement [20–23].

Primary outcome and additional variables

We selected patients with sepsis from the EARLI and VALID cohorts. Sepsis was defined as documented or suspected infection in the presence of two or more characteristics of the systemic inflammatory response syndrome [24]. Enrollment and data collection for both cohorts began before the advent of Sepsis 3, and our coding for sepsis reflects the prior definition. Patients were defined as having ARDS if they met Berlin criteria for ARDS on at least 1 day between hospital days one through five in EARLI and between hospital days one through four in VALID [1]. We additionally identified patients who met the American-European Consensus Conference (AECC) criteria for acute lung injury (ALI) during the same time frame [25]. Shock was defined as use of vasopressors within the first 48 h of ICU stay. Code status at admission was assessed in EARLI based on documented preferences in medical records.

Severity of illness was assessed using APACHE II and SAPS II in both cohorts. In EARLI, APACHE III was also assessed. Modified APACHE scores that exclude points related to oxygenation were generated [10]. The primary outcome in both cohorts was in-hospital mortality. Secondary outcomes included ICU mortality, hospital length of stay (LOS), ICU LOS, and ventilator-free days (VFDs).

P/*F* ratios were used to stratify patients by severity of ARDS. Additional detail is provided in the online data supplement.

Statistical methods

Student's *t* tests, Pearson's Chi-square test, and Mann–Whitney–Wilcoxon tests were used to compare baseline variables between cohorts as well as within cohorts stratified by development of ARDS and mortality. We generated a directed acyclic graph (DAG) to illustrate the relationship between ARDS and death and to categorize variables as potential confounders or effect mediators (Supplementary Figure S1) [26]. Multivariate logistic, linear, and zero-inflated negative binomial regression models were developed for primary and secondary outcomes as described in detail in the online data supplement.

Sensitivity analyses were performed in EARLI by restricting analyses to patients with pulmonary sepsis and shock and patients without limitations in code status, and by excluding patients who died within the first 5 days of hospitalization and therefore may have died before development of ARDS was possible. We also performed a sensitivity analysis of hospital and ICU LOS in which we included all participants (not just survivors). In both cohorts, patients, who met the AECC criteria for ALI but were not mechanically ventilated, were excluded from the primary analysis [25]. Sensitivity analyses were also performed by including these patients as cases.

In both cohorts, we determined the attributable fraction of mortality from ARDS (AF_{ARDS}) and the population attributable fraction of mortality from ARDS (population AF_{ARDS}) using methods outlined previously (additional detail in the online supplement) [27–29]. The AF_{ARDS} is the proportion of deaths attributable to ARDS among all deaths in patients who developed ARDS. The population AF_{ARDS} is the proportion of deaths attributable to ARDS among all deaths in the population of patients with sepsis. Estimates were based on indirect standardization, which computes the weighted average of stratum-specific estimates in the reference population, using weights from the study population. Strata were defined by modified APACHE II quartiles. An additional sensitivity analysis was performed among pooled data from EARLI and VALID to assess for a data-driven *P*/*F* cutoff for severe ARDS that best captures mortality. A two-sided P value less than 0.05 was considered statistically significant. Analyses were performed using STATA 15 software (College Station, TX) and Proc STDRATE in SAS (v9.4).

Results

Baseline characteristics and clinical outcomes

Patient selection is presented in Fig. 1. Table 1 presents baseline characteristics from each cohort. The EARLI population was generally older and more racially diverse compared to the VALID population. Most patients in both cohorts were cared for by a medical ICU service (compared to surgical service). While patients in each cohort had similar modified APACHE II scores, the EARLI cohort had higher SAPS II scores. While the proportion of patients requiring mechanical ventilation was similar, significantly more patients developed ARDS in EARLI compared to VALID. EARLI patients were more likely to meet severe ARDS criteria compared to VALID. Hospital LOS was longer in VALID. ICU and in-hospital mortality were higher in EARLI.

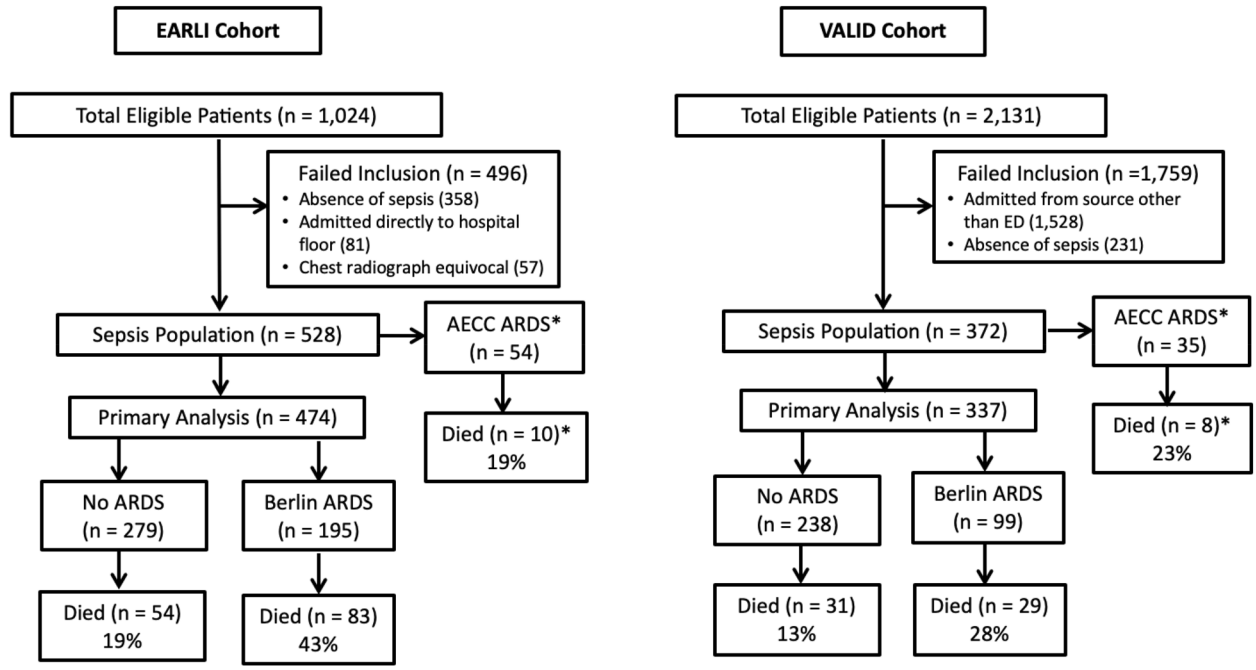
Table 1 also shows each cohort stratified by development of ARDS. In both cohorts, patients who developed ARDS were more likely to have sepsis from a pulmonary source, had higher baseline severity of illness scores, and were more likely to require vasopressor use in the first 48 h than patients who did not develop ARDS. Patients in both cohorts with ARDS had greater hospital and ICU mortality, longer LOS, and fewer VFDs. Limited data on mechanical ventilation of ARDS patients are presented in Supplemental Table 2.

Comparison of clinical outcomes adjusted for severity of illness

EARLI

Of 474 patients, 137 (29%) died prior to hospital discharge (Table 2A). Patients who died were older and more likely to have a limit on code status at the time of admission when compared to patients who survived. Patients who died were also more severely ill, with higher modified APACHE II and III scores, higher SAPS II scores, increased vasopressor use in the first 48 h, and more likely to develop ARDS than survivors. Among those who died, 61% developed ARDS during hospitalization compared with 33% among survivors ($p < 0.001$).

The unadjusted in-hospital mortality rate was 43% for patients with ARDS compared to 19% without (Table 3; OR = 3.09; 95% CI 2.05, 4.66; $p < 0.001$). In creating adjusted models, no variables in addition to those prespecified (modified APACHE score, age, limitation on code status at admission, and being admitted from a nursing home) met criteria for inclusion in the model as outlined in the methods. In logistic regression adjusted for modified APACHE II, age, limitation on code status, and admission from nursing home, the OR for hospital death among patients with ARDS in EARLI was attenuated by adjustment, but remained statistically significant. In addition, ARDS was associated with increased risk of ICU death in all unadjusted and adjusted models (Table 3A). Results were similarly unchanged when analyses were expanded to the AECC ALI criteria that did not require mechanical ventilation (Supplementary Table S3).



*Denotes patients who met the AECC definition of acute lung injury, but who were not intubated. These patients were excluded from primary analyses and are not included in Table 1.

Fig. 1 Study flowcharts for the EARLI and VALID cohorts

The other sensitivity analyses (excluding patients admitted from a nursing home or having a limitation on code status at admission and excluding patients who died within the first 5 days of hospitalization) did not significantly alter the results (data not shown). Relative to patients with sepsis who did not develop ARDS, patients who developed ARDS had a longer hospital and ICU LOS in both adjusted and unadjusted models, whether limited to only survivors or among all patients (online data supplement Table S4 and S5).

In EARLI, we additionally adjusted for modified APACHE III or unmodified SAPS II in place of modified APACHE II. The association between ARDS and in-hospital mortality was no longer statistically significant when including a modified APACHE III or SAPS II, though the ORs remained similar. For ICU mortality, hospital LOS, and ICU LOS, results were largely unchanged when adjusting for the alternative severity of illness measures (Table 3, Supplementary Tables S3 and S4).

We also performed analyses stratifying by severity of ARDS using the Berlin criteria (1). Severe ARDS conferred independent risk of both hospital and ICU mortality in both unadjusted and adjusted models (Fig. 2, Supplementary Table S6). In adjusted models, severe ARDS was associated with hospital and ICU mortality with ORs of 2.42 (95% CI 1.24, 4.72; $p=0.01$) and 3.08 (95% CI 1.53, 6.21; $p=0.002$), respectively. In contrast, mild and moderate ARDS were not independently associated with mortality. In EARLI, the AF_{ARDS} was 27% (CI, 14–37%) and the population AF_{ARDS} was 16% (95% CI, 5–27%).

VALID

Of 337 patients, 60 (18%) died prior to hospital discharge (Table 2B). Patients who died were more likely to be white. They also had higher modified APACHE II scores, SAPS II scores, and increased vasopressor use and were more likely to develop ARDS than survivors. Among those who died, 48% developed ARDS during hospitalization compared with 25% among survivors ($p<0.001$).

The unadjusted in-hospital mortality rate was 28% for patients with ARDS compared to 13% for patients without (OR = 2.77; 95% CI 1.56, 4.91; $p=0.001$) (Table 3B). Similar to findings in EARLI, in multivariate logistic regression, development of ARDS in the overall VALID sample was an independent risk factor for both hospital and ICU death. Results were similar in models using SAPS II as a marker for severity of illness. Again, results were largely unchanged when analyses were expanded to include the AECC ALI criteria that did not require mechanical ventilation (Supplementary Table S3) or

Table 1 Baseline characteristics of EARLI and VALID cohorts, together and stratified by ARDS

Clinical variable*	All patients		EARLI ($n=474$)			VALID ($n=337$)		
	EARLI ($n=474$)	VALID ($n=337$)	No ARDS ($n=279$)	ARDS ($n=195$)	p value	No ARDS ($n=238$)	ARDS ($n=99$)	p value
Age, years	66 ± 17	56 ± 16	65 ± 17	68 ± 16	0.07	56 ± 15	53 ± 17	0.11
Male gender, %	255 (54)	169 (50)	153 (55)	102 (52)	0.59	117 (49)	52 (53)	0.57
White race, %	239 (50)	267 (79)	139 (50)	100 (51)	0.75	182 (76)	85 (86)	0.05
Any limitation on code status at admission, %	88 (19)	–	52 (19)	36 (18)	0.96	–	–	–
Admitted from nursing facility, %	96 (20)	–	54 (19)	42 (22)	0.56	–	–	–
Pulmonary sepsis, %	277 (58)	172 (51)	125 (45)	152 (78)	< 0.001	98 (41)	74 (75)	< 0.001
Primary Service Medicine, %	429 (91)	319 (95)	246 (88)	183 (94)	0.07	228 (96)	91 (92)	0.15
APACHE II score	27 ± 9	27 ± 9	24 ± 8	31 ± 10	< 0.001	25 ± 9	30 ± 8	< 0.001
Modified APACHE II score†	25 ± 9	25 ± 8	23 ± 7	29 ± 9	< 0.001	24 ± 8	28 ± 8	< 0.001
APACHE III score	95 ± 39	–	83 ± 33	113 ± 40	< 0.001	–	–	–
Modified APACHE III score†	90 ± 36	–	80 ± 31	104 ± 38	< 0.001	–	–	–
SAPS II	53 ± 22	50 ± 18	46 ± 18	62 ± 23	< 0.001	46 ± 17	58 ± 19	< 0.001
Vasopressor use in first 48 h, %	276 (58)	175 (52)	139 (50)	137 (70)	< 0.001	112 (47)	63 (64)	0.01
Mechanical ventilation, %	275 (58)	205 (61)	107 (38)	168 (100)	< 0.001	106 (43)	99 (100)	< 0.001
ARDS, %	195 (41)	99 (29)	–	–	–	–	–	–
Mild ARDS, defined as PF or SF > 200–300, %	43 (22)	32 (32)	–	–	–	–	–	–
Moderate ARDS, defined as PF or SF 100–200, %	76 (39)	42 (42)	–	–	–	–	–	–
Severe ARDS, defined as PF or SF < 100, %	76 (39)	25 (25)	–	–	–	–	–	–
Hospital LOS	8 (5, 13)	9 (6, 15)	7 (5, 11)	9 (5, 16)	0.004	9 (6, 13)	12 (7, 20)	0.001
Hospital LOS‡	8 (5, 13)	10 (7,17)	7 (5, 11)	10 (7, 19)	< 0.001	9 (6, 14)	15 (10, 23)	< 0.001
ICU LOS	4 (3, 7)	5 (3, 9)	4 (3, 5)	5 (3, 11)	< 0.001	4 (3, 6)	8 (5, 13)	< 0.001
ICU LOS‡	4 (3, 6)	4 (3, 8)	4 (3, 5)	5 (4, 11)	< 0.001	4 (3, 5)	9 (5, 13)	< 0.001
Ventilator-free days	25 (0, 28)	25 (16, 28)	28 (23, 28)	16 (0, 26)	< 0.001	28 (24, 28)	20 (1, 24)	< 0.001
ICU mortality, %	105 (22)	46 (14)	36 (13)	69 (35)	< 0.001	21 (9)	25 (25)	< 0.001
Hospital mortality, %	137 (29)	60 (18)	54 (19)	83 (43)	< 0.001	31 (13)	29 (28)	< 0.001

Table excludes all patients who met the AECC definition of acute lung injury but were not intubated

LOS length of stay

*Data shown as mean ± standard deviation, number (percent), or median (interquartile range) as appropriate

† Modified APACHE scores exclude points related to oxygenation

‡ Restricted to survivors

excluding patients who died within the first 5 days (data not shown).

As in EARLI, development of ARDS conferred increased risk of prolonged hospital and ICU LOS as well as fewer VFDs (Supplementary Tables S3 and S4). In addition, the association between ARDS and mortality was also stratified by severity of ARDS using the Berlin criteria (1). In VALID, severe ARDS again conferred independent risk of in-hospital mortality in unadjusted and adjusted models (Fig. 2, Supplementary Table S6). The OR for hospital and ICU mortality adjusted for APACHE II was 2.12 (95% CI 1.16, 3.92; $p=0.02$) and 2.67 (95% CI 1.35, 5.27; $p=0.01$), respectively. The analysis of in-hospital mortality did not reach statistical significance in the model adjusted for SAPS II, though ORs were similar to other models and those in EARLI (online data Supplementary Table S5). In VALID, the AF_{ARDS} was 37% (10–51%) and the population AF_{ARDS} was 18% (95% CI, 0.3%, 32%).

In a sensitivity analysis performed on pooled data from EARLI and VALID to determine a data-driven threshold for capturing mortality of severe ARDS, the risk of mortality appeared to plateau at a P/F ratio of 120 (Supplementary Figure S3).

Table 2 Patient characteristics stratified by in-hospital mortality, EARLI and VALID cohorts

Clinical variable*	Survived ($n=337$)	Died ($n=137$)	p value
EARLI patient characteristics			
Age, years	64 ± 17	70 ± 15	< 0.001
Male gender, %	176 (53)	79 (57)	0.28
White race, %	174 (52)	65 (47)	0.41
Any limitation on code status at admission, %	55 (16)	33 (24)	0.05
Admitted from nursing facility, %	65 (19)	31 (23)	0.41
Pulmonary sepsis, %	188 (56)	89 (65)	0.07
APACHE II score	24 ± 8	34 ± 9	< 0.001
Modified APACHE II score†	22 ± 7	32 ± 8	< 0.001
APACHE III score	82 ± 30	129 ± 39	< 0.001
Modified APACHE III score†	78 ± 28	121 ± 37	< 0.001
SAPS II	45 ± 17	71 ± 20	< 0.001
Vasopressor use in first 48 h, %	172 (51)	104 (76)	< 0.001
Mechanically ventilated, %	164 (49)	111 (81)	< 0.001
ARDS, %	112 (33)	83 (61)	< 0.001
Hospital LOS	8 (5, 13)	7 (3, 13)	0.002
ICU LOS	4 (3, 6)	5 (3, 10)	0.11
Clinical variable*	**Survived ($n=277$)**	**Died ($n=60$)**	**p value**
VALID patient characteristics			
Age, years	55 ± 16	58 ± 16	0.23
Male gender, %	138 (50)	31 (52)	0.80
White race, %	213 (77)	54 (90)	0.02
Pulmonary sepsis, %	134 (48)	38 (63)	0.04
APACHE II score	26 ± 8	32 ± 8	< 0.001
Modified APACHE II score†	24 ± 8	30 ± 8	< 0.001
SAPS II	47 ± 17	62 ± 19	< 0.001
Vasopressor use in first 48 h, %	133 (48)	42 (70)	0.002
Mechanically ventilated, %	152 (55)	53 (88)	< 0.001
ARDS, %	70 (25)	29 (48)	0.001
Hospital LOS	10 (7, 17)	6.5 (4, 10)	< 0.001
ICU LOS	4 (3, 8)	6 (4, 9.5)	0.01

*Data shown as mean ± standard deviation, number (percent), or median (interquartile range) as appropriate

† Modified APACHE scores exclude points related to oxygenation

Discussion

We determined the association between development of ARDS and mortality in two separate ICU cohorts of critically ill patients with sepsis. In both cohorts, development of ARDS was independently associated with higher hospital and ICU mortality, accrual of fewer VFDs, and prolonged hospital and ICU LOS. While it may not be surprising that severe ARDS portends a worse prognosis than moderate or mild disease, the varied ability to detect statistically significant mortality differences based on severity of ARDS is, to our knowledge, a novel finding. Most recently, Fuchs et al. showed no detectable difference in 28-day mortality among ventilated patients with or without ARDS, but did find that severe ARDS served as a risk factor for 2-year mortality [17]. Our significant results for in-hospital mortality compared to the results of Fuchs et al. may relate to differences in overall severity of illness and our focus on a predominantly medical ICU population with sepsis.

Our findings are directly relevant to the growing interest in prognostic enrichment for improving critical care trial design. Prognostic enrichment is defined as preferentially targeting enrollment of patients with the highest rates of disease-attributable (and, hopefully, modifiable) outcomes—in this case, mortality. With increasing recognition that current definitions of sepsis and ARDS do not identify patients with uniform

Table 3 Association of ARDS with mortality in unadjusted and adjusted models, EARLI and VALID cohorts

EARLI logistic regression models ($n=474$)	OR (95% CI)	p value
Unadjusted model of ARDS for in-hospital mortality	3.09 (2.05, 4.66)	< 0.001
Adjusted for modified APACHE II*	1.65 (1.02, 2.67)	0.04
Adjusted for modified APACHE III*	1.61 (0.98, 2.64)	0.06
Adjusted for SAPS II*	1.48 (0.9, 2.44)	0.12
Unadjusted model of ARDS for ICU mortality	3.70 (2.34, 5.84)	< 0.001
Adjusted for modified APACHE II*	2.05 (1.23, 3.44)	0.01
Adjusted for modified APACHE III*	2.03 (1.2, 3.45)	0.01
Adjusted for SAPS II*	1.85 (1.1, 3.13)	0.02
VALID logistic regression models ($n=337$)	**OR (95% CI)**	**p**
Unadjusted model of ARDS for in-hospital mortality	2.77 (1.56, 4.91)	0.001
Adjusted for modified APACHE II†	2.12 (1.16, 3.92)	0.02
Adjusted for SAPS II†	1.79 (0.95, 3.36)	0.07
Unadjusted model of ARDS for ICU mortality	3.49 (1.85, 6.6)	< 0.001
Adjusted for modified APACHE II†	2.67 (1.35, 5.27)	0.01
Adjusted for SAPS II†	2.14 (1.06, 4.33)	0.03

Modified APACHE scores exclude points related to oxygenation

*In addition to severity of illness variable listed in the table, adjusted models include age, limitation on code status at admission, and being admitted from a nursing home

† In addition to severity of illness variable listed in the table, adjusted models include age

and distinct disease processes, and that this heterogeneity may be confounding clinical trials, prognostic enrichment may offer one reasonable approach [30]. While targeting patients with more severe ARDS has had some success [6, 31], this study provides the first empiric evidence to support such a strategy. Our findings suggest that prognostic enrichment focusing on patients with severe ARDS, either as defined by the Berlin definition of $P/F < 100$, or perhaps by $P/F < 120$, as suggested by our data-driven comparison of mortality risk, may identify individuals most likely to die from factors related specifically to ARDS, and therefore may provide a population in which we are better able to identify beneficial treatments. This finding is consistent with a prior autopsy study which reported that patients with severe ARDS were more likely to experience refractory hypoxemia prior to death and have diffuse alveolar damage than patients with mild or moderate disease who were more likely to die of refractory shock [32].

We also estimated AF_{ARDS} and population AF_{ARDS} and found similar results in both cohorts. Attributable fraction of mortality is the proportion of deaths that can be statistically attributed to an underlying cause, in this case, ARDS [28]. Population attributable fraction of mortality is the proportion of deaths within a cohort of patients, all of whom are at risk of the underlying cause in question: In this case, the proportion of deaths due to ARDS among all patients with sepsis. The AF_{ARDS} was 27% in EARLI and 37% in VALID. The population AF_{ARDS} was 16% in EARLI and 18% in VALID. It is helpful to put these results in the context of other studies estimating attributable mortality of important critical care diseases. The attributable fraction of mortality from sepsis was recently estimated at 15% [33]. The population attributable fraction of mortality from ICU-acquired infections and ICU delirium has been estimated at 11% and 7%, respectively [29, 34]. While ARDS may confer mortality fractions notably higher than these other important ICU conditions, any absolute changes in mortality by fully treating or preventing ARDS would still be relatively low. As recently illustrated by Shankar-Hari et al., these data have major implications for considering the size of clinical trials necessary to detect such changes [33].

This study has several strengths. First, it includes two large and diverse prospective cohorts of critically ill patients from distinct centers. The similarity of the association between ARDS and in-hospital mortality in these very different populations strengthens the validity of our findings and suggests generalizability. Second, we found relatively consistent results within each cohort when adjusting for up to three distinct severity of illness metrics. Third, in developing adjusted models, we searched methodically for possible confounders and did not find other contributory variables. Fourth, all patients were meticulously phenotyped for both sepsis and ARDS. Finally, in contrast to most studies assessing ARDS and attributable mortality, this study expands the populations

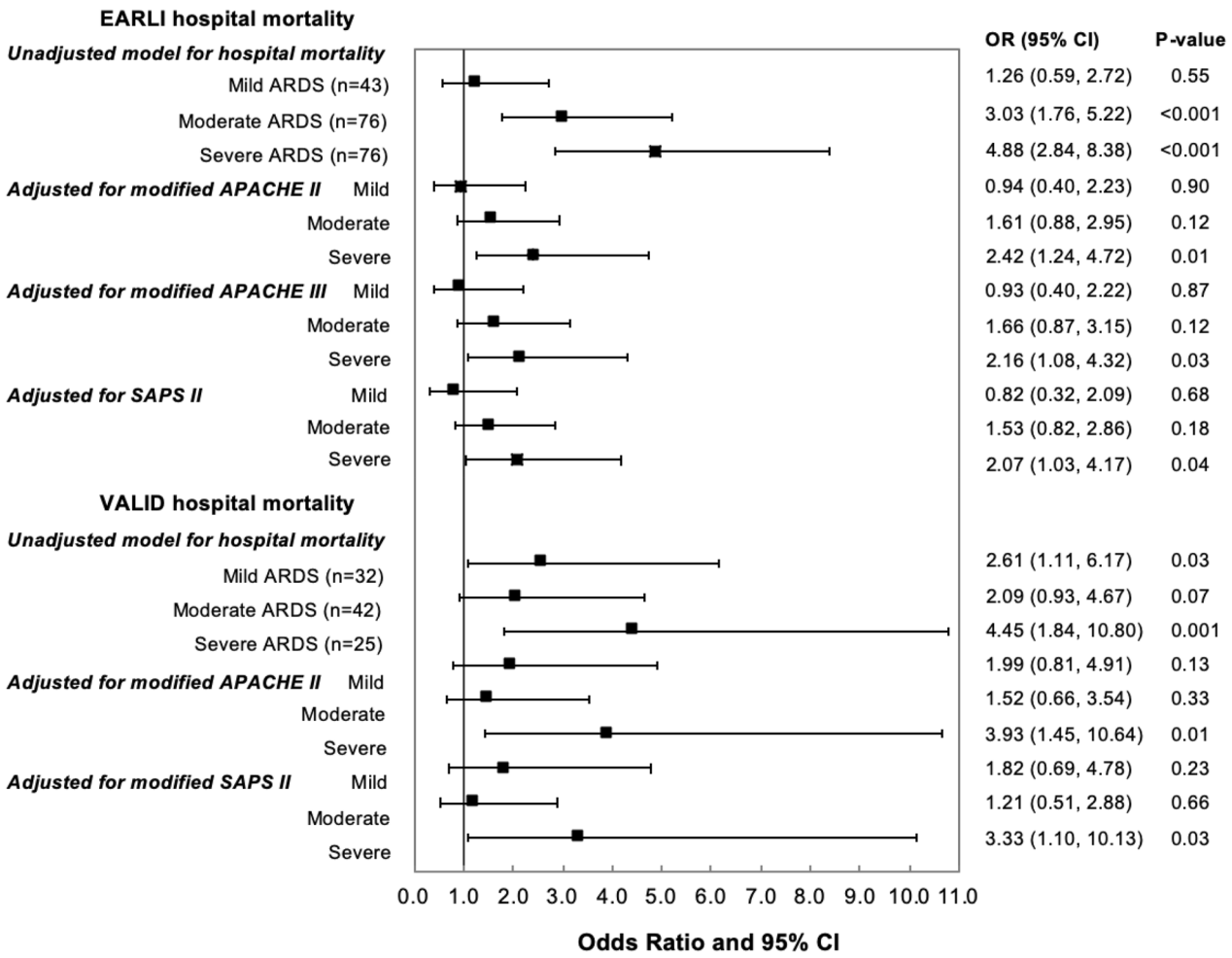


Fig. 2 Odds ratios with 95% confidence intervals for in-hospital mortality stratified by severity of ARDS. In addition to severity of illness variables listed in the table, adjusted models for EARLI include age, limitation on code status at admission, and being admitted from a nursing home. Adjusted models for VALID include age

to include both medical and surgical patients, thereby increasing generalizability of results beyond previously published studies.

This study has limitations. First, there were some discrepancies in specific data collected in each cohort. Most notably, we did not have information on code status or admission from a nursing home in the VALID population. However, incorporation of these variables did not significantly affect any of the EARLI models. In addition, we were unable to generate APACHE III scores from the VALID data. To better align the cohorts, we chose to utilize APACHE II for our primary analyses. While we adjusted for multiple confounders, the possibility of residual confounding remains. Specifically, we did not control for measures of other acute organ failures beyond what is captured in APACHE and SAPS scores. As depicted in our DAG, we hypothesize that other acute organ failures may lie on the indirect causal path between ARDS and death, and so were not included in our models. However, if the association between ARDS and mortality is driven predominantly by other organ failures (such as renal or hepatic) that develop later in a patient's ICU stay, or those variables are instead predominantly confounders, our analysis may not precisely capture that relationship. This caveat is important because some prior studies have identified increased mortality in ARDS with other organ failures or comorbidities [35, 36]. Our study does not explain the cause of the observed higher mortality in patients with severe ARDS, but future studies focusing on severe ARDS should explore this question. Because we began enrollment and data collection for both cohorts before the advent of Sepsis 3, our coding for sepsis reflects the prior definition. However, as we enrolled critically ill

patients, it is unlikely that our patients would not fulfill the more recent criteria for sepsis [37]. Finally, as our study focused on patients with sepsis, the most common ARDS risk factor, findings may not be generalizable to patients with other risk factors for ARDS.

This study provides important new evidence about ARDS-attributable mortality in patients with sepsis and quantifies the AF_{ARDS}. In two separate cohorts of ICU patients with sepsis, ARDS is independently associated with hospital and ICU mortality as well as VFDs, ICU LOS, and hospital LOS. Importantly, patients with the most severe ARDS primarily drove the relationship between ARDS and mortality. These findings suggest that to successfully identify novel therapeutics or changes in practice that may impact mortality, clinical trials for ARDS will require significantly larger study populations or should focus primarily on patients with severe ARDS.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-020-06010-9) contains supplementary material, which is available to authorized users.

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Acknowledgements
We wish to thank the patients and their families who participated in this study. We also thank the ICU staff at both of our cohort sites, and in particular the ICU nurses. Dr. Calfee received financial support for this study from the National Heart Lung, and Blood Institute (HL140026). Dr. Ware received financial support for this study from the National Heart Lung, and Blood Institute (HL103836 and HL135849).

Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Publisher's Note

Received: 7 August 2019 Accepted: 11 March 2020
Published online: 23 March 2020

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