Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain outcomes of low dose corticosteroid use in acute lung injury.
2. Describe low dose corticosteroids regimens in acute lung injury.
3. Use this information in a clinical setting.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

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Objective: **Controversy remains as to whether low-dose corticosteroids can reduce the mortality and morbidity of acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) without increasing the risk of adverse reactions. We aimed to evaluate all studies investigating prolonged corticosteroids in low-to-moderate dose in ALI or ARDS.**

Data Sources: **MEDLINE, EMBASE, Current Content, and Cochrane Central Register of Controlled Trials, and bibliographies of retrieved articles.**

Study Selection: **Randomized controlled trials (RCTs) and observational studies reported in any language that used 0.5–2.5 $mg \cdot kg^{-1} \cdot d^{-1}$ of methylprednisolone or equivalent to treat ALI/ARDS.**

Data Extraction: **Data were extracted independently by two reviewers and included study design, patient characteristics, interventions, and mortality and morbidity outcomes.**

Data Synthesis: **Both cohort studies (five studies, n = 307) and RCTs (four trials, n = 341) showed a similar trend toward mortality reduction (RCTs relative risk 0.51, 95% CI 0.24–1.09; $p = 0.08$; cohort studies relative risk 0.66, 95% CI 0.43–1.02; $p = 0.06$). The overall relative risk was 0.62 (95% CI 0.43–0.91; $p = 0.01$). There was also improvement in length of ventilation-free days, length of intensive care unit stay, Multiple Organ Dysfunction Syndrome Score, Lung Injury Scores, and improvement in Pao_2/Fio_2. There was no increase in infection, neuromyopathy, or any major complications. There was significant heterogeneity in the pooled studies. Subgroup and meta-regression analyses showed that heterogeneity had minimal effect on treatment efficacy; however, these findings were limited by the small number of studies used in the analyses.**

Conclusion: **The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions. The consistency of results in both study designs and all outcomes suggests that they are an effective treatment for ALI or ARDS. The mortality benefits in early ARDS should be confirmed by an adequately powered randomized trial.(Crit Care Med 2009; 37:1594–1603)**

KEY WORDS: steroids; acute respiratory distress syndrome; acute lung injury

***See also p. 1800.**

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Dr. Tang has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Tang organized the study concept and design. Drs. Tang, Eslick, and Seppelt acquired the data. Drs. Tang and Craig analyzed and interpreted data. Drs. Tang, Eslick, Seppelt, Craig, and McLean drafted the manuscript. Statistical analysis was performed by Dr. Tang.

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Acute lung injury has a substantial impact on public health. It has a very high hospital mortality rate of 38% to 50% and substantial associated morbidity (1, 2). In the United States alone, acute lung injury (ALI) causes 74,500 deaths each year (1), far exceeding that of breast cancer or human immunodeficiency virus (3, 4). Among those who survived, only 34% were well enough to be discharged home directly (1). It is estimated that the annual incidence of ALI will double in the next 25 years, as the population ages (1). The development of an effective therapy, therefore, has important implication for the planning of critical care services, rehabilitation, and resource provision.

ALI is characterized by an intense host inflammatory reaction against the pulmonary parenchyma, triggered by insults, such as pneumonia, sepsis, and trauma. Corticosteroids have been investigated as a potential treatment for ALI because of their anti-inflammatory properties. Early trials using time-limited high-dose corticosteroids failed to demonstrate a survival benefit (5–8). More recently, trials that used prolonged low-to-moderate dose corticosteroid regimens showed promise in reducing morbidity and mortality (9, 10). However, controversy remains because earlier mortality benefit in unresolving ARDS (9) has not been confirmed in a more recent multicenter trial (11). In addition, several recent meta-analyses add further uncertainties because they produced conflicting findings (12–14).

So far, several important issues remain unresolved. First, it is unclear whether low-to-moderate dose corticosteroids improve both mortality and morbidity outcomes. The recent meta-analyses were limited because they included studies of high-dose corticosteroids (12, 14) and they did not assess all the relevant outcomes (12–14). Second, clinicians have raised significant concern over the side effect profile of corticosteroids, particularly, the increase in infectious and neuromyopathic complications. Again, existing meta-analyses did not fully address these concerns. Third, there is considerable un-

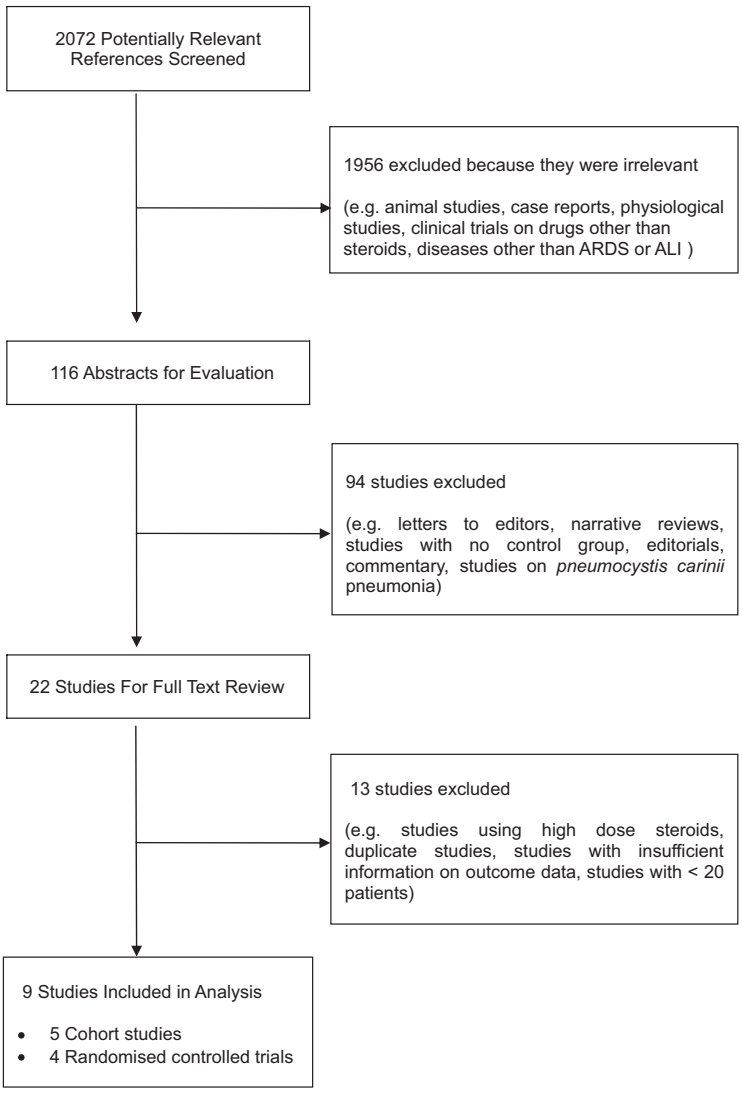

Figure 1. Study identification, inclusion, and exclusion. *ARDS*, acute respiratory distress syndrome; *ALI*, acute lung injury.

Table 1. Study and subject summary characteristics

	Keel et al (31)	Varpula et al (32)	Huh et al (33)	Lee et al (34)	Annane et al (35)	Meduri et al (9)	Confalonieri et al (20)	ARDSNet (11)	Meduri et al (10)
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	RCT (crossover design)	RCT	RCT	RCT (crossover design)
Year of study	1995	1998	1998	2003	1999	1996	2003	2003	2002
Country	Switzerland	Finland	South Korea	South Korea	France	USA	Italy	USA	USA
Total (n)	31	31	48	20	177	24	46	180	91
Mean age (yrs)	50	43	61	67	60	48	63	49	51
Subjects	Nontrauma patients with ARDS	Patients with primary ALI	Patients with ARDS	Post-thoracic surgery patients	Septic shock patients with ARDS	Patients with severe ARDS	Patients with severe pneumonia with Pa_{O_2}/Fi_{O_2} <250	Patients with persistent ARDS	Patients with severe early ARDS
Dose equivalent (methylprednisolone)	100–250 mg/d	120 mg/d	140 mg/d	140 mg/d	40 mg/d	140 mg/d	48 mg/d	140 mg/d	70 mg/d
Days of ALI/ARDS (d)[a]	15.0	9.7	8.0	4.4	0.0	9.2	0.0	11.3	3.0
Length of treatment (d)	8.0	27.0	7.0	9.5	7.0	32.0	7.0	25	28
Tapering of therapy	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Mortality of treatment vs. control groups[b]	38% vs. 67%	19% vs. 20% (30 d)	43% vs. 74%	8% vs. 88%	53% vs. 75% (28 d)	12% vs. 62%	0.0% vs. 30%	29% vs. 29% (60 d)	24% vs. 43%

RCT, randomized controlled trial; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.
[a]Number of days of established ALI/ARDS before steroid treatment; [b]hospital mortality is given unless otherwise specified in parentheses.

Table 2. Adverse events

	Keel et al (31)	Varpula et al (32)	Huh et al (33)	Lee et al (34)	Annane et al (35)	Meduri et al (9)	Confalonieri et al (20)	ARDSNet (11)	Meduri et al (10)
Number of patient (treatment:control)	13:18	16:15	14:34	12:8	85:92	16:8	23:23	89:91	63:28
Infection		9:5		4:0	12:12	12:6	0:4	20:30	27:17
Neuromyopathic complications							0:3	26:21	4:1
Gastrointestinal bleeding					5:2		1:1		1:0
Hyperglycemia							5 (31%):4 (50%)		45 (71.4%):18 (64.3%)
Other adverse events (n)[a]				Arrhythmia (12), psychosis (4), and pneumothorax (2)	Psychiatric disorder (1)		Acute renal failure (3), arrhythmia (4), liver failure (1), heart failure (2), and hepatitis (1)		Pneumothorax (11), pancreatitis (2)

[a]Number in parentheses indicate total events of treatment and control groups.

Table 3. Subgroup analysis on mortality

	Subtotal (n)	Risk Ratio (95% Confidence Interval)	p [a]
Early vs. late ARDS			
Early (less than 7 d)	334	0.48 (0.22–1.03)	0.64
Late (7 d or more)	314	0.67 (0.44–1.04)	
Tapering of steroid			
Yes	425	0.59 (0.39–0.89)	0.15
No	223	0.36 (0.03–3.94)	
Formulation			
Hydrocortisone	223	0.36 (0.03–3.94)	0.15
Methylprednisolone	425	0.59 (0.39–0.89)	
Year of study[b]			
Pre-2000	311	0.68 (0.47–0.99)	0.65
Post-2000	337	0.46 (0.19–1.10)	
Crossover RCT design			
Yes	115	0.41 (0.16–1.02)	0.06
No	226	0.37 (0.03–4.71)	

ARDS, acute respiratory distress syndrome; RCT, randomized controlled trial.
[a]p Values of test of interaction between subgroups; [b]year 2000 was chosen as a cutoff point when the ARDS network low tidal volume trial was published (21).

certainty over how the therapy should be administrated. The impact of important clinical variables, such as dose or treatment duration, on the effectiveness of the corticosteroids is unclear.

We performed a systematic review and quantitative synthesis to address all the above issues. In particular, we included studies missed by previous meta-analyses and assessed all relevant mortality and morbidity outcomes. Furthermore, we comprehensively evaluate the side effect profile of low-to-moderate dose corticosteroids. Finally, we undertook subgroup and meta-regression analyses to determine the association between the effects of corticosteroids and important clinical variables, such as dose, treatment duration, and timing of the therapy. Our study, therefore, represents the most comprehensive review to date on the therapeutic effect of prolonged corticosteroids therapy in ALI.

METHODS

Search Strategy and Selection Criteria. We prespecified our search strategy, selection criteria, and subgroup analysis before undertaking our study. We report our study's findings in accordance with the Quality of Reporting of Meta-analyses conference statement (15).

We searched, without language restriction, for all publications on ALI and ARDS between January 1967 and September 2007 using electronic databases, including MEDLINE, EMBASE, Current Content, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Because the number of randomized trials is few and often underpowered, we included both randomized and nonrandomized studies. Additionally, we included studies that enrolled patients with only acute respiratory distress syndrome (ARDS), a more severe form of ALI (16).

The search strategy used medical subject heading terms and text words: 1) ALI; 2) ARDS; and 3) acute respiratory failure. We hand searched the reference lists of each primary study for additional publications.

We included all cohort studies and randomized trials that 1) used low-dose corticosteroid (e.g., 0.5–2.5 $mg \cdot kg^{-1} \cdot d^{-1}$ of methylprednisolone or equivalent); 2) enrolled patients with ALI or ARDS; and 3) included subjects aged 18 years or older. Our primary outcome was hospital mortality. Secondary outcomes were length of mechanical ventilation, length of intensive care unit stay, Multiple Organ Dysfunction Syndrome Score, Lung Injury Score, and Pao_2/Fio_2 ratios. Outcome data on adverse events included infection, neuromyopathic complications, gastrointestinal bleeding, and hyperglycemia. Data on other complications (e.g., arrhythmia, psychiatric disorders, and organ failure), where available, were also collected.

Studies were excluded if they were duplicated studies, did not use a control group, used high-dose corticosteroid therapy (e.g., 30 $mg \cdot kg^{-1} \cdot d^{-1}$ of methylprednisolone or equivalent), or enrolled subjects with other systemic inflammatory diseases, such as *Pneumocystis carinii* or idiopathic pulmonary fibrosis.

Data Extraction. Data were extracted independently by two reviewers and disagreements were resolved by consensus. Information extracted included year of publication, country of origin, clinical settings, trial duration, participant demographics, sample size, proportion of patients with sepsis, drug dosage and formulation, duration of established ALI before corticosteroid treatment, phase of ARDS (early vs. late), whether there was tapering of the corticosteroids when treatment ended, disease severity indices, such as Pao_2/Fio_2 ratios and Acute Physiology and Chronic Health

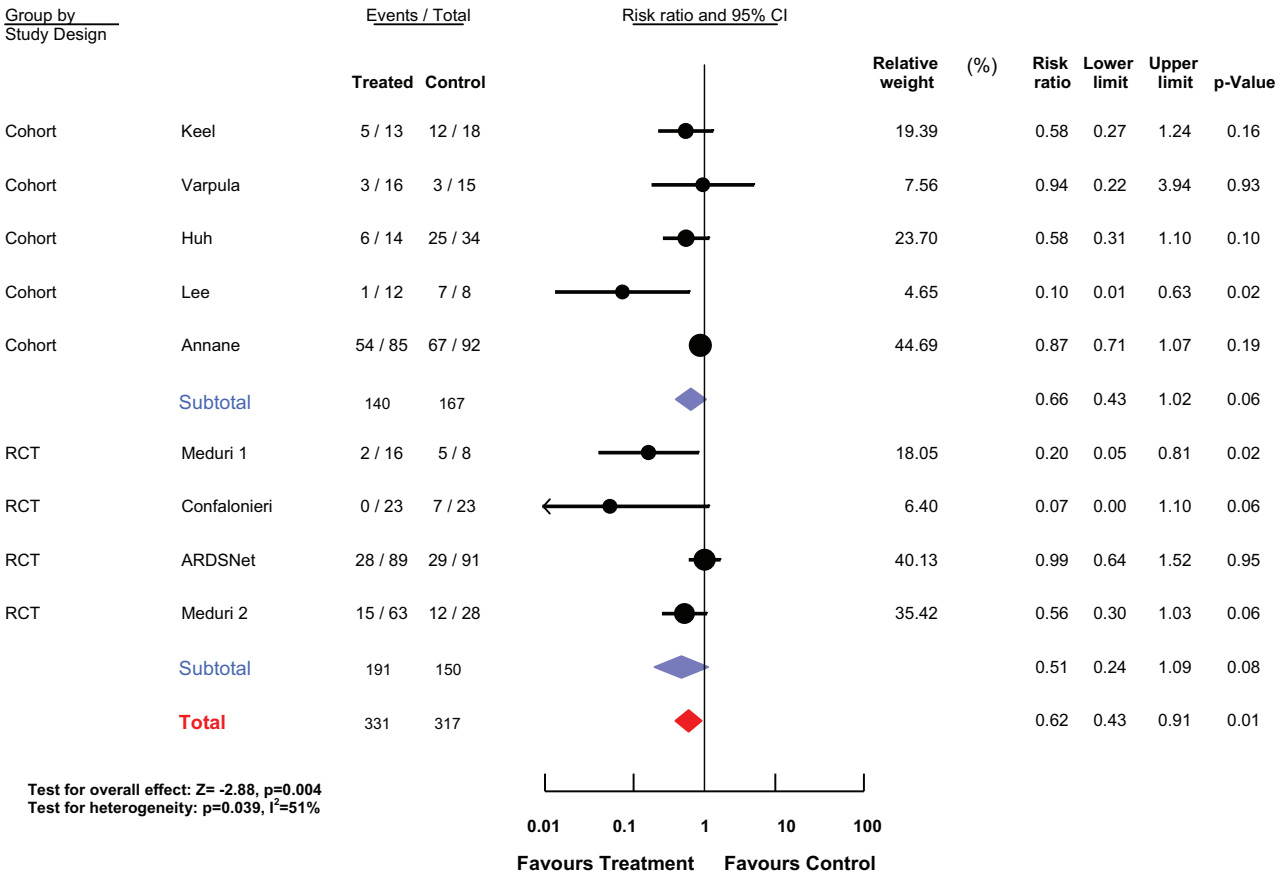

Figure 2. Effect of steroid on mortality. Size of data markers is proportional to the weight of each study in the forest plot. *RCT*, randomized controlled trial; *CI*, confidence interval.

Evaluation Scores. We contacted authors if further study details were needed.

Quality Assessment. The methodologic quality of each study was assessed by a four-item checklist. Randomized trials were assessed using criteria based on the Cochrane Collaboration guidelines, namely, reporting of randomization method, allocation concealment, blinding of outcome assessment, and completeness of follow-up (17). Cohort studies were assessed using criteria based on the Health Technology Assessment Program guidelines, which provided evidence-based recommendations on the assessment of nonrandomized trials (18). The criteria included baseline comparability of the treatment against control groups, adjustment for confounders, blind outcome assessment, and completeness of follow-up.

Statistical Analysis. For all studies, we calculated the risk ratio (relative risk) for all the dichotomous outcomes, such as death, infection, or neuropathy/myopathy. We calculated weighted difference in means between treatment and control groups for continuous outcomes, including length of mechanical ventilation, length of intensive care unit stay, Multiple Organ Dysfunction Syndrome Scores, and Lung Injury Scores. For Pao_2/Fio_2 ratios, we calculated the standardized weighted difference in means between groups to account for the variation in ventilator setting practices between studies (i.e., all ratios were normalized by their own SD to make them comparable with each other). The number to treat was calculated as the inverse of the absolute risk reduction, based on the pooled risk ratio and the baseline risk (19). Heterogeneity was assessed using Cochran's Q statistic and quantified using the I^2 statistic, which indicated the proportion of variability across studies that was due to heterogeneity rather than sampling error.

The outcome measures were pooled using a random effects model because we anticipated the presence of significant heterogeneity, caused by differences in treatment regimens and variations in local critical care practices. We explored sources of heterogeneity by using subgroup and meta-regression analyses. Variables for such analyses were planned before the study was undertaken. They included, for meta-regression, treatment duration, percentage of patients with sepsis, age, dose, sex, baseline Pao_2/Fio_2 ratios, and Acute Physiology and Chronic Health Evaluation Scores; for subgroup analysis, early/late ARDS, tapering of corticosteroids, formulation, year of study, and study design. A test of interaction was done on all subgroups to establish if the difference in effect size between subgroups was statistically significant. Results were considered as statistically significant for p values <0.05.

RESULTS

Of the 2072 references screened, nine studies were included in the final analysis (Fig. 1). Four studies were randomized controlled trials (RCTs) and five studies were cohort studies (Table 1). In total, 648 subjects were analyzed, with 307 subjects in cohort studies and 341 in randomized trials. The study population was relatively young (mean age 51 years), with a mean Acute Physiology and Chronic Health Evaluation II Score of 18 and mean baseline Pao_2/Fio_2 ratio of 126 mm Hg. Most studies (n = 8) included

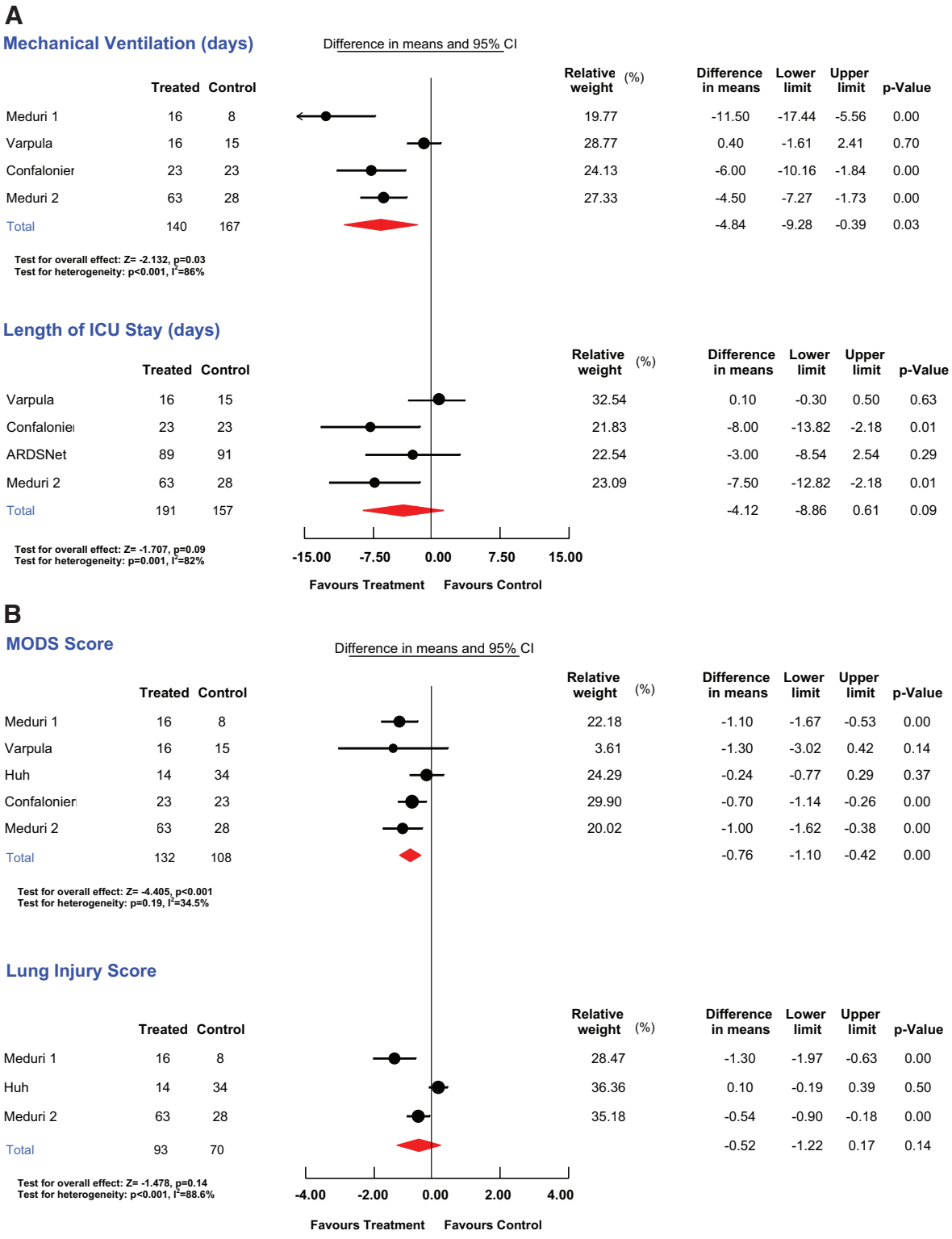

Figure 3. *A*, Effect of steroid on duration of mechanical ventilation and length of intensive care unit (*ICU*) stay (days). Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% confidence interval (*CI*). *B*, Effect of steroid on multiple organ dysfunction syndrome (*MODS*) and lung injury scores. Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% CI. *C*, Effect of steroid on the Pao_2/Fio_2 ratios. Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% CI. *MV*, mechanical ventilation; *ARDS*, acute respiratory distress syndrome; *LIS*, lung injury score.

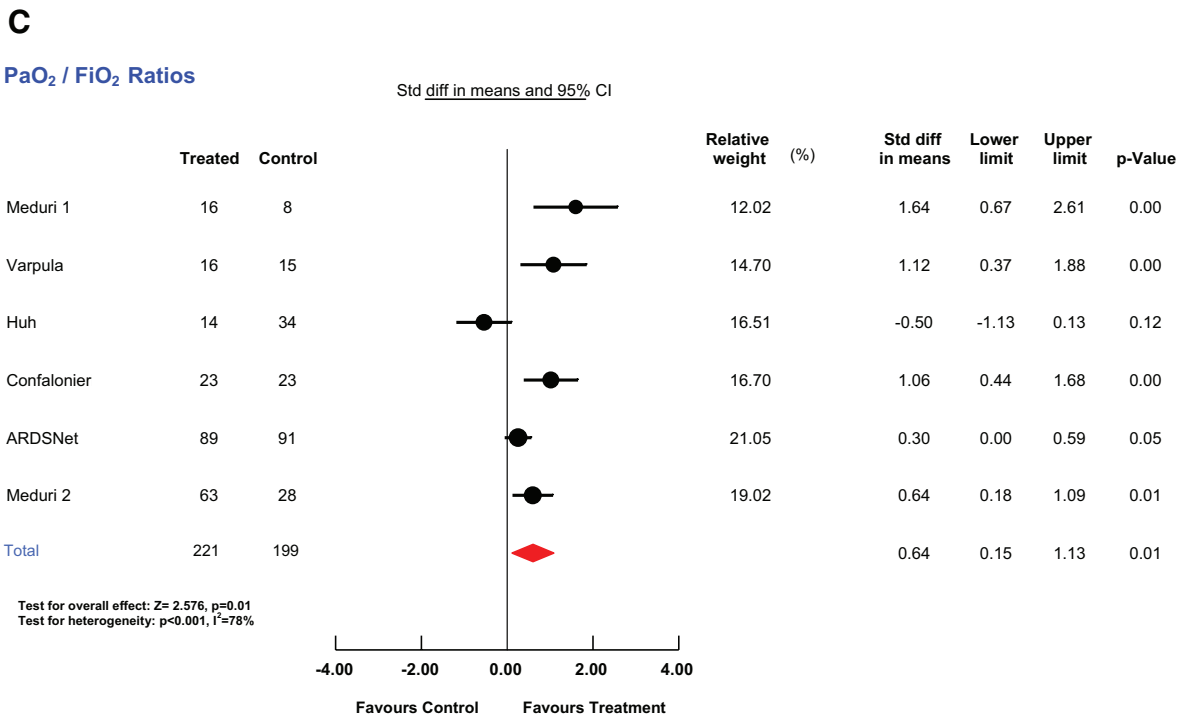

Figure 3. (Continued).

patients with sepsis, varying from 22% to 100%. There were significantly more male than female subjects, with a median male/female ratio of 2.3.

Treatment regimens varied considerably between studies (Table 1). Corticosteroid dose ranged from 40 to 250 mg/d of methylprednisolone or equivalent (mean 140 mg/d). Duration of treatment was also different among studies, ranging from 7 to 32 days (mean 8 days). Corticosteroid doses were tapered in most studies (n = 7) when treatment ended. However, one trial rapidly removed treatment 48 hours after extubation (11). Four studies used corticosteroids in the early phase of the disease (within 1 week of diagnosis) and five studies in the later phase of the disease. A reduction in mortality was reported in most studies (Table 1).

Incidence of adverse reactions was reported in most studies (Table 2). The most common complications reported were infection, followed by neuropathy/myopathy and gastrointestinal bleeding. Hyperglycemia was mentioned in only two studies (10, 20). Other less frequently reported complications included arrhythmia, pneumothorax, renal failure, liver failure, heart failure, or psychiatric disorder (Table 2).

Methodologic quality was fair in most studies. Randomized trials provided data on 75% of the quality assessment items and cohort studies provided data on 82% of such items.

Mortality Outcomes. Both cohort studies and RCTs showed a trend toward mortality reduction (Fig. 2). RCTs had a relative risk of 0.51 (95% CI 0.24–1.09) and cohort studies had a relative risk of 0.66 (95% CI 0.43–1.02). The direction of effect was consistent in all studies, with all favoring corticosteroids compared with controls. Mortality reduction did not reach statistical significance in either randomized trials ($p = 0.08$) or cohort studies ($p = 0.06$) because of small sample size. When both groups of studies were combined, the mortality reduction reached statistical significance ($p = 0.01$; Fig. 2) with an overall relative risk of 0.62 (95% CI 0.43–0.91).

Morbidity Outcomes. Corticosteroid treatment improved all morbidity outcomes (Fig. 3). It reduced the duration on mechanical ventilation and length of stay in intensive care units by more than 4 days. When ventilator-free days were used instead of duration of mechanical ventilation, the results were very similar (4.8 vs. 4.4 days). The corticosteroid treatment reduced disease severity scores, namely, the Multiple Organ Dysfunction Syndrome Score by 32% and Lung Injury Score by 18%. It also improved oxygenation (Pao_2/Fio_2 ratios) by over half of an SD. Again, the direction of effect was consistently in favor of corticosteroids in all summary estimates, with over half reaching statistical significance (Fig. 3).

Adverse Effects. The corticosteroid treatment had a favorable side effect profile (Fig. 4). There was no difference in the incidence of infection or neuromyopathic complications between the treatment and control groups. We also examined other major adverse events, including gastrointestinal bleedings and life-threatening complications, such as major organ failure (heart, kidney, and liver). When all major adverse events were combined (including infection and neuromyopathic complications), again we found no difference between treatment and control groups (Fig. 4).

Examination of Heterogeneity. There was moderate-to-large heterogeneity, as indicated by Cochran's Q and I^2 statistics, in mortality and morbidity outcomes (Figs. 2 and 3). For mortality outcome, the degree of heterogeneity was moderate ($I^2 = 51\%$) and for morbidity outcomes, the degree of heterogeneity was large ($I^2 > 75\%$ in all but one outcome). We, therefore, examined the impact of heterogeneity on overall treatment effect by performing subgroup and meta-regression analyses. Subgroup analysis indicated that the treatment effect was con-

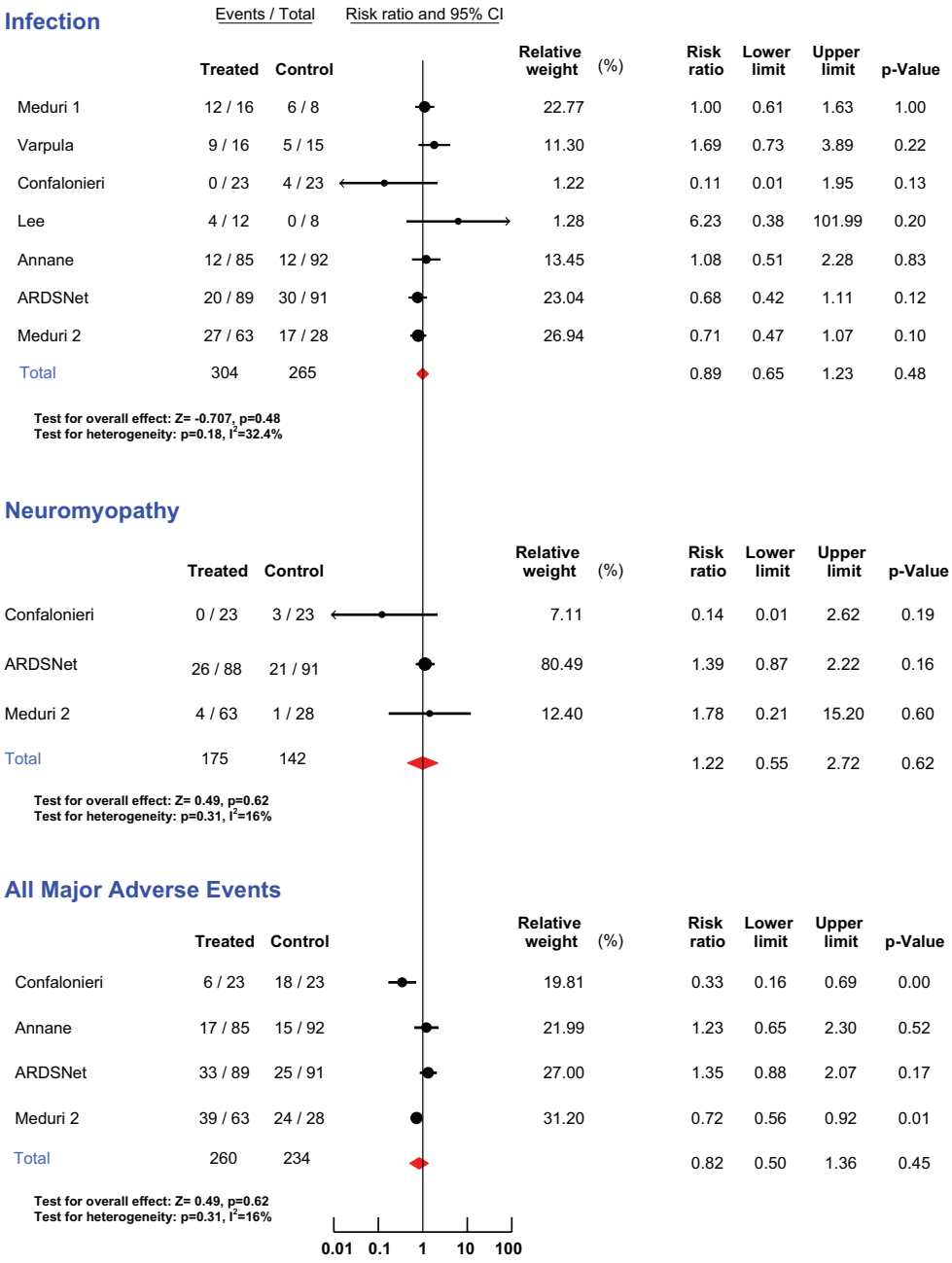

Figure 4. Complications. Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% confidence interval (*CI*).

sistent, despite variations in treatment regimens between studies (Table 3). It showed that the difference in relative risk between subgroups was not statistically significant with regard to time (early vs. late ARDS), formulation (hydrocortisone vs. methylprednisolone), or whether tapering was used. The treatment effect was also similar between studies performed before and after the publication of the National Institute of Health ARDS network low tidal volume ventilation study (21). For randomized trials, the use (or not) of a crossover design did not affect the treatment effect significantly. Meta-regression analysis showed that an increase in disease severity (reflected by an increase in Acute Physiology and Chronic Health Evaluation Scores) was associated with a lesser treatment effect (Table 4). None of the other variables affected treatment effect, including age, sex, dose, time and duration of treatment, percentage of patients with sepsis, and baseline Pao_2/Fio_2.

DISCUSSION

Use of corticosteroid in ALI is associated with a reduced mortality risk and an improvement in all morbidity outcomes. The effect on mortality was consistent in both randomized and nonrandomized studies. Importantly, the treatment was not accompanied by an increase in adverse events, such as infection, neuromyopathy, or other major complications.

Acute respiratory failure is the most common form of organ failure in critically ill patients (22) and ALI accounts for one quarter of such cases (1). Despite the anticipated worldwide increase in the prevalence of ALI, there is currently no proven pharmacologic therapy for this highly lethal disease

Table 4. Univariate meta-regression analysis

	Slope	95% Confidence Intrerval	*p*
Treatment duration (d)	−0.006	−0.03 to 0.02	0.57
Sepsis patients (%)	0.002	−0.003 to 0.008	0.40
Age (yrs)	0.001	−0.03 to 0.03	0.96
Dose (mg/methylprednisolone)	−0.002	−0.005 to 0.001	0.29
Gender (male/female)	−0.03	−0.1 to 0.05	0.46
Baseline Pao_2/Fio_2	−0.01	−0.02 to 0.001	0.07
Duration of ARDS before treatment began (d)	−0.012	−0.04 to 0.02	0.48
APACHE III[a]	0.01	0.002–0.02	0.015

ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation.
[a]Results are similar for APACHE II scores.

Table 5. Comparing outcomes between cohort studies and RCTs

	Cohorts Point Estimates (95% CI)	RCTs Point Estimates (95% CI)	p^a
Mortality	0.66 (0.43–1.02)	0.51 (0.24–1.09)	0.60
Mechanical Ventilation (d)	0.40 (−1.61 to 2.41)	−6.56 (−10.08 to −3.04)	<0.0001
Length of ICU stay (d)	0.10 (−0.30 to 0.50)	−6.15 (−9.35 to −2.94)	<0.0001
MODS scores	−0.44 (−1.25 to 0.37)	−0.88 (−1.19 to −0.58)	0.07
Lung Injury Score	0.10 (−0.19 to 0.39)	−0.86 (−1.6 to −0.13)	<0.0001
Pao_2/Fio_2	0.30 (−1.29 to 1.89)	0.78 (0.29–1.27)	0.16
Infection	1.40 (0.81–2.41)	0.76 (0.57–1.01)	0.05
Neuromyopathy	NA	1.22 (0.55–2.72)	NA
All major adverse events	1.23 (0.65–2.30)	0.73 (0.40–1.35)	0.18

CI, confidence interval; MODS, multiple organ dysfunction syndrome; RCT, randomized controlled trials; ICU, intensive care units; NA, not available.
[a]*p* Values of test of interaction between cohort studies and RCTs.

(23). Corticosteroids have been the most studied drugs for ALI and are the only agents that have shown promise as a potential treatment. However, current evidence to support their use is sparse because of the small number of randomized trials available. We, therefore, combined data from both randomized and nonrandomized studies. The increase in sample size has allowed us to detect a significant treatment effect in terms of mortality reduction. The in-hospital number needed to treat was 4 (95% CI 2.4–10), making low-dose corticosteroid therapy a highly effective treatment for ALI.

Combining RCTs and cohort studies together in a meta-analysis has both advantages and disadvantages. The advantage is that, by including a greater number of studies, the increase in sample size helped minimize type II error. This was especially the case on the primary outcome (i.e., mortality). The disadvantage is that cohort studies do not control for unknown variables and, hence, can potentially confound the findings. In fact, estimates from cohort studies on secondary outcome data are significantly different from those of RCTs (Table 5). However, it is important to note that RCTs contributed more weight in the secondary outcomes (RCTs weighting in random effect model; mechanical ventilation 71.2%, length of intensive care unit stay 67.5%, Multiple Organ Dysfunction Syndrome Score 72.1%, Lung Injury Score 63.6%, and Pao_2/Fio_2 ratios 68.8%). As a result, the summary estimates on morbidity outcome were dominated by RCTs.

There is significant heterogeneity in the included studies. The heterogeneity comes mostly from differences in the magnitude, and in some cases, the direction of the treatment effect. We anticipated the presence of significant heterogeneity *a priori* and, therefore, used a random effect model in all our analyses. Random effect model assumes that individual treatment effect varies from one study to another because of patient-level and study-level characteristics. Mathematically, it captures the within-studies and the between-studies differences. As a result, the pooled estimates provided by the random effect model take into account the heterogeneity among the studies.

Several patient-level variables previously thought to influence treatment effect did not play a significant role in our findings. For example, low-dose corticosteroids have been shown to reduce mortality in patients with sepsis in two meta-analyses (24, 25). It was possible, therefore, that some of the therapeutic effect of corticosteroid therapy in ALI might have been contributed by its effect on sepsis. However, we found that the proportion of septic patients did not have an impact on the treatment effect. This suggests that the effect of corticosteroids on patients with ALI was independent of its effect on sepsis. In fact, the recently completed Corticosteroid Therapy of Septic Shock study showed that corticosteroid did not reduce mortality in a largely surgical population with septic shock (26). Previously, it has also been unclear as to when corticosteroids should be given for ALI. There is concern that the efficacy of the corticosteroid therapy may be lost once the end-stage fibrosis has been established (27). In addition, there is a suggestion that commencing corticosteroids very late (beyond 2 weeks) might even increase the risk of death (11), although mortality difference lost significance when adjusted for baseline imbalances (28). Our findings, however, suggested that the reduction in mortality risk is not significantly affected by the timing of the treatment. Finally, there is also concern that abrupt cessation of the corticosteroid therapy could cause rebound inflammation, hence, reducing treatment effect. Although our findings suggested that the treatment effect was consistent whether corticosteroids were tapered at the end of the treatment, ample experimental and clinical data provide evidence for rebound inflammation and physiologic deterioration with rapid removal of corticosteroids (13).

Evaluation of study-level variables also revealed interesting findings. In randomized trials, the use of a crossover design has been thought to bias results in favor of the corticosteroid treatment (29). However, we found that the risk reduction was similar between trials that used crossover design and those that did not use such a design. The year of study was also thought to be important because of the publication of the National Institute of Health ARDS network low tidal volume ventilation study in 2000 (21). This study demonstrated the benefit of a more conservative ventilation strategy, which protected lungs from the trauma of excessive tidal volume ventilation. It is, therefore, possible that after 2000, the popular adoption of low tidal volume ventilation

strategy might have contributed to a reduced incidence of pulmonary inflammation in patients with ALI, hence, diluting the effect of any anti-inflammatory therapy, such as corticosteroids. However, our findings suggested that the treatment effect of post-2000 studies did not differ significantly from pre-2000 studies.

The above findings on patient-level and study-level variables need to be interpreted with caution. Although subgroup and meta-regression analyses were useful in demonstrating that the impact of these variables on the overall treatment effect was minimal, they can be underpowered to detect such effects because of the small number of studies available for analysis. It is still possible, for example, that tapering of corticosteroids is needed to prevent rebound inflammation. This caveat needs to be borne in mind when investigators design future RCT.

Potential limitations of our systematic review include the need to combine results from nonrandomized and randomized studies. In particular, on mortality outcome, cohort studies carried more weight than the RCTs in the random effect model (59.5% vs. 40.5%). The pooled estimate was, therefore, biased slightly more toward the cohort studies. However, on morbidity outcomes, cohort studies provided more conservative estimates (Table 5). Therefore, the overall effect of corticosteroids on morbidity was, if anything, underestimated. Another limitation of our study was that not all studies monitored closely all the potential adverse events. It was, therefore, possible that some events might be underreported. A further limitation was that we were unable to assess the effect of corticosteroids on nonresponders vs. responders to corticotrophin stimulation, a test used to predict the presence of adrenal insufficiency and identify those patients who are most likely to respond to corticosteroid therapy, because most studies did not provide such information. Corticosteroids also have a wide range of systemic effects, such as those on plasma interleukin-6 levels, neutrophil counts, C-reactive protein levels, and shock reversal. Again, we could not calculate summary estimates on these outcomes because they were not reported in most studies. There are other important outcomes of ALI, such as residual pulmonary dysfunction and sequelaes related to neuromuscular, cognitive, and psychological dysfunction (30). We could not assess them because the duration of follow-up was too short in most studies to include such long-term outcomes. Finally, other variables (e.g., ventilation mode, weaning protocol, or critical care resources) may also affect the mortality/morbidity outcomes and steroids alone may not help if these other variables are not controlled. However, we did not have enough data to assess the impact of these variables.

This study has implications for the design of future clinical trials. Given the wide variations in treatment regimens, future RCTs should focus on establishing a standardized treatment regimen. Aspects of the regimen that need to be standardized included (1) timing; (2) dosage and formulation; (3) duration; and (4) length of tapering. Additionally, trial enrolment should include stratified subgroups to determine the effect of corticosteroids on nonresponders vs. responders to corticotrophin stimulation.

CONCLUSIONS

The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes and a favorable side effect profile. The consistency of results in both study designs and all outcomes suggests that they are an effective treatment for ALI or ARDS. However, to confirm our findings, an adequately powered randomized trial is needed in the future.

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