Has Mortality from Acute Respiratory Distress Syndrome Decreased over Time?

A Systematic Review

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Rationale: **It is commonly stated that mortality from acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) is decreasing.**
Objectives: **To systematically review the literature assessing ARDS mortality over time and to determine patient- and study-level factors independently associated with mortality.**
Methods: **We searched multiple databases (MEDLINE, EMBASE, CINAHL, Cochrane CENTRAL) for prospective observational studies or randomized controlled trials (RCTs) published during the period 1984 to 2006 that enrolled 50 or more patients with ALI/ARDS and reported mortality. We pooled mortality estimates using random-effects meta-analysis and examined mortality trends before and after 1994 (when a consensus definition of ALI/ARDS was published) and factors associated with mortality using meta-regression models.**
Measurements and Main Results: **Of 4,966 studies, 89 met inclusion criteria (53 observational, 36 RCTs). There was a total of 18,900 patients (mean age 51.6 years; 39% female). Overall pooled weighted mortality was 44.3% (95% confidence interval [CI], 41.8–46.9). Mortality decreased with time in observational studies conducted before 1994; no temporal associations with mortality were demonstrated in RCTs (any time) or observational studies (after 1994). Pooled mortality from 1994 to 2006 was 44.0% (95% CI, 40.1–47.5) for observational studies, and 36.2% (95% CI, 32.1–40.5) for RCTs. Meta-regression identified study type (observational versus RCT, odds ratio, 1.36; 95% CI, 1.08–1.73) and patient age (odds ratio per additional 10 yr, 1.27; 95% CI, 1.07–1.50) as the only factors associated with mortality.**
Conclusions: **A decrease in ARDS mortality was only seen in observational studies from 1984 to 1993. Mortality did not decrease between 1994 (when a consensus definition was published) and 2006, and is lower in RCTs than observational studies.**

Keywords: acute lung injury; meta-analysis; prognosis; survival

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

It is commonly stated and assumed that mortality from acute respiratory distress syndrome (ARDS) is decreasing.

What This Study Adds to the Field

We found that mortality from ARDS has not decreased substantially since the publication of a consensus definition in 1994. Based on our findings, a baseline mortality risk from ARDS of 40 to 45% for observational studies and 35 to 40% for randomized control trials should be expected. These results highlight the need for future effective therapeutic interventions for this highly lethal syndrome.

Acute lung injury (ALI), including the more hypoxemic subgroup of acute respiratory distress syndrome (ARDS), is a worldwide public health problem (1–3). An American-European Consensus Conference (AECC) standardized definitions for ALI and ARDS in 1994 (4). It is commonly stated that mortality from ALI/ARDS has decreased since the initial case descriptions (1–3, 5, 6), and overall mortality in recent large randomized controlled trials (RCTs) in patients with ALI/ARDS has been approximately 30% (7–10), significantly lower than previously reported (11–13). In fact, it has been suggested that a mortality of 25 to 30% should now be the reference standard for subsequent clinical trials and clinical practice in ALI/ARDS (14).

The claim that mortality in ARDS has decreased is controversial. Data from RCTs may underestimate "real-world" mortality because RCTs are often performed in specialized centers, and selection criteria of RCTs (15), designed to improve safety and maximize potential treatment effects, also generate a group of patients who are less sick compared with the overall ALI/ARDS population (16). On the other hand, observational studies conducted during the early to mid-1990s (17–21) and a recent meta-analysis (22) support the assertion that ALI/ARDS mortality is decreasing over time. However, these observational studies were from single centers, and four of five included many patients with traumatic injuries, who have a better prognosis (17–20). The meta-analysis concluded that ARDS mortality has declined between 1994 and 2006, but the search strategy was not comprehensive, and some studies conducted predominantly before 1994 were labeled as post-1994 studies (22).

In view of the limitations of the existing literature, we conducted a systematic review and meta-analysis using a comprehensive search strategy and meta-regression analysis to

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document current mortality for ARDS, to evaluate whether mortality has changed over time, and to determine which patient and study factors are independently associated with mortality. Some of the results of this study have been previously reported in the form of an abstract (23).

METHODS

Search Strategy

We electronically searched OVID versions of MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL (1984 to November 2006) using a sensitive strategy without language restrictions to identify relevant studies. We supplemented the search by reviewing personal files and references of included studies. Complete details of the study methods are provided in the online supplement.

Study Selection

We reviewed identified titles and abstracts independently and in duplicate. Full-text copies of potentially relevant studies were distributed to six pairs of independent reviewers for selection. Disagreements were resolved by a third reviewer and by consensus. We selected prospective observational studies and RCTs enrolling 50 or more adults with ALI/ARDS (using any definition) and reporting mortality. We excluded reports in abstract form, studies of subtypes of ALI/ARDS (e.g., trauma), observational studies evaluating a specific intervention (e.g., extracorporeal membrane oxygenation), and duplicate reports.

Data Extraction

Six pairs of independent reviewers assessed methodologic quality and extracted data (24, 25). The primary outcome was intensive care unit (ICU) mortality; this information was available in 24 studies. If unavailable, we substituted (in order of preference) 28/30-day (24 studies), hospital (27 studies), 45-day (one study), 60-day (six studies), or 90-day mortality (1 study), or mortality at an unspecified time (six studies). In RCTs we combined mortality across both intervention and control groups because the large majority (31 out of 36) did not demonstrate mortality differences. We used the median year of the study enrollment period as the year of study conduct. Three studies provided mortality for different historical cohorts (17, 18, 21); we treated each cohort as an individual study.

We extracted data on potential determinants of mortality: year of study conduct, patients' age and sex, integrated severity of illness score (the percentage of the maximum possible value of the severity score used in each study), exclusion of patients due to poor prognosis, baseline ratio of Pa_{O_2} to FI_{O_2}, and delivered tidal volumes. Definitions of ARDS were allocated into three categories: the 1994 AECC definition of ARDS (4), more stringent definitions, and less stringent definitions, including ALI. When studies provided mortality for both ARDS and ALI, we included only the ARDS cases.

Data Analysis

We performed a meta-analyses using random-effects models to obtain pooled estimates of mortality and 95% confidence intervals (CIs) for all observational studies and all RCTs separately. This procedure was performed separately for each year. We used Cochran's Q statistic and I^2 to test for heterogeneity among studies.

A random-effects logistic meta-regression was used to explore associations between mortality and year of study conduct, age, sex, severity scores, exclusions for poor prognosis, and ARDS definitions. Study year was modeled via broken-line regression as having a potentially different effect before and after 1994, when the AECC definition of ALI/ARDS was published (4). We used multiple imputation to generate values for missing data on age in 10 studies and severity scores for 23 studies.

To determine if the use of different types of mortality would affect our findings, we performed a sensitivity analysis in which the meta-regression analysis was repeated using hospital mortality instead of ICU mortality as the primary outcome. If this was unavailable, we substituted (in order of preference) 28/30-day, ICU, 45-day, 60-day, or 90-day mortality, or mortality at an unspecified time.

We used Stata version 10.0 (StataCorp LP, College Station, TX) for meta-regression, StatsDirect version 2.6 (StatsDirect Ltd, Cheshire,

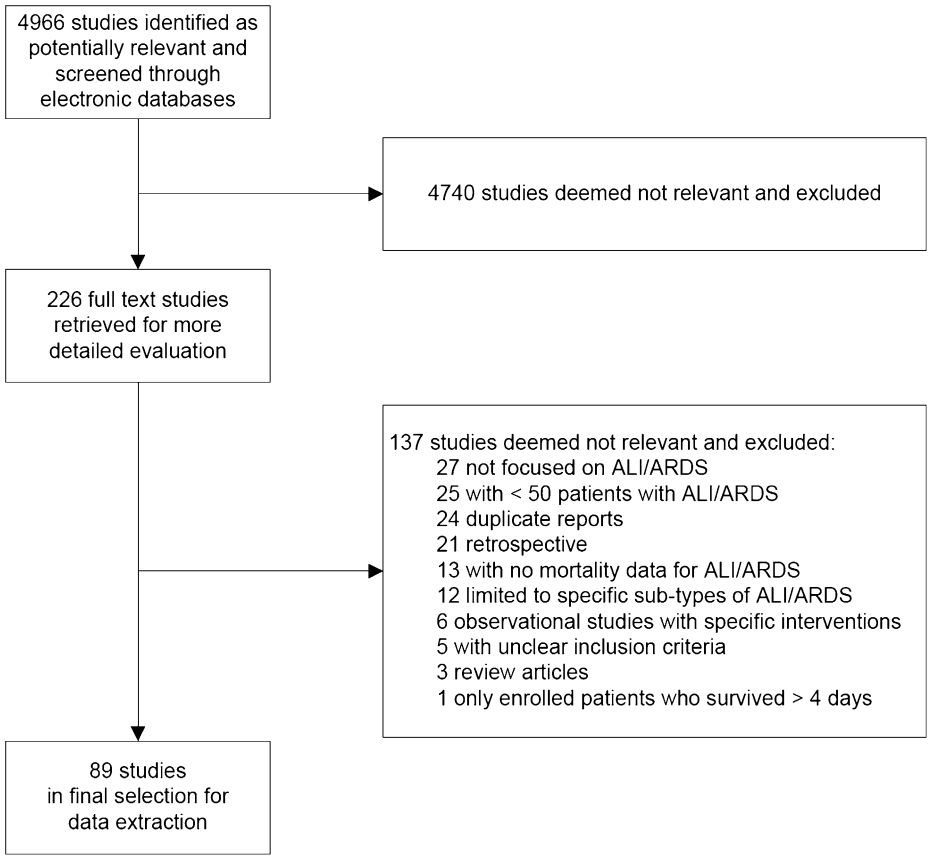

Figure 1. Flow chart of study selection. Only one reason is provided for each excluded study, although many were excluded for multiple reasons. A list of the 137 studies excluded after full text review is provided in the online supplement.

TABLE 1. CHARACTERISTICS OF INCLUDED STUDIES

Characteristics*	All Studies (*n* = 89)	Observational Studies (*n* = 53)	Randomized Controlled Trials (*n* = 36)	*P* Value†
Patient characteristics‡				
Total no. of patients	18,900	11,124	7,776	
Sample size, median (interquartile range)	134 (81–264)	143 (86–251)	109 (68–309)	0.413
Age, mean ± SD, yr	51.6 ± 7.8	51.4 ± 8.1	52.0 ± 7.6	0.725
Sex (male/female), n (%)	8,859 (61)/5,779 (39)	4,605 (61)/2,932 (39)	4,254 (60)/2,847 (40)	0.141
Baseline $Pa_{O_2}/F_{I_{O_2}}$ ratio, mean ± SD	129 ± 31	114 ± 22	145 ± 30	<0.001
Delivered tidal volume, ml/kg ± SD	9.1 ± 1.4	9.2 ± 1.3	8.9 ± 1.6	0.625
Risk factors for ALI/ARDS, n (%)				0.103
Predominantly pulmonary	5 (6)	2 (4)	3 (8)	
Predominantly extrapulmonary	5 (6)	1 (2)	4 (11)	
Mixed	79 (89)	50 (94)	29 (81)	
Study characteristics, n (%)				
Studies using following definition				0.028
More stringent ARDS definition§	36 (40)	19 (36)	17 (47)	
AECC ARDS definition‖	34 (38)	26 (49)	8 (22)	
Less stringent ARDS definition¶	19 (21)	8 (15)	11 (31)	
Studies conducted before 1994	26 (29)	18 (34)	8 (22)	0.232
Multicenter studies	52 (58)	21 (40)	31 (86)	<0.001
Study location**				0.963
North America	43 (48)	23 (43)	20 (56)	
Europe	38 (43)	22 (42)	16 (44)	
South America	6 (7)	3 (6)	3 (8)	
Asia	6 (7)	4 (8)	2 (6)	
Australia/Oceania	4 (4)	3 (6)	1 (3)	
Africa	3 (3)	2 (4)	1 (3)	
Exclusion criteria for poor prognosis, n (%)				
Deemed to have a poor prognosis	23 (26)	3 (6)	20 (56)	<0.001
Do-not-resuscitate status	7 (8)	1 (2)	6 (17)	0.016
Acute nonpulmonary organ failure	18 (20)	1 (2)	17 (47)	<0.001
Malignancies	12 (13)	3 (6)	9 (25)	0.012
Above a certain age	9 (10)	2 (4)	7 (19)	0.028
Others††	15 (17)	6 (11)	9 (25)	0.091
Any of the above	42 (47)	11 (21)	31 (86)	<0.001

Definition of abbreviations: AECC = American European Consensus Conference; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; RCT = randomized controlled trial.

* Data provided as number of studies (%) unless otherwise specified. Some percentages do not add up to 100% due to rounding off of decimals.

† *P* values refer to comparisons between observational studies and RCTs.

‡ Sex available from 73 studies, age from 79 studies, $Pa_{O_2}/F_{I_{O_2}}$ ratio from 64 studies, V_T from 30 studies (V_T not calculated for nine RCTs that compared ventilation with different tidal volumes).

§ ARDS definition more stringent than AECC definition.

‖ ALI not included.

¶ ARDS definition less stringent than AECC definition. Studies providing a single mortality for ALI/ARDS are included in this category.

** Several studies were conducted in more than one continent.

†† Examples are neutropenia, survival <24 h, intracranial bleeding, barotrauma, $F_{I_{O_2}} > 0.8$ more than 48 h.

UK) for the meta-analyses, and SAS version 9.1 (SAS Institute Inc., Cary, NC) for imputation. A P value < 0.05 was considered to indicate statistical significance.

RESULTS

Study Selection

The electronic database search strategy yielded 4,966 articles. Figure 1 details the selection process. Overall inter-reviewer agreement for study selection was high (κ, 0.85; SE, 0.04). The final selection included 89 studies, of which 85 were published in English, two in German, one in Chinese, and one in Russian. In total, 18,900 patients were enrolled in 53 observational studies and 36 RCTs. Lists of the included and excluded studies are provided in the online supplement.

Study Characteristics

Table 1 describes the characteristics of the included studies. RCTs included patients with less severe hypoxemia and were more likely to use a less stringent definition for ALI/ARDS. More RCTs (31/36 studies, 86%) had explicit criteria excluding patients due to poor prognosis than observational studies (11/53 studies, 21%) ($P < 0.001$). Overall, the scientific quality of the studies was good (Table 2).

Mortality

The overall pooled weighted mortality from studies published between 1984 and November 2006 was 44.3% (95% CI, 41.8–46.9). Mortality was higher in observational studies than in RCTs (48.2 versus 37.5%; $P < 0.001$). There was significant heterogeneity for mortality across all studies (homogeneity, $P < 0.001$; $I^2 = 92.7\%$), across observational studies (homogeneity, $P < 0.001$; $I^2 = 90.0\%$) and across RCTs (homogeneity, $P < 0.001$; $I^2 = 91.7\%$) (Figure 2 and Figure 3).

Figure 4 depicts the annual pooled weighted mortality by year of study conduct. Visual inspection suggests a slight decrease in mortality over time, but the predominant effect appears before publication of the AECC definition of ALI/

TABLE 2. METHODOLOGIC QUALITY OF INCLUDED STUDIES

Characteristic	No. (%)
Observational studies (n = 53)	
Adequate description of patient characteristics*	40 (75)
Consecutive patients enrolled	44 (83)
Adequate description of ventilator strategy	24 (45)
Adequate description of weaning strategy	6 (11)
Good follow-up (>90%) until selected mortality outcome	53 (100)
Randomized controlled trials (n = 36)	
Concealed randomization	35 (97)
Baseline prerandomization similarity	30 (83)
Blinding	19 (53)
Ventilator strategy standardized between treatment groups	35 (97)
Weaning protocol standardized between treatment groups	35 (97)
Rescue therapies standardized between treatment groups	35 (97)
Crossovers did not occur	22 (61)
Intention-to-treat analysis	28 (78)
Good follow-up (>90%) until mortality outcome	36 (100)

* Deemed adequate only if study reported age, any clinical severity score or organ failure score, any measure of oxygenation defect, and the causes of acute lung injury/acute respiratory distress syndrome.

ARDS in 1994. Considering only studies conducted from 1994 onward, pooled weighted mortality was 44.0% (95% CI, 40.1–47.5) for observational studies and 36.2% (95% CI, 32.1–40.5) for RCTs.

Meta-regression Analysis

In the multivariable meta-regression model for observational studies, the only variables that were significantly associated with mortality were year of study conduct for studies conducted before 1994 (odds ratio [OR] for each additional 5 yr, 0.68; 95% CI, 0.52–0.90; $P = 0.007$) and patient age (OR 1.33 for every 10 yr increase; 95% CI, 1.08–1.63; $P = 0.008$) (Table 3). In a separate meta-regression model for RCTs, none of the studied variables was significantly associated with mortality (Table 3).

In a third meta-regression model including all 89 studies, predictors of mortality were type of study (observational versus RCT: OR, 1.36; 95% CI, 1.08–1.73; $P = 0.011$) and patient age (OR, 1.27 for every 10 yr increase; 95% CI, 1.07–1.50; $P = 0.006$) (Table 3). The definition of ARDS (AECC definition versus a more stringent definition versus a less stringent definition) was not significantly associated with mortality (Table 3).

Sensitivity analysis in which the meta-regression analysis was repeated using hospital instead of ICU mortality as the preferred primary outcome revealed the identical variables identified as being significantly and independently associated with mortality (*see* Figure E1 in the online supplement).

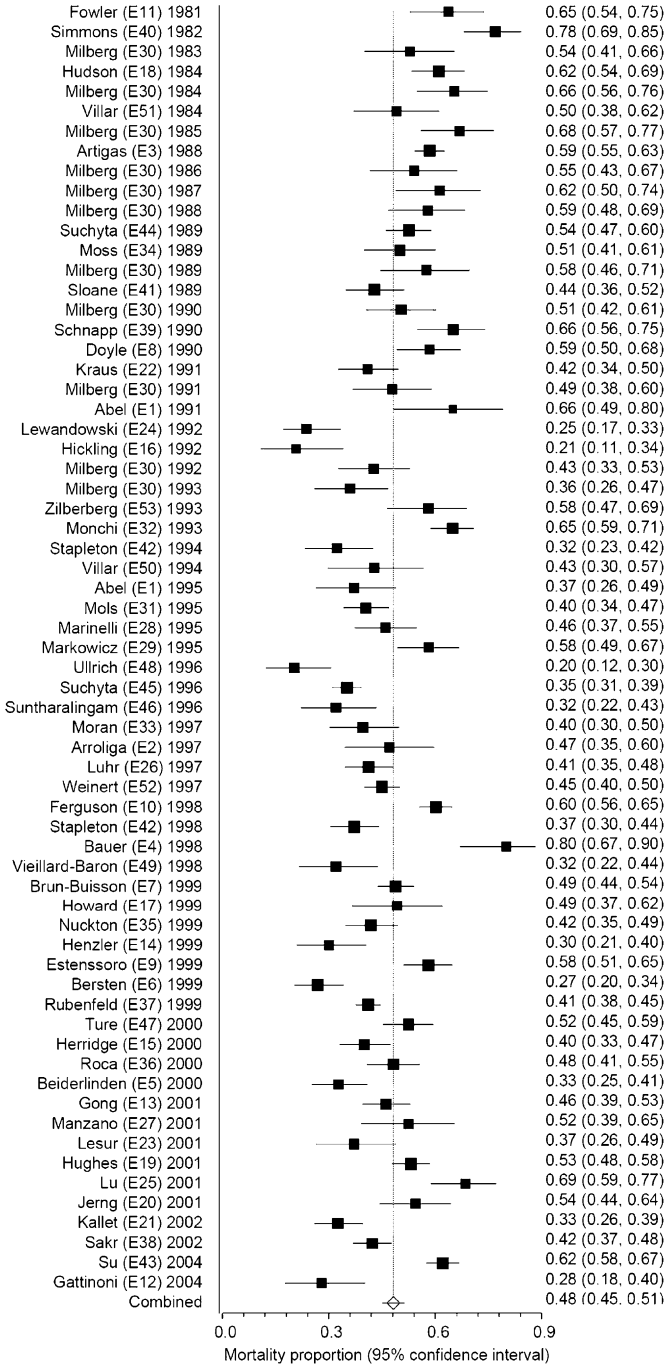

Figure 2. Forest plot of mortality in observational studies using a random-effects model. Individual mortality for each study and the pooled weighted estimate are shown with 95% confidence intervals. *Vertical line* represents the pooled weighted estimate. For studies providing mortality for different time periods, an individual point estimate is provided for each period. Numbers in parentheses refer to the reference numbers in the online supplement.

DISCUSSION

The main finding of our systematic review is that mortality due to ARDS has remained static at 44.0% for observational studies and 36.2% for RCTs since a standard definition was introduced in 1994, contrary to commonly held perceptions (1–3). Although mortality decreased over time in observational studies conducted from 1984 to 1993, it was consistently higher in observational studies than in RCTs. Of the variables studied, patient age was the only other factor explaining between-study variability in mortality, a finding consistent with previous multicenter epidemiologic studies (3, 26).

Based on the relatively low mortality observed in recent multicenter RCTs, it has been suggested that the current benchmark for mortality of ALI/ARDS in clinical practice and future clinical trials should be 25 to 30% (14). However, we found an overall mortality of 36.2% in RCTs conducted between 1994 and 2006, higher than this benchmark, and an even higher mortality in observational studies. Characteristics of RCTs that tend to reduce overall mortality compared with observational studies include performance in specialized centers, possibly with ventilation protocols shown to improve outcomes (7), and exclusion of patients with poor prognosis

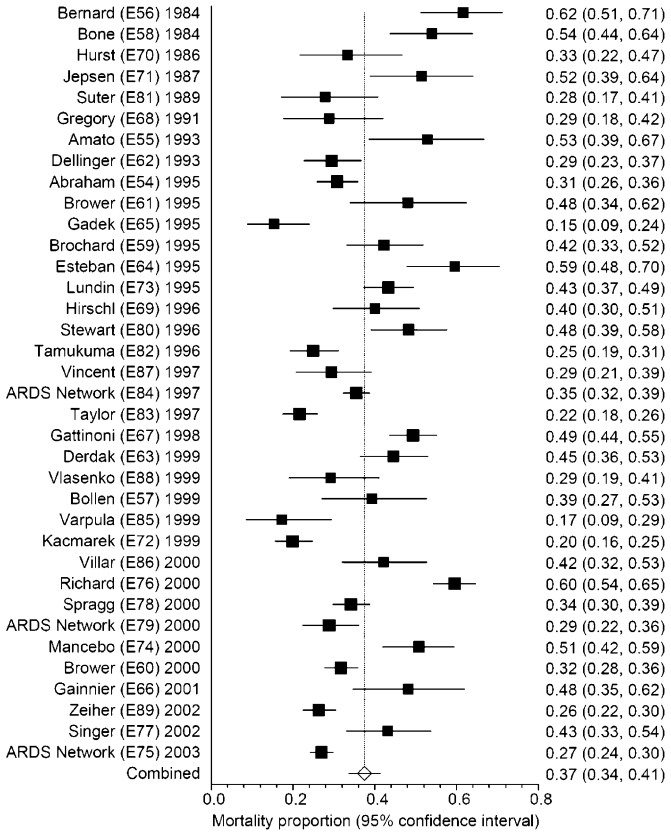

Figure 3. Forest plot of mortality in randomized controlled trials using a random effects model. Individual mortality for each study and the pooled weighted estimate are shown with 95% confidence intervals. *Vertical line* represents the pooled weighted estimate. Numbers in parentheses refer to the reference numbers in the online supplement.

(15). For example, various ARDS Network trials had previously excluded 88% of patients meeting the inclusion criteria (7–9), and data from screening logs have shown a 10% absolute lower mortality in included compared with excluded patients (16). This is comparable to the mortality difference between observational studies and RCTs observed in our study.

Five observational studies of ARDS have shown a decrease in mortality over time (17–21). However, these studies were conducted from the 1980s to the mid-1990s in single centers and included many trauma patients, a subset of ALI/ARDS with a better prognosis (17–20). The extent to which their findings apply to patients with ALI/ARDS in general is therefore unclear. Our review excluded two of these studies: one included only trauma patients (19), and the other was retrospective (20). An analysis of death records in the United States also suggested that the number of deaths from ARDS, while increasing between 1979 and 1993, may have decreased slightly between 1993 and 1996 (27). However, this study used administrative datasets (using ICD-9 codes) to identify ARDS and only included nonsurvivors, so it is unclear whether this reduction is due to a change in mortality or in the number of ARDS cases identified. Indeed, recent data from multicenter observational studies suggest that ARDS mortality in unselected patients may range from 39% (28) to as high as 50 to 60% (26, 29, 30).

Other investigators have reviewed mortality trends in ARDS across centers over time. An older meta-analysis by Krafft and colleagues showed no relation between publication year and mortality for studies published between 1967 and 1994 (31). However, this meta-analysis is not directly comparable with ours, given the different time periods (many studies published before 1984) and criteria for included studies (many retrospective studies with very small sample sizes).

More importantly, our findings seem to conflict with a recent systematic review that suggested a decrease in ARDS mortality since 1994 (22). When two systematic reviews on the same topic arrive at opposite conclusions, it is important to evaluate their methodologic differences and compare their study selection processes (32). In contrast with this other review, our search strategy required reviewers to work in duplicate, used more search terms and multiple databases, allowed only prospective studies, excluded small studies with fewer than 50 patients with ALI/ARDS, and was not restricted to the English language. In addition, the other review considered only the last cohort in studies with multiple historical cohorts and only the control group in RCTs. Because that review used the last (instead of the median) year of enrollment, several studies conducted primarily in the 1980s and early 1990s were labeled as "post-1994 studies" in their analysis (33–38). In addition, the authors included several reports of large studies that appear to contain overlapping patient populations (7, 8, 29, 39–41), some of which had a low mortality (7, 8, 40, 41). The combination of coding some high-mortality studies that enrolled patients before 1994 as "post-1994 studies" and the duplicate counting of some patients from recent RCTs with low mortality may thus have contributed to the downward trend observed by these investigators. Finally,

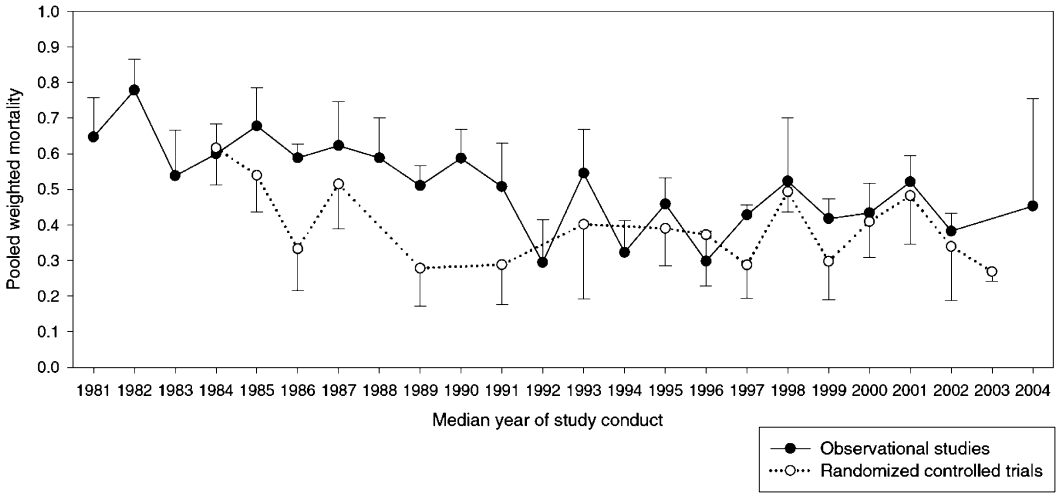

Figure 4. Annual pooled weighted mortality from 1981 to 2006 for all included studies, by year of conduct. The *solid points* show data for observational studies; the *open points* show data for randomized controlled trials. Upper and lower confidence intervals are shown for observational studies and randomized controlled trials, respectively. Interpolation lines are included to facilitate visual interpretation and do not indicate trends between point estimates.

TABLE 3. META-REGRESSION ANALYSIS OF ASSOCIATION BETWEEN STUDY VARIABLES AND MORTALITY ESTIMATES

	Observational Studies			Randomized Controlled Trials			All Studies		
Study Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Type of study (observational vs. randomized controlled trials)	—	—	—	—	—	—	1.36	1.08–1.73	0.011
Year of conduct pre-1994*	0.68	0.52–0.90	0.007	0.77	0.51–1.15	0.201	0.70	0.56–0.88	0.002
Year of conduct post-1994†	0.89	0.65–1.21	0.448	0.94	0.61–1.46	0.799	0.94	0.75–1.19	0.620
Age‡	1.33	1.08–1.63	0.008	1.25	0.90–1.72	0.177	1.27	1.07–1.50	0.006
Sex	0.58	0.08–4.29	0.588	0.60	0.02–15.3	0.759	0.56	0.09–3.74	0.541
Severity of illness scores§	1.01	0.97–1.04	0.748	1.01	0.96–1.06	0.754	1.01	0.98–1.04	0.582
Any exclusion for poor prognosis‖	0.86	0.65–1.13	0.275	1.03	0.54–1.93	0.937	0.90	0.70–1.15	0.388
ARDS definition used¶									
Definition more stringent than AECC	0.94	0.64–1.39	0.755	1.07	0.63–1.82	0.806	1.00	0.75–1.32	0.974
Definition less stringent than AECC	0.86	0.57–1.29	0.466	0.79	0.43–1.45	0.450	0.82	0.60–1.12	0.208

Definition of abbreviations: AECC = American European Consensus Conference; ARDS = acute respiratory distress syndrome; CI = confidence interval; OR = odds ratio.

* Association of mortality and year of conduct when year is 1994 or earlier. OR estimates are for each 5-yr increase.

† Association of mortality and year of conduct when year is after 1994. OR estimates are for each 5-yr increase.

‡ Odds ratio estimates for each 10-yr increase in age.

§ Integrated severity of illness score obtained as percentage of maximum possible value of the score used in each study.

‖ Presence or absence of one or more exclusion criteria known to be directly associated with a poor prognosis.

¶ Use of a definition for acute respiratory distress syndrome that is more stringent or less stringent than the AECC definition.

although both systematic reviews included 42 studies in common, ours included an additional 27 post-1994 studies.

Mortality trends over time offer important insights to the state of medical care for a particular disease. Similar to other investigators who have found stable mortality risks for diseases such as stroke, schizophrenia, chronic obstructive pulmonary disease, and diabetes (42–44), our findings raise the question of why mortality for patients with ARDS has not improved. Several plausible explanations exist. The number of effective therapeutic interventions for ARDS continues to pale in comparison to the number of failed interventions (1, 2). Even positive results from RCTs generated in selected populations may be significantly diluted and have limited generalizability when applied to unselected ICU populations. Furthermore, the extent to which effective therapies from RCTs are adapted into clinical practice is variable. For example, the use of tidal volume limitation—arguably the only mortality-reducing intervention specifically for ARDS— is in evolution but is not universally practiced (30, 45). Because ALI/ARDS has been defined as a syndrome that includes patients with multiple pathophysiologic mechanisms, therapeutic progress may not be related to specific disease-related interventions but rather to the optimization of general supportive care. In this way the consensus definition of ALI/ARDS may itself have contributed to the plateau in mortality seen after 1994 because it captures an extremely heterogeneous patient population that may be unlikely to respond to a given intervention. Meanwhile, examples of supportive measures that could have improved outcome (in addition to avoidance of ventilator-induced lung injury) include early aggressive resuscitation and appropriate antibiotics in sepsis and sedation protocols (46–48). Although guidelines exist to promote these practices (49), variable adherence may contribute to the lack of improvement in outcomes (50). It has also been suggested that standardized disease definitions and improved coding practices may produce samples with lower disease severity and hence lower mortality (51). It is tempting to speculate that the decreases in mortality before 1994 reflect differences and changes in the definitions of ARDS before the current consensus definition (4). However, our study is unable to confirm this hypothesis because the definition of ARDS was not an independent predictor of mortality.

Strengths of our study include a comprehensive search of the international literature, duplicate data extraction, and predefined criteria for methodologic assessment and analysis. This systematic review also has limitations. First, the outcome of ICU mortality, although feasible and reliably reported, is dependent on the ICU discharge decision, which may vary across institutions and time. Twenty-four included studies reported ICU mortality, and we therefore substituted other mortality rates (28/30 days, hospital or other mortality as available). However, it is reassuring to note that the need for these substitutions did not show any association with the year of study conduct, and a sensitivity analysis using hospital mortality as the preferred primary outcome did not change our findings. Second, differences in case-mix and/or the availability of ICU beds in the various countries during the study period may have influenced the types of patients admitted to the ICU and their outcomes over time. We made every possible effort to adjust for such baseline differences but were limited by the data provided in the individual studies. Multiple imputation of data was required to generate values for age and illness severity score for studies that did not provide such information (in 10 and 23 studies, respectively). However, because data on baseline Pa_{O_2}/FI_{O_2} ratios and delivered tidal volumes were not available from 25 and 50 studies, respectively, we could not include these variables in the meta-regression analysis and are thus unable to comment on the impact of these care practices on mortality. Third, we used the median year of conduct for each study as the independent variable in analyses of the effect of year on mortality. This was necessary because many studies were conducted over several years. Fourth, unpublished data and studies that were reported only in abstract form were not included, thus potentially leading to publication bias, particularly for RCTs. However, the effect of any small unpublished RCTs showing high overall mortality would be unlikely to change our main findings. Fifth, although we evaluated only ARDS whenever possible, 14 studies grouped data for all patients with ALI (including both ARDS and mild ALI). Inclusion of such studies with a proportion of patients with mild ALI and less severe oxygenation impairment may have generated some bias toward better prognosis after 1994. Despite this potential bias, our results indicate that mortality has remained relatively constant since 1994. Sixth, given the heterogeneous nature of ALI/ARDS and our exclusion of studies that enrolled patients with specific risk factors for ALI/ARDS, our findings may not be applicable to specific subgroups, such as trauma populations

(17–20). Correspondingly, although the pooled mortality estimates reported in our study reflect international trends in ARDS outcomes, they must not be used for prognostication for the individual patient.

In conclusion, our systematic review has shown that mortality due to ARDS has remained relatively unchanged since 1994, coincident with the publication of the current syndrome definition. Higher mortality was associated with observational study design and increased patient age. Based on our findings, clinicians and investigators should expect a baseline mortality risk from ARDS of 40 to 45% for observational studies and 35 to 40% for RCTs. Most importantly, our results highlight the need for future effective therapeutic interventions for this highly lethal syndrome. They also compel us to revisit the manner in which studies of these interventions are conducted and their results implemented to ensure their applicability in the "real world."

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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