Systematic Review and Meta-Analysis

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Dexamethasone for the treatment of acute respiratory distress syndrome

A systematic review and meta-analysis

Long-hua Feng, MM[a,*], Xiao-dan Li, MM[a,*], Xiao-yu Zhang, MM[b], Peng-jiang Cheng, MB[a], Zheng-yun Feng, MB[a,*]

Abstract

Background: This meta-analysis aimed to evaluate the efficacy and safety of dexamethasone in the treatment of acute respiratory distress syndrome (ARDS).

Methods: A systematic search of electronic databases was carried out from inception to May 1, 2022, including PUBMED, EMBASE, Cochrane Library, Wangfang, VIP, and CNKI. Other searches were also checked for dissertations/theses and the reference lists of the included studies. Two team members examined all citations and selected eligible articles. Randomized controlled trials (RCTs) reporting the efficacy and safety of dexamethasone for the treatment of ARDS were included, and the quality of eligible RCTs was assessed using the Cochrane Risk of Bias Tool. If necessary, we conducted data synthesis and meta-analysis. The primary outcome was all-cause mortality. Secondary outcomes were mechanical ventilation duration (day), ventilator-free status at 28 days; intensive care unit (ICU) free (day), ICU mortality, hospital mortality, sequential organ failure assessment (SOFA) as mean and range, SOFA as No. of patients, peak airway pressure (cmH_2O), arterial oxygen pressure (mm Hg), days with PaO_2 > 10kPa, PaO_2, and the occurrence rate of adverse events.

Results: Four studies involving 702 patients were included in this analysis. This study showed that dexamethasone could significantly reduce all-cause mortality (odds ratio (OR) = 0.62, 95% confidence interval (CI) [0.44, 0.88], I^2 = 30%, P < .001), and decrease ventilator-free status at 28 days (MD = 3.65, 95% CI [1.49, 5.80], I^2 = 51%, P < .001). No significant differences in occurrence rates of adverse events were found between dexamethasone and routine or standard care.

Conclusions: Evidence from the meta-analysis suggests that dexamethasone is an effective and relatively safe treatment for all-cause mortality and ventilator-free status at 28 days in patients with ARDS. Owning to the small number of eligible RCTs, the conclusions of present study are warranted in the future study.

Abbreviations: ARDS = acute respiratory distress syndrome, CI = confidence interval, ICU = intensive care unit, MD = mean difference, OR = Odds Ratio, RCTs = randomized controlled trials, SOFA = sequential organ failure assessment.

Keywords: acute respiratory distress syndrome, dexamethasone, efficacy, safety

1. Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening acute inflammatory disorder that begins within 7 days of acute onset.[1–4] It is characterized by very poor oxygenation, reduced pulmonary infiltrates, and bilateral radiographic infiltrates.[5–9] Several risk factors are responsible for this disorder, including lung infection or aspiration, sepsis, trauma, and drug overdose.[10–15] In addition, patients with advanced age, smoking, alcohol consumption, and aortic vascular and cardiovascular surgery.[16–21] Its incidence is estimated to range from 15 to 70 cases per 100,000 persons annually, accounting for approximately 5% of hospitalized and ventilated patients.[22]

Unfortunately, no drug has proven effective the treatment of patients with ARDS. Dexamethasone has potent anti-inflammatory and weak mineralocorticoid effects.[23] It has been reported that it has 4–5 times potent than prednisone and 20–30 times potent than naturally occurring hormone cortisol.[24] Studies have suggested that dexamethasone may benefit ARDS.[25–30] In addition, previous randomized controlled trials (RCTs) have investigated the efficacy of dexamethasone for the management

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[a] Department of Respiratory Medicine, Chongqing Qianjiang Central Hospital, Chongqing, China, [b] Department of Critical Care Medicine, Chongqing Qianjiang Central Hospital, Chongqing, China.

**Correspondence: Zheng-yun Feng, Department of Respiratory Medicine, Chongqing Qianjiang Central Hospital, No. 63 Chengxi 9th Road, Qianjiang District, Chongqing 409000, China (e-mail: desi7@21cn.com).*

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of ARDS.[31–34] However, there is still insufficient evidence-based medicine evidence to address this issue. Therefore, this systematic review and meta-analysis systematically and comprehensively explored the efficacy and safety of dexamethasone for ARDS treatment.

2. Methods

2.1. Ethical statement

Ethical permission was not required in this systematic review and meta-analysis because only secondary data from published clinical studies were collected and analyzed.

2.2. Eligibility criteria

2.2.1. Types of studies. RCTs that investigated the efficacy of dexamethasone in patients with ARDS were included. All other studies, including duplicates, reviews, case reports, case series, observational studies, wrong comparisons, combined therapy, and nonRCTs, were excluded. In addition, we also excluded trials with insufficient information and studies without a full-text.

2.2.2. Types of intervention and comparison. All the patients in the experimental group received dexamethasone, whereas all the patients in the control group received any treatment. However, we excluded the controls treated with any form of dexamethasone.

2.2.3. Types of patients. All participants (aged ≥ 18 years) diagnosed with ARDS were included in this study, regardless of nationality, sex, or educational background.

2.2.4. Types of outcome measurements. The primary outcome was all-cause mortality. Secondary outcomes were mechanical ventilation duration (day), ventilator-free status at 28 days; intensive care unit (ICU) free (day), ICU mortality, hospital mortality, sequential organ failure assessment (SOFA) as mean and range, SOFA as No. of patients, peak airway pressure (cmH_2O), arterial oxygen pressure (mm Hg), days of PaO_2 > 10kPa, PaO_2, and the occurrence rate of adverse events (new infection, bacteremia, hyperglycemia, ventilator-associated pneumonia, catheter-related bloodstream infection, catheter-associated urinary tract infections, and upper gastrointestinal bleeding).

2.3. Search strategy and study selection

Studies were identified through electronic databases from the beginning of the study to May 1, 2022, in PUBMED, EMBASE, Cochrane Library, Wangfang, VIP, and CNKI. In addition, we searched for other sources, such as dissertations/theses and reference lists of the included studies. After removing duplicates, we checked all records for titles, abstracts, and full texts of potential articles against eligibility criteria. The search strategy of PUBMED is presented in Table 1.

2.4. Data extraction

Two team members independently performed data extraction using a previously designed form. It consisted of publication information (e.g., study location, first author, year of publication, study design and setting, and sample size), patient characteristics (such as age, sex, and inclusion and exclusion criteria), intervention and control details, outcome indicators, results, conclusions, and follow-up information. Any differences in views were resolved through discussion with another member.

Table 1

Search strategy of PUBMED.

Number	Search terms
1	Lung injury
2	Acute respiratory distress
3	Adult respiratory distress
4	Acute respiratory distress syndrome
5	Respiratory distress syndrome, adult
6	ARDS
7	Acute lung injury
8	Acute lung injuries
9	Shock lung
10	Or 1-9
11	Dexamethasone
12	Hexadecadrol
13	Glucocorticoid receptor
14	MK-125
15	Corticosteroid
16	Or 11–15
17	Randomized controlled trial
18	Controlled clinical trial
19	Clinical trials
20	Random
21	Randomly
22	Control
23	Allocation
24	Placebo
25	Blind
26	Trial
27	Study
28	Or 17–27
29	10 and 16 and 28

2.5. Risk of bias assessment

Two team members assessed the methodological quality of the eligible RCTs using the Cochrane Risk of Bias Tool through 7 aspects, each of which was rated as high, unclear, or low risk of bias. Any divergence was addressed by a third team member through a discussion.

2.6. Statistical analysis

In this meta-analysis, data were analyzed using RevMan 5.4 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). The treatment effect of continuous values was presented as the mean difference (MD) and 95% confidence interval (CI), and that of dichotomous values was estimated as odds ratio (OR) and 95% CI. Statistical analysis was performed using I^2 statistics. A value of I^2 ≤50% indicated minor heterogeneity, and a fixed-effects model was used to pool the data. A value of I^2 >50% suggested significant heterogeneity, and a random-effects model was used to synthesize the data. We conducted a meta-analysis based on sufficient similarities between the eligible studies. If a meta-analysis could be conducted, the study findings would be reported using narrative descriptions and summaries.

3. Results

3.1. Literature search

We identified 1086 records from these databases (Fig. 1). After eliminating duplicates and scanning titles and abstracts with 935 irrelevant records, full-text papers from 34 articles were obtained and evaluated for eligibility. After carefully checking the full literature, 30 articles were excluded because of duplicates, incorrect comparisons, combined therapy, and nonRCT (Fig. 1). Finally, 4 RCTs met the eligibility criteria for this study (Fig. 1).

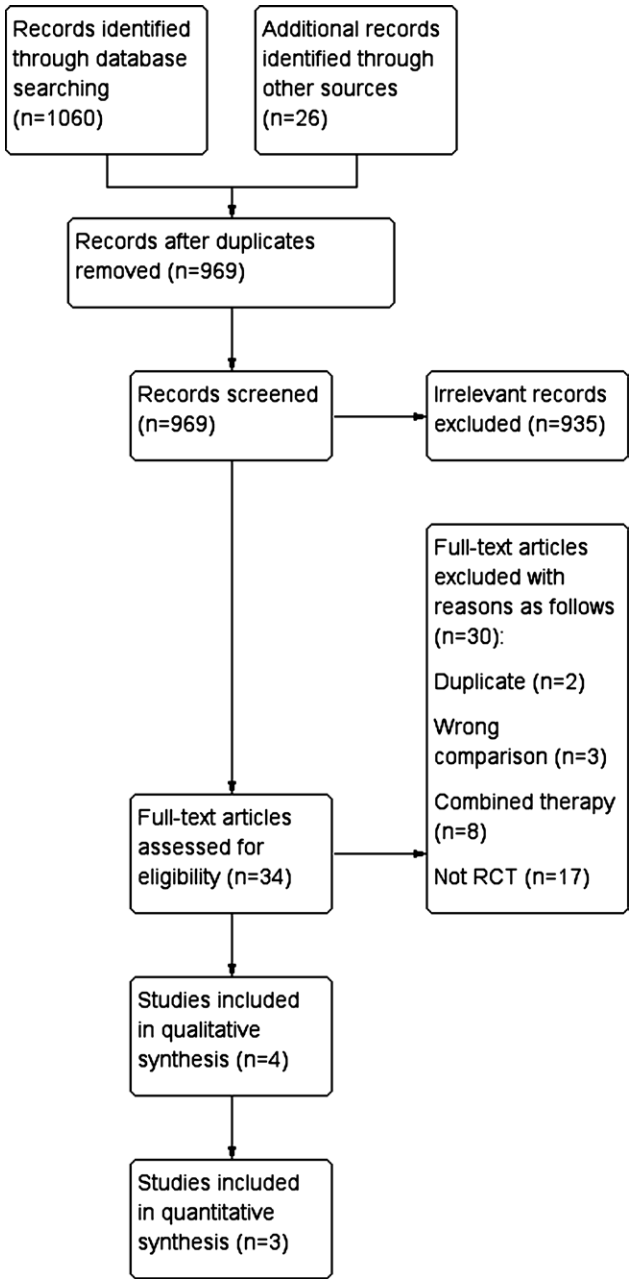

Figure 1. Flow diagram of study selection.

3.2. Study characteristics

The 4 RCTs analyzed 702 participants, with sample sizes ranging from 38 to 299. Three studies compared dexamethasone with routine care and 1 study compared dexamethasone with standard care. The general characteristics of the 4 RCTs that were included in this study are listed in Table 2.

3.3. Risk of bias assessment

The results of the risk of bias assessment for the 4 RCTs are presented in Figure 2. All 4 studies sufficiently reported random sequence generation, details of selective reporting, and other biases.[31–34] Two studies reported details of allocation concealment.[32,33] Only 1 study provided sufficient information on blinding to participants, investigators, and outcome assessors[33] (Fig. 2).

3.4. Meta-analysis of all cause mortality

Three RCTs with 614 patients assessed all-cause mortality. The results showed significant differences in all cause mortality (OR = 0.62, 95% CI [0.44, 0.88], I^2 = 30%, P < .001; Figure 3).[32–34]

3.5. Meta-analysis of mechanical ventilation duration (Day)

Two studies with 576 patients evaluated mechanical ventilation duration (days). No significant differences were identified in the mechanical ventilation duration (days) between the 2 groups (MD = −3.13, 95% CI [−6.93, 0.67], I^2 = 78%, P = .11; Figure 4).[32,33]

3.6. Meta-analysis of ventilator free at 28 days

Two studies with 576 patients evaluated ventilator-free status at 28 days, and significant differences were identified between the 2 groups (MD = 3.65, 95% CI [1.49, 5.80], I^2 = 51%, P < .001; Figure 5).[32,33]

3.7. Efficacy of other outcomes

Individual studies also investigated ICU free (days), ICU mortality, hospital mortality, SOFA score as mean and range, SOFA score as no. of patients, peak airway pressure (cmH_2O), arterial oxygen pressure (mm Hg), number of days with PaO_2 > 10kPa, PaO_2. No data were pooled for outcomes (Table 3).

Table 2

General characteristics of included studies.

Study	Location	Sample size (T/C)	Age (yr, T/C)	Gender (M/F)	Intervention	Control	Outcomes	Follow-up (d)
Chen 2016[29]	China	45/43	T:33.66 ± 9.56 C:34.05 ± 8.98	T:28/17 C:27/16	Dexamethasone	Routine care	⑨ ⑩	5
Tomazini 2020[30]	Brazil	151/148	T:60.1 ± 15.8 C:62.7 ± 13.1	T:90/61 C:97/51	Dexamethasone	Standard care	①②③④⑦⑧⑬⑭⑮⑯⑰⑱	28
Villar 2020[31]	Spain	139/138	T:56 ± 14 C:58 ± 15	T:96/43 C:95/43	Dexamethasone	Routine care	①②③⑤⑥⑬⑭⑮	60
Zhu 1998[32]	China	20/18	T:36.5 ± 15.4 C:35.8 ± 15.3	T:NR C:NR	Dexamethasone	Routine care	①⑪⑫⑲	9

Notes: T, treatment group; C, control group; M, Male; F, female; NR, not report; ① all-cause mortality; ② mechanical ventilation duration (day); ③ ventilator-free status at 28 days; ④ ICU free (day);⑤ ICU mortality; ⑥ hospital mortality; ⑦ sequential organ failure assessment (SOFA) as mean and range; ⑧ SOFA as No. of patients; ⑨ peak airway pressure (cmH_2O); ⑩ arterial oxygen pressure (mm Hg); ⑪ days of PaO_2 > 10kPa; ⑫ PaO_2; ⑬ new infection; ⑭ bacteremia; ⑮ insulin use for hyperglycemia; ⑯ ventilator-associated pneumonia; ⑰ catheter-related bloodstream infection; ⑱ catheter-associated urinary tract infections; ⑲ upper gastrointestinal bleeding.

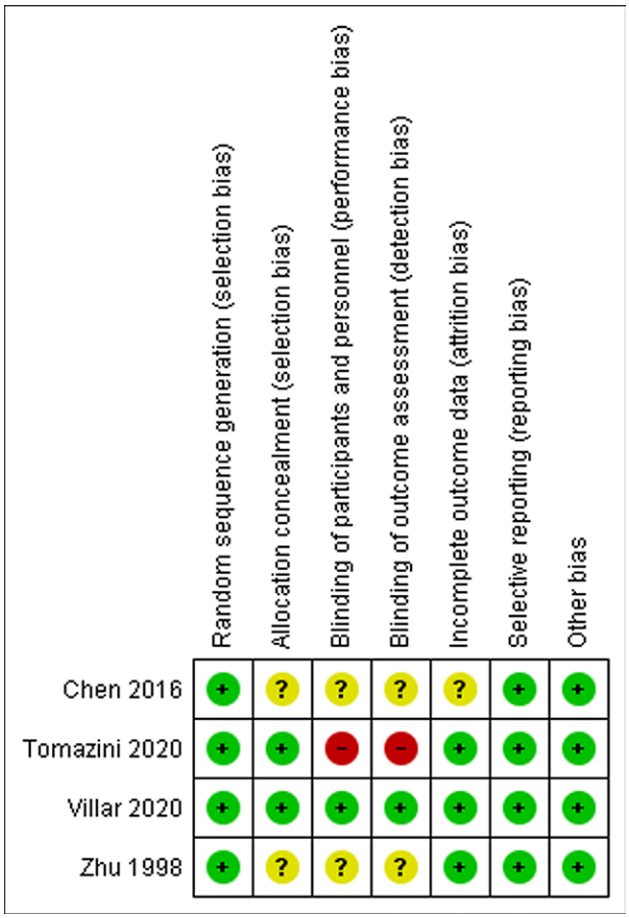

Figure 2. Risk of bias summary.

3.8. Occurrence rate of adverse events

Three studies, involving 614 patients investigated the occurrence rate of adverse events. The meta-analysis results did not show significant differences in new infections (OR = 0.79, 95% CI [0.54, 1.15], I^2 = 0%, *P* = .21; Figure 6, Table 4),[32–34] bacteremia (OR = 1.07, 95% CI [0.60, 1.92], I^2 = 0%, *P* = .81; Figure 6, Table 4),[32–34] and hyperglycemia (OR = 1.21, 95% CI [0.85, 1.75], I^2 = 0%, *P* = .29; Figure 6, Table 4).[32–34] The results for ventilator-associated pneumonia (OR = 0.59, 95% CI [0.31, 1.11]), catheter-related bloodstream infection (OR = 1.24, 95% CI [0.48, 3.24]), catheter-associated urinary tract infections (OR = 2.96, 95% CI [0.12, 73.25]), and upper gastrointestinal bleeding (OR = 0.89, 95% CI [0.05, 15.44]) are presented in Table 4.

4. Discussion

ARDS is an intense inflammatory lung disorder that responds to acute lung injury and systemic insult. Currently, no proven effective drugs are widely used to manage this condition. Previous studies have focused on the role of corticosteroids in ARDS treatment, with inconsistent findings. Other studies have explored the efficacy of dexamethasone because of its potential antiinflammatory and weaker mineralocorticoid effects compared to other corticoids.

Previous studies reported that dexamethasone can be used to treat ARDS. However, their efficacy and safety remain controversial. To date, evidence-based medicine has been insufficient to address this issue. Therefore, it is important to explore the efficacy and safety of dexamethasone for treating patients with ARDS. Based on comparative efficacy and safety evidence, this systematic review and meta-analysis summarizes the current clinical evidence of dexamethasone for the treatment of ARDS.

This study included 4 RCTs involving 702 participants with ARDS. The efficacy and safety of dexamethasone were

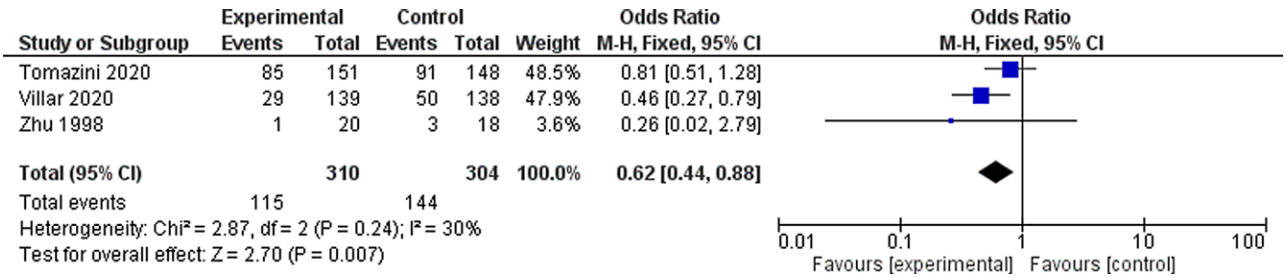

Figure 3. Meta-analysis of all-cause mortality.

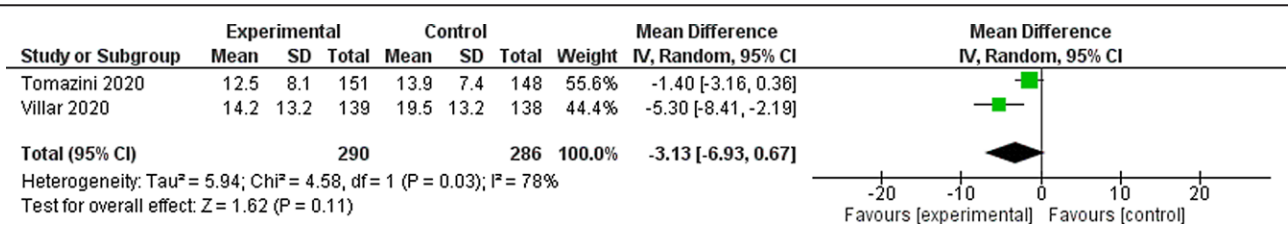

Figure 4. Meta-analysis of mechanical ventilation duration.

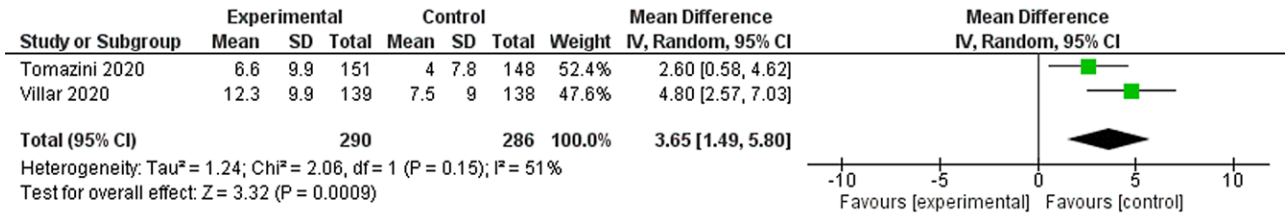

Figure 5. Meta-analysis of ventilator-free status at 28 days.

Table 3

Qualitative synthesis of efficacy.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
1.1ICU free (d)	1	299	Mean Difference (IV, Random, 95% CI)	0.28 [−0.49, 1.02]
1.2 ICU mortality	1	277	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.29, 0.89]
1.3 Hospital mortality	1	277	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.32, 0.92]
1.4 SOFA (mean, range)	1	247	Mean Difference (IV, Random, 95% CI)	−1.16 [−1.94, −0.38]
1.5 SOFA (No. of patients)	1	247	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.68, 2.25]
1.6 Peak airway pressure (cmH_2O)	1	88	Mean Difference (IV, Random, 95% CI)	−1.00 [−2.40, 0.40]
1.7 Arterial oxygen pressure (mm Hg)	1	88	Mean Difference (IV, Fixed, 95% CI)	6.40 [4.41, 8.39]
1.8 Days of PaO_2 > 10kPa	1	38	Mean Difference (IV, Fixed, 95% CI)	−3.20 [−4.45, −1.95]
1.9 PaO_2	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [−0.22, 2.02]

ICU = intensive care unit, SOFA = sequential organ failure assessment, CI = confidence interval.

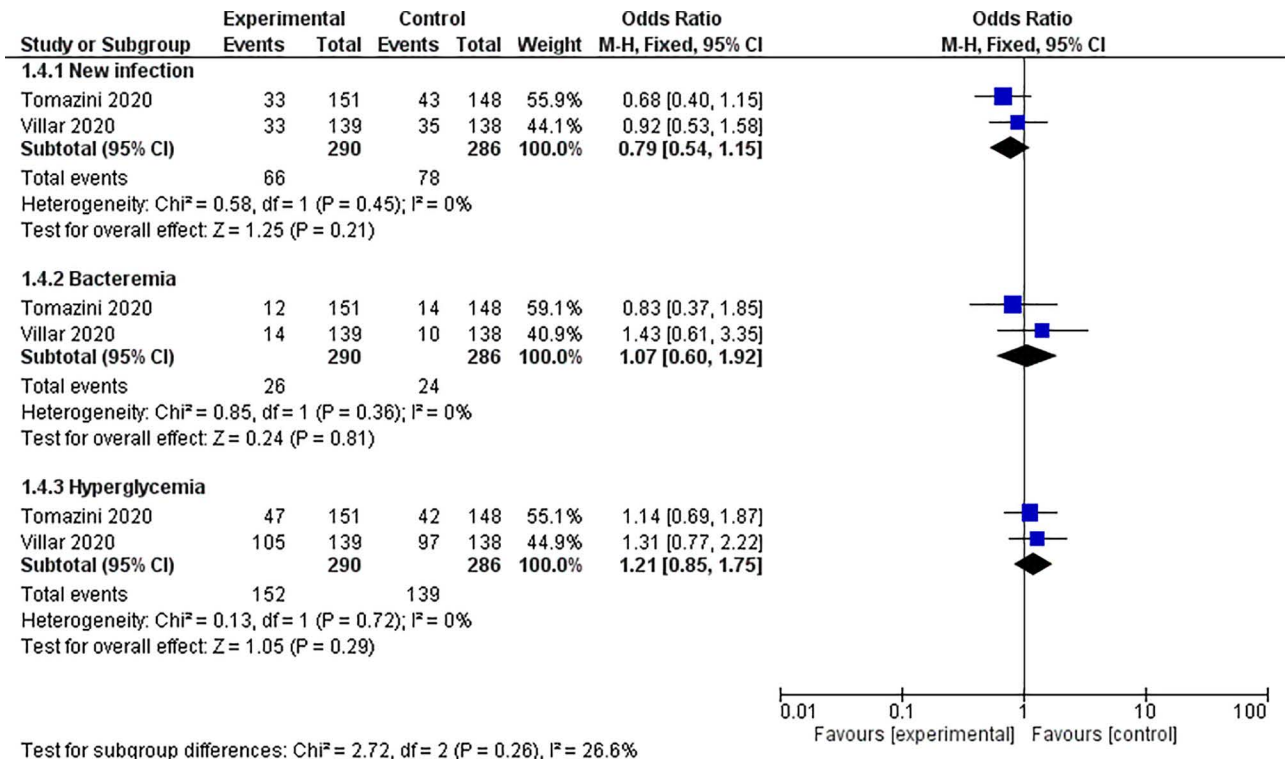

Figure 6. Meta-analysis of adverse events.

comprehensively and systematically compared with those of routine or standard care for the treatment of ARDS. The results showed that patients who received dexamethasone had better outcomes than those who did not, on all-cause mortality and ventilator-free status at 28 days. This indicates that dexamethasone may be beneficial in patients with ARDS. Regarding safety, there were no significant differences in the occurrence of adverse events between the 2 treatments.

This study has several limitations. First, although our search strategy was strict and comprehensive, there may have been some potential studies that were not included in this study. Second, the number of clinical studies of dexamethasone in ARDS is

Table 4

Qualitative synthesis of adverse events.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
2.1 New infection	2	576	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.15]
2.2 Bacteremia	2	576	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.60, 1.92]
2.3 Hyperglycemia	2	576	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.85, 1.75]
2.4 Ventilator-associated pneumonia	1	299	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.11]
2.5 Catheter-related bloodstream infection	1	299	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.48, 3.24]
2.6 Catheter-associated urinary tract infections	1	299	Odds Ratio (M-H, Fixed, 95% CI)	2.96 [0.12, 73.25]
2.7 Upper gastrointestinal bleeding	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.05, 15.44]

CI = confidence interval.

limited. Third, the generalizability of our findings to patients with long-term follow-up visits is unclear. Fourth, insufficient data were collected for the primary and secondary outcomes, which may have decreased the reliability of the present results.

5. Conclusion

In summary, the current evidence suggests that dexamethasone may benefit patients with ARDS in terms of all-cause mortality and ventilator-free status at 28 days. However, further studies are required to validate the findings.

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