Intermediate- to high-dose dexamethasone versus low-dose dexamethasone in patients with COVID-19 requiring respiratory support: A systematic review and meta-analysis of randomized trials

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Abstract

The present review critically appraised the randomized clinical trials involving intermediate to high-dose dexamethasone and low-dose dexamethasone and reported pooled mortality risk estimates associated with these two dexamethasone dosing regimens. The systematic searching of electronic databases was limited to randomized clinical trials comparing intermediate to high-dose dexamethasone with low-dose dexamethasone in patients with COVID-19 requiring respiratory support. The primary outcome was all-cause mortality after pooling data from included trials using a random-effects model. A total of eight trials with 1,800 patients randomized to receive intermediate to high-dose dexamethasone and 1,715 patients randomized to low-dose dexamethasone were included. The meta-analysis of six trials revealed no significant difference in the risk of 28-day all-cause mortality between intermediate-to-high dose and low-dose dexamethasone (odds ratio 1.16, 95% confidence interval, 0.77-1.74). Similarly, the meta-analysis of five trials revealed no significant difference between the two doses regarding 60-day all-cause mortality (odds ratio 0.96, 95% confidence interval 0.74-1.26). The results suggest intermediate to high-dose dexamethasone to be as effective as low-dose dexamethasone in reducing mortality risk among patients with COVID-19 requiring respiratory support. However, a higher dexamethasone dose could expose COVID-affected patients to an increased risk of adverse events, such as hyperglycemia.

Keyword: COVID-19; corticosteroid; dexamethasone; glucocorticoid; steroid

Introduction

The efficacy of low-dose dexamethasone in patients with COVID-19 with a regimen of 6 mg daily for ten days has been established since the early pandemic (RECOVERY Collaborative Group et al. 2021). However, despite the positive findings (e.g., Recovery Trial), questions have been raised about whether using a higher dose of dexamethasone in patients with COVID-19 could produce - clinically effective - excessive inflammatory responses, especially in severely or critically ill patients to improve their prognosis. Therefore, we conducted a systematic review with meta-analysis to estimate mortality risk using intermediate to high-dose dexamethasone compared with low-dose dexamethasone.

Methods

We performed a literature search in six electronic databases: PubMed, Scopus, and Web of Science for published studies, and medRxiv, Research Square, and SSRN for preprints from inception to 20 March 2023. The search strategy in the electronic databases was built based on the following keywords and their MeSH terms (if applicable): “COVID-19”, “SARS-CoV-2”, “dexamethasone”, “corticosteroid”, “steroid”, and “glucocorticoid”. We also hand-searched the bibliographies of included articles and relevant reviews to retrieve additional relevant records. We limited the search to human and adult studies with no restrictions on publication date or publication status.

Two investigators (CSK and SSH) independently screened all retrieved references for inclusion based on the study title and abstract. In addition, the two investigators (CSK and SSH) retrieved and reviewed the full text of articles deemed possibly eligible for inclusion. We resolved disagreement during the review process through a discussion with a third investigator (DSR) and by consensus.

We restricted our search to randomized clinical trials that evaluated the mortality outcome with intermediate to high dose dexamethasone against low dose dexamethasone in adult participants ($\geqslant$18 years) who were infected with SARS-CoV-2 and required any form of respiratory support (e.g., oxygen therapy, non-invasive ventilation, and invasive ventilation). A low dose or an intermediate to a high dose of dexamethasone was classified based on the a priori–defined cutoff of 10 mg per day. We excluded non-randomized trials, single-arm trials, observational studies, case reports, reviews, conference abstracts, animal studies, and non-English language publications.

Two investigators (CSK and DSR) independently extracted data from each included trial using a standardized data collection form. Data extracted included characteristics of the included studies (first author’s surname, year of publication, and country where the trial was performed), trial design, details of

the population enrolled (mean/median age and illness severity), details of the study interventions (dose, frequency, and duration), mortality outcomes, and adverse events. We resolved discrepancies in the data extracted by the two investigators by discussion or, if necessary, by adjudication by a third investigator (SSH).

Two investigators (CSK and SSH) independently assessed the risk of bias for each of the included trials using the Cochrane Risk of Bias Tool version 2 (Sterne et al. 2019), which is structured into a fixed set of bias domains. Disagreements were resolved by discussion with a third investigator (DSR) and by consensus. Therefore, we adjudicated the risk of bias as 'low' only if all domains were assessed as low risk of bias.

The outcome of interest was all-cause mortality at two different time points: 28 days and 60 days and above.

A random-effects model was used to estimate the pooled odds ratio for the development of outcomes of interest with the use of intermediate to high-dose dexamethasone relative to the use of low-dose dexamethasone at 95% confidence intervals. To evaluate the robustness of the pooled estimate, we also fitted an inverse variance heterogeneity (IVhet) model. In addition, we examined the heterogeneity between studies using the I^2 statistics and the χ^2 test, with substantial heterogeneity predetermined at 50% and $p < 0.10$, respectively. Finally, publication bias was assessed visually using Begg's funnel plot. All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Results

Our systematic literature search of electronic databases retrieved 1,935 records. Of 1,527 records identified (after deduplication), 11 records were assessed for eligibility. Three studies were excluded due to the observational study design. In total, we included eight randomized controlled trials (Bouadma et al. 2022; Granholm et al. 2022; RECOVERY Collaborative Group et al. 2023; Maskin et al. 2021; Munch et al. 2021; Rabascall et al. 2022; Taboada et al. 2021; Toroghi et al. 2022; Wu et al. 2022) in our systematic review, with 1,800 patients randomized to receive intermediate to high dose dexamethasone and 1,715 patients randomized to low dose dexamethasone.

The characteristics of the included randomized trials are shown in **Table 1**. The regimen of intermediate to high dose dexamethasone in the intervention group differed across the included trials: five trials (Bouadma et al., 2022; RECOVERY Collaborative Group, 2023; Maskin et al., 2021; Taboada et al., 2021; Wu et al., 2022) administered dexamethasone using dose-tapering strategies (16 to 20 mg daily for five days, followed by 8 to 10 mg daily for additional five days), one trial (Rabascall et al. 2022) administered

dexamethasone using weight-based dosing strategy (0.2 mg/kg daily for 10 days), while the remaining two trials (Granholm et al. 2022; Munch et al. 2021; Toroghi et al. 2022) administered dexamethasone 12 to 24 mg daily for ten days. The regimen of low-dose dexamethasone in the comparative group across the included trials (Bouadma et al., 2022; Granholm et al., 2022; RECOVERY Collaborative Group. 2023; Maskin et al., 2021; Munch et al., 2021; Rabascall et al., 2022; Taboada et al., 2021; Toroghi et al., 2022; Wu et al. 2022) was 6-8 mg daily for ten days.

We adjudicated two trials (Bouadma et al. 2022; Granholm et al. 2022; Munch et al. 2021) as having a low risk of bias in all domains and, thus, an overall low risk of bias. We rated the remaining trials as having overall some concerns of bias (some concerns of bias in at least one domain): the five trials reported by Maskin et al. (2021), Taboada et al. (2021), Rabascall et al. (2022), RECOVERY Collaborative Group. (2023) and Wu et al. (2022), respectively, had some concerns in the domain of deviations from intervention due to open-label trial design, while the trial reported by Toroghi et al. (2022) had some concerns in the domain of deviations from intervention due to single-blind trial design.

The meta-analysis of six trials (RECOVERY Collaborative Group. 2023; Maskin et al., 2021; Munch et al., 2021; Rabascall et al., 2022; Taboada et al., 2021; Wu et al., 2022) using a random-effects model revealed no significant difference in the risk of 28-day all-cause mortality between intermediate-to-high dose and low-dose dexamethasone. The estimated effect of low-dose dexamethasone on 28-day all-cause mortality (**Figure 1**; pooled odds ratio=1.16, 95% confidence interval 0.77-1.74) indicated mortality benefits than intermediate-to-high dose dexamethasone, but with limited evidence against our model hypothesis of 'no significant difference' at the current sample size. The IVhet model also produced a similar mortality estimate. Notably, one large trial reported by RECOVERY Collaborative Group (2023) demonstrated a statistically significant higher risk of 28-day all-cause mortality with intermediate-to-high dose compared with low-dose dexamethasone.

Similarly, the meta-analysis of five trials (Bouadma et al. 2022; Granholm et al. 2022; Maskin et al. 2021; Taboada et al. 2021; Toroghi et al. 2022) using a random-effects model revealed no significant difference between intermediate-to-high dose and low-dose dexamethasone regarding 60-day all-cause mortality. The estimated effect of intermediate-to-high dose dexamethasone on the 60-day all-cause mortality (**Figure 1**; pooled odds ratio=0.96, 95% confidence interval 0.74-1.26) revealed some clinical benefits with intermediate-to-high dose than low dose dexamethasone, but with limited evidence against our model hypothesis of 'no significant difference' at the current sample size. The IVhet model also produced non-

significant evidence of mortality benefits (pooled odds ratio = 0.92, 95% confidence interval 0.69 to 1.21) with similar heterogeneity.

Funnel plots revealed a gross asymmetry to either side, indicating that publication bias may be present (**Figure 2**). In addition, studies were scattered asymmetrically around the summary effect.

Discussion

In this systematic review and meta-analysis, we found no significant mortality benefits with the use of intermediate to a high dose of dexamethasone in patients with COVID-19 requiring respiratory support compared with low-dose dexamethasone. Our systematic review and meta-analysis provide the most up-to-date evidence (when writing this manuscript) of administering intermediate to a high dose of dexamethasone compared with low dose dexamethasone on mortality outcome. The methodologic strengths of our systematic review and meta-analysis include a focused research question with a defined population, intervention, comparator, and outcome.

The findings of our review have important implications for clinical practice, especially in the context where clinicians want to trial a higher than the recommended dose of dexamethasone (6 mg daily for ten days) in patients with COVID-19 who are severely or critically ill, recognizing the positive effects of dexamethasone in COVID-19 patients. In this patient population, additional anti-inflammatory therapies may be clinically more effective in reducing the mortality risk than escalating the dose of dexamethasone. For example, available data suggest that baricitinib and tocilizumab provide a mortality benefit for patients with COVID-19 in the severe course of the disease, even if they are already receiving low-dose dexamethasone [Abani et al. 2022; Domingo et al. 2021].

The use of higher doses of dexamethasone is not without safety concerns. One of the dose-related complications with dexamethasone is the development of hyperglycemia, which may negate its mortality benefits in patients with COVID-19 (Kow et al. 2021). The trial reported by Toroghi et al. (2022) observed a higher proportion of patients in the high-dose group (47.8%) and intermediate-dose group (37.5%) developed hyperglycemia compared to the low-dose group (29.8%). In addition, using a higher dose of dexamethasone may predispose to a higher risk of secondary infections. In the trial reported by Toroghi et al. (2022), a higher proportion of patients in the high-dose group (8.7%) and intermediate-dose group (2.5%) developed secondary infections compared to the low-dose group (2.1%).

Our systematic review and meta-analysis are limited by the lack of information from the included studies on the rate of SARS-CoV-2 vaccination and the predominating SARS-CoV-2 variants during the study period,

which can influence the risk of mortality among patients with COVID-19. Nevertheless, the lack of information mentioned above is understandable since the variants of concerns were not widely circulated, sequencing for variants of concerns was not widely available, and COVID-19 vaccination was not publicly available during the study period for most of the included studies.

Overall, our systematic review and meta-analysis of currently existing data from published randomized clinical trials suggest that administering intermediate to high-dose dexamethasone in patients with COVID-19 requiring respiratory support has similar mortality benefits compared with low-dose dexamethasone. Nevertheless, one large trial (RECOVERY Collaborative Group. (2023)) indicated 28-day mortality benefits with low doses compared with intermediate-to-high dose dexamethasone. Although higher-dose dexamethasone may be associated with safety concerns and no apparent superiority over low-dose, prioritizing low-dose dexamethasone in this population of patients would be beneficial.

Ethics declarations

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Informed consent on studies with human and animal subjects: Not applicable

Data availability: The data presented in this study are available in the manuscript.

Author and co-author contribution: Chia Siang Kow and Dinesh Sangarran Ramachandram were involved in study design, execution, analysis, manuscript drafting, and discussion. Syed Shahzad Hasan was involved in study design, analysis, and manuscript drafting.

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Figure Legend:

Figure 1: Pooled odds ratio for all-cause mortality with the administration of intermediate to high dose dexamethasone among patients with COVID-19 requiring respiratory support relative to low dose dexamethasone

Figure 2: Funnel plot with 95% confidence interval on the odds ratio of included studies in the meta-analysis (n = 9)

Table 1: Characteristic of included studies

Study (year)	Study design	Country	Age (median)	Regimen of intermediate to high dose dexamethasone	Regimen of low dose dexamethasone	Mortality events (28 days)		Mortality events (60 days and above)		Risk of bias[1]
						Intermediate to high dose dexamethasone (n/N; %)	Low dose dexamethasone (n/N; %)	Intermediate to high dose dexamethasone (n/N; %)	Low dose dexamethasone (n/N; %)	
Bouadma et al [3] (2022)	Randomized, double-blind, controlled trial	France	Intermediate to high dose dexamethasone=68.1 Low dose dexamethasone=66.3	20 mg daily for 5 days, then 10 mg daily for additional 5 days	6 mg daily for 10 days	N/A	N/A	70/273; 25.6	74/277; 26.7	Low
Maskin et al [4] (2021)	Randomized controlled, open-label trial	Argentina	Intermediate to high dose dexamethasone=63.6 Low dose dexamethasone=60.0	16 mg daily for five days, then 8 mg daily for additional 5 days	6 mg daily for 10 days	20/49; 40.8	19/51; 37.3	23/49; 46.9	24/51; 47.1	Some concerns
Taboada et al [5] (2021)	Randomized controlled, open-label trial	Spain	Intermediate to high dose dexamethasone=63.9 Low dose dexamethasone=64.8	20 mg daily for 5 days, then 10 mg daily for additional 5 days	6 mg daily for 10 days	6/98; 6.1	6/102; 5.9	7/98; 7.1	8/102; 7.8	Some concerns
Toroghi et al [6] (2021)	Randomized, single-blind, controlled trial	Iran	High dose dexamethasone=56.0 Intermediate dose dexamethasone=59.0 Low dose dexamethasone=59.0	High dose: 24 mg daily for 10 days Intermediate dose: 16 mg daily for 10 days	8 mg daily for 10 days	N/A	N/A	High dose: 19/48; 39.6 Intermediate dose: 12/48; 25.0	8/48; 16.7	Some concerns
Munch et al [8] (2021) and Granholm et al [7] (2022)	Randomized, double-blind, controlled trial	4 countries	Intermediate to high dose dexamethasone=65.0 Low dose dexamethasone=64.0	12 mg daily for 10 days	6 mg daily for 10 days	133/503; 26.4	155/497; 31.2	164/503; 32.6	184/497; 37.0	Low
Rabascall et al [9] (2022)	Randomized controlled, open-label trial	United States	Intermediate to high dose dexamethasone=55.5 Low dose dexamethasone=57.2	0.2 mg/kg daily, with a maximum dose of 20 mg daily, for 10 days	6 mg daily for 10 days	12/70; 17.1	15/72; 20.8	N/A	N/A	Some concerns
RECOVERY Collaborative Group et [10] (2022)	Randomized controlled, open-label trial	6 countries	Intermediate to high dose dexamethasone=60.2 Low dose dexamethasone=62.1	20 mg daily for 5 days, then 10 mg daily for additional 5 days	6 mg daily for 10 days	121/659; 18.4	75/613; 12.2	N/A	N/A	Some concerns
Wu et al [11] (2022)	Randomized controlled,	United States	Intermediate to high dose dexamethasone=56.1	20 mg daily for 5 days, then 10 mg	6 mg daily for 10 days	11/52; 21.2	5/55; 9.1	N/A	N/A	Some concerns

	open-label trial	Low dose dexamethasone=57.9	daily for additional 5 days

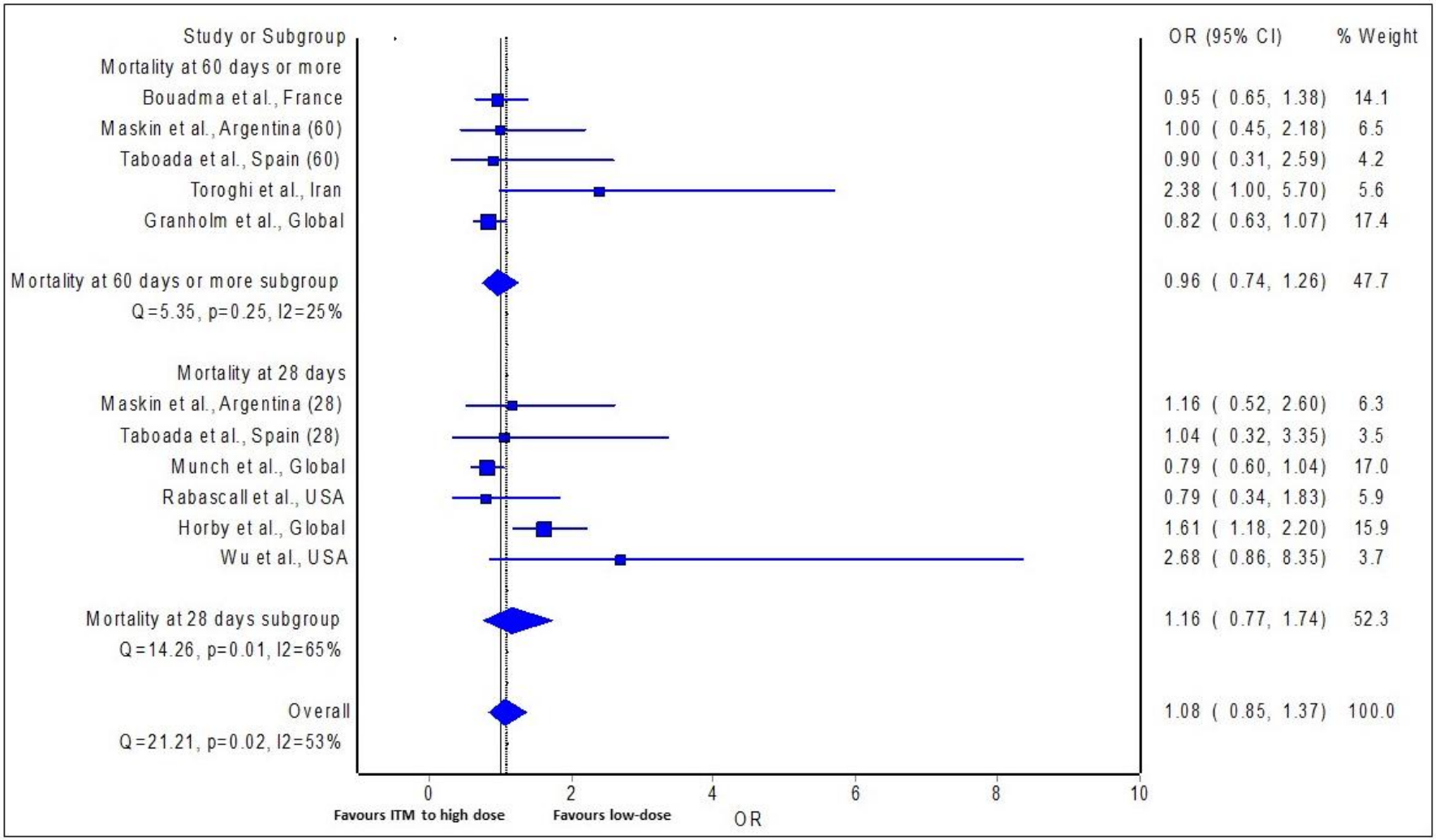

Figure 1: Pooled odds ratio for all-cause mortality with the administration of intermediate to high dose dexamethasone among patients with COVID-19 requiring respiratory support relative to low dose dexamethasone

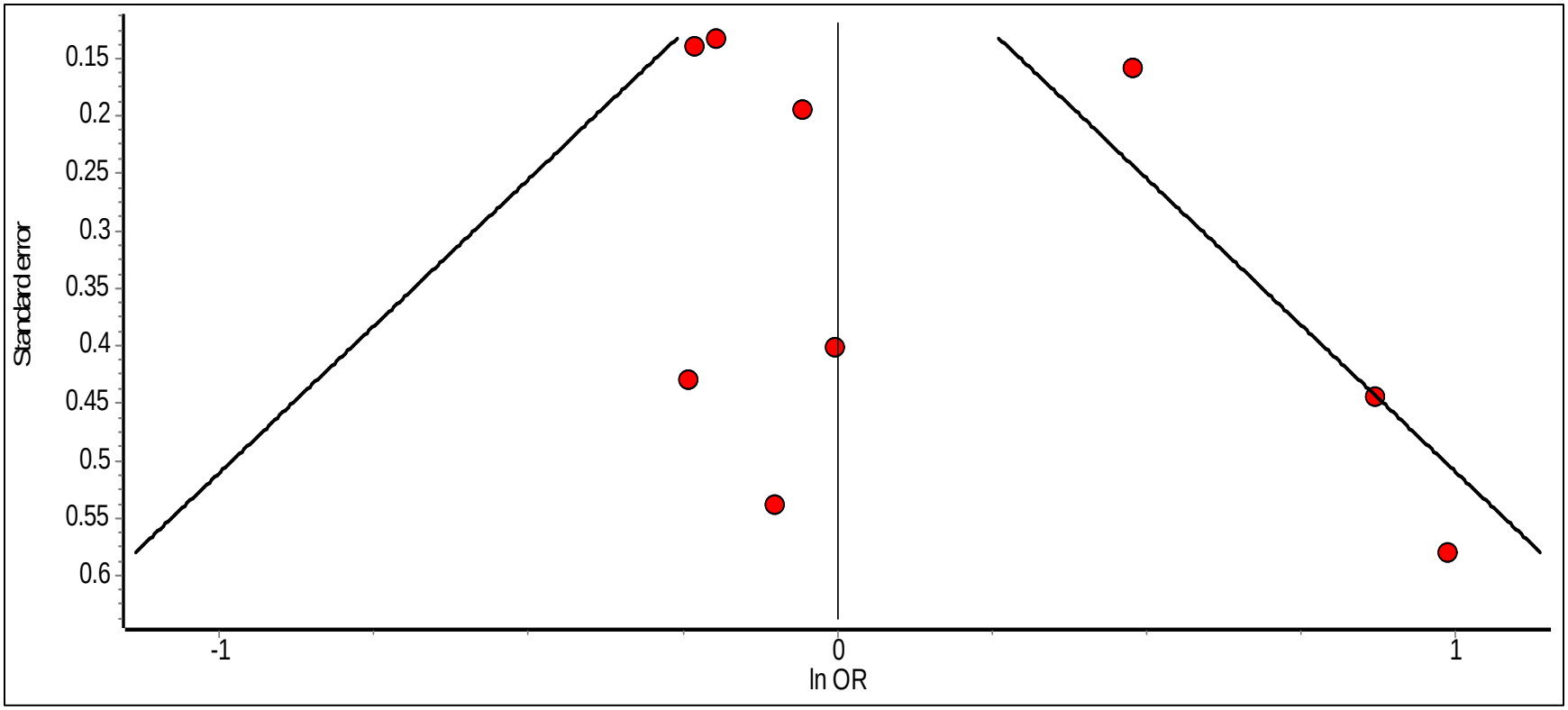

Figure 2: Funnel plot with 95% confidence interval on the odds ratio of included studies in the meta-analysis (n = 9)