Pentoxifylline and prednisolone for improving mortality in severe alcoholic hepatitis: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the efficacy of pentoxifylline and prednisolone on mortality in severe alcoholic hepatitis.

METHODS

We searched studies from Pubmed, the Cochrane Library, and Scopus. For Pubmed, MeSH terms "pentoxifylline", "prednisolone" and "alcoholic hepatitis" but other databases used the following keywords: pentoxifylline and prednisolone and alcoholic hepatitis. All randomized controlled trials (RCTs) that related were included. We included those studies with participants with severe alcoholic hepatitis. The primary outcome was mortality and secondary outcomes were adverse events. We included trials irrespective of language or publication status.

RESULTS

We included seven RCTs with 1,214 patients, carried out between 2009 and 2015. Meta-analysis showed that for 28 days mortality pentoxifylline did not significantly reduce mortality rate in those with severe alcoholic hepatitis compared to prednisolone (relative risk [RR], 1.05; 95% confidence interval [CI], 0.60 to 1.85; I^2=63%), prednisolone did not significantly increase the mortality rate in those with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.07; 95% CI 0.77 to 1.48; I^2=0%) but pentoxifylline significantly decrease the mortality rate in those with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.47; 95% CI, 1.00 to 2.18; I^2=0%).

CONCLUSION

For short-term treatment, there were no differences in 28 days mortality rates between pentoxifylline and prednisolone, prednisolone and prednisolone plus pentoxifylline and pentoxifylline and prednisolone plus pentoxifylline and for long-term treatment, there were no differences in the mortality rates between prednisolone and prednisolone plus pentoxifylline, pentoxifylline, and prednisolone plus pentoxifylline.

INTRODUCTION

Alcoholic liver disease includes various forms of liver injuries i.e., fatty liver, alcoholic hepatitis, and cirrhosis.[1] High burden of alcoholic liver disease expected in the next decade.[2,3] Management of alcoholic hepatitis includes alcohol cessation, hemodynamic and nutritional support. In severe alcoholic hepatitis, prednisolone and pentoxifylline might be considered to be used.[4] The use of corticosteroid aims to moderate the immune and proinflammatory cytokine response which is highly increased in alcoholic hepatitis and is one of the causes of liver injury.[5-8] For pentoxifylline, prevention of hepatorenal syndrome without any decrease in proinflammatory cytokines is its main efficacy for alcoholic liver disease.[9-,11] Although many studies have examined the efficacies of prednisolone and pentoxifylline for patients with severe alcoholic hepatitis, their results comparing between prednisolone versus with pentoxifylline, prednisolone alone versus prednisolone plus pentoxifylline and pentoxifylline alone versus pentoxifylline plus prednisolone are still controversy. Hence, we conducted a systematic review to assess the benefits and harms of pentoxifylline and prednisolone in patients with severe alcoholic hepatitis.

METHODS

SEARCH STRATEGY

We systematically searched literature through electronic databases of PubMed, the Cochrane Library, Scopus and to identify further articles we hand searched references lists of included studies. A search in Pubmed was undertaken using MeSH terms "pentoxifylline", "prednisolone" and "alcoholic hepatitis", and for other databases, we used the following keywords: pentoxifylline and prednisolone and alcoholic hepatitis. No language restriction was imposed.

INCLUSION AND EXCLUSION CRITERIA

The selection of articles to be assessed in this review were divided into two steps; firstly, information from the titles and abstracts were screened by three independent review authors to exclude non-relevant articles. Later, all relevant articles were read in full text by three review authors then independently assessed and selected trials to be included in this review when disagreements occur, the fourth review author decided.

The following inclusion criteria had to be met; (i) we included all double-blind randomized controlled trials (RCTs) of pentoxifylline and prednisolone in patients with severe alcoholic hepatitis, (ii) patients were those with severe alcoholic hepatitis (Maddrey's Discriminant Function for Alcoholic Hepatitis ≥32), (iii) studies had to compare between using pentoxifylline versus prednisolone, prednisolone alone versus prednisolone plus pentoxifylline and pentoxifylline alone versus prednisolone plus pentoxifylline for treatment in the patients with severe alcoholic hepatitis, (iv) the primary outcome was mortality and secondary outcomes were adverse events such as upper gastrointestinal hemorrhage, hepatorenal syndrome, hepatic encephalopathy and infection (lung infection, sepsis). There were no exclusion criteria in this systematic review.

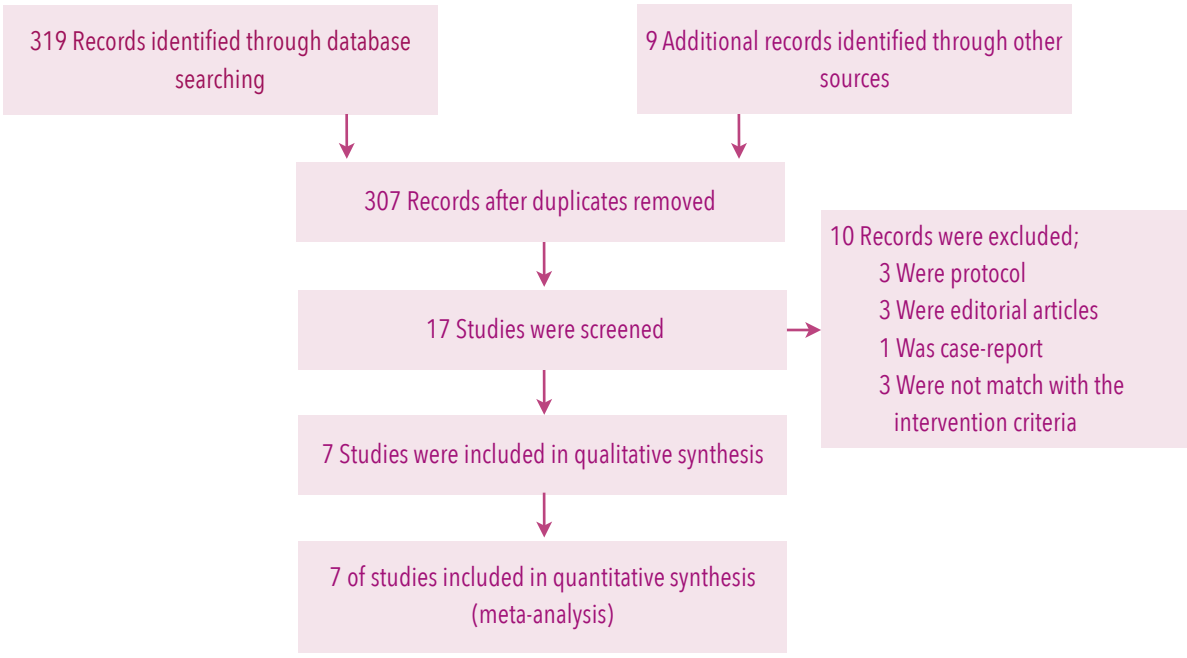

Figure 1. Flowchart presenting the number of articles retrieved, included and excluded in this systematic review

DATA EXTRACTION

Three authors extracted the data from the included studies. Each of them, we abstracted the first author, title, year of publication, number of the patients, interventions, outcome data of various time points.

QUALITY OF REPORTING AND RISK OF BIAS

We assessed the risk of bias of the included studies using the Cochrane risk of bias tool regarding sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources of bias. Each domain was classified as "high, unclear or low risk of bias."

STATISTICAL ANALYSIS

For each outcome, we calculated relative risk (RR) and its 95% confidence intervals (CI). $P<0.05$ or CI did not include the value of 1 was considered statistically significant. Heterogeneity between studies was assessed by chi-square and I^2 statistic ($I^2 \geq 50\%$ indicated substantial heterogeneity). We used a random effect model for the meta-analysis when the heterogeneity was statistical significance. Funnel plots were created to evaluate publication bias. Statistical analysis was calculated by Review Manager V5.3 (RevMan, the program provided by the Cochrane Collaboration).

SENSITIVITY ANALYSIS

We conducted a sensitivity analysis comparing results including only low-risk studies.

RESULTS

Our search strategies identified 320 publications. We removed 13 duplicates. Later 290 were

Figure 2. Risk of bias
Panel A, risk of bias summary of the included studies; Panel B, risk of bias graph of the included studies

excluded because of the not relevant of title and abstract or other reasons (Figure 1). A further 10 publications were excluded because they did not match with our inclusion criteria; 3 were protocols, 3 were editorials, 3 did not match our intervention criteria and 1 was a case-report. Any of them were excluded from our exclusion criteria, the remaining 7 records were included in the qualitative analysis and the meta-analysis.

CHARACTERISTICS OF THE INCLUDED STUDIES

We identified and included seven RCTs with 1,274 patients with severe alcoholic hepatitis, four trials compared pentoxifylline to prednisolone, three trials compared prednisolone alone to prednisolone plus pentoxifylline, two trials compared pentoxifylline to prednisolone plus pentoxifylline (Table 1).

BIAS RISK ASSESSMENT

Seven trials were assessed using the Cochrane risk of bias tool. Risk of bias was assessed according to five components: random sequence, generation, allocation concealment, blinding of participant, incomplete outcome data and selective reporting. Of the seven included trials, six was assessed as having a low risk of bias[9-11,13-15] and one was assessed as having a high risk of bias.[12] The risk of bias graph was summarized in Figure 2.

RANDOM SEQUENCE GENERATION

One study did not report the methods of generating a random sequence,[12] while six studies specified the methods and they were classified as "low risk."[9,11,13-16]

ALLOCATION CONCEALMENT

Five studies did not report details on allocation concealment and they were classified as "unclear."[11-13,15,16] One study reported open-labeled method and they were classified as "high risk."[9] While one study specified this method and they were classified as "low risk."[14]

Table 1. Characteristic of the included studies

Study	Participant		Interventions	Results
	N	Sex		
Binay 2009[11]	68	Both male and female	PTX vs. prednisolone	• The mortality rate of prednisolone group was higher than that of PTX at 3 months (35.3% vs. 14.7%; P=0.04). • PTX was associated with a significantly lower MELD score at the end of 28 d of therapy (15.5±3.6 vs.17.8±4.6;P=0.04).
Seung 2014[9]	121	Both male and female	PTX vs. prednisolone	• No difference for the 1-month survival rate of PTX and prednisolone (75.8% and 88.1%, respectively; P=0.08) • No difference for the 6-month survival rate between PTX compared with prednisolone (64.0% vs. 72.9%; P=0.23).
José 2012[12]	60	Both male and female	PTX vs. prednisolone	No difference for the 28-day mortality rate between PTX compared with prednisolone (46.7% vs. 60%; P=0.30).
Philippe 2013[15]	270	Both male and female	Prednisolone vs. prednisolone plus PTX	No difference at the 6-month survival rate between prednisolone compared prednisolone plus PTX (69.9% vs. 69.2%, P=0.91).
Sandeep 2012[14]	140	Only male	Prednisolone vs. prednisolone plus PTX	No difference between survival rate in prednisolone plus PTX vs. prednisolone at the 1 and 6 months (1 month 72.2% vs. 73.5%; P=1.00; 6 month 30.6% vs. 23.5%, P=0.417).
Binay 2014[16]	60	Both male and female	PTX vs. prednisolone plus PTX	No difference between mortality rate in PTX and prednisolone plus PTX in 3 month (16.7% vs. 30%, P =0.37) and 12 months (20% vs. 33.3%, P=0.32)
Mark 2015[13]	1,053	Both male and female	(i) PTX vs. prednisolone, (ii) Prednisolone vs. prednisolone plus PTX, and (iii) PTX vs. prednisolone plus PTX	At the 28-day mortality rate of placebo, PTX, prednisolone and prednisolone plus PTX was 17%, 19%, 14% and 13% • The odds ratio between PTX compared with no PTX was 1.07 (95% CI; 0.77 to 1.49; P=0.69). • The odds ratio between prednisolone compared with no prednisolone was 0.72 (95% CI, 0.52 to 1.01; P=0.06)

PTX= pentoxifylline

BLINDING

Four studies were undertaken on a double-blind study and they were classified as "low risk."[11,13,15,16] Two studies were not double-blind in the patients and physicians and they were classified as "high risk."[9,14] One study did not report details on blinding and they were classified as "unclear."[12]

SELECTIVE REPORTING

All included studies were classified as "low risk."[9,11,12-16]

INCOMPLETE OUTCOME DATA

Five studies were classified as "low risk."[9,11,14-16] One study was classified as "high risk."[13] One study

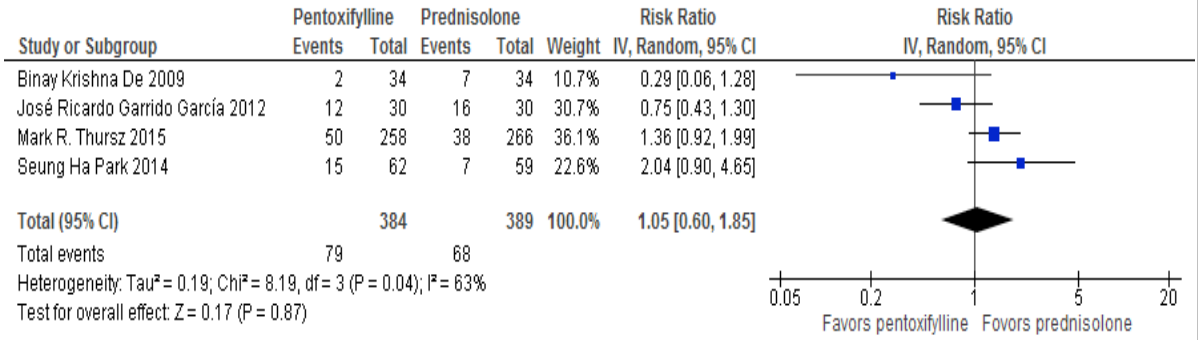

Figure 3. Forest plot of comparison prednisolone versus pentoxifylline, outcome: 28-day mortality

did not report detail on incomplete outcome data and they were classified as "unclear."[12]

OTHER POTENTIAL SOURCES OF BIAS

Three included studies were independent of the industry influence and they were classified as "low risk."[9,13,15] The remaining studies did not report other sources of bias and they were classified as "unclear."[11,12,14,16]

MORTALITY

PREDNISOLONE VS. PENTOXIFYLLINE

28-day mortality

Meta-analysis on data for 28 days mortality showed that pentoxifylline did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.05; 95% CI, 0.60 to 1.85, random-effect model) (Figure 3). The heterogeneity was measured as having I^2 equal to 63%.

These findings were also similar to our sensitivity analysis which suggested that pentoxifylline not significantly increase mortality rate in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.19; 95% CI, 0.56 to 2.51, random-effect model) (Figure S-1). The heterogeneity was measured as having I^2 equal to 61%.

PREDNISOLONE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

28-day mortality

The meta-analysis of 28 days mortality showed that prednisolone alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.07; 95% CI, 0.77 to 1.48, fixed-effect model) (Figure 4). The heterogeneity was measured as having I^2 equal to 0%.

6-month mortality

The meta-analysis of 6 months mortality showed that prednisolone alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR 1.14; 95% CI, 0.99 to 1.30, fixed-effect model) (Figure 4), The heterogeneity was measured as having I^2=0%.

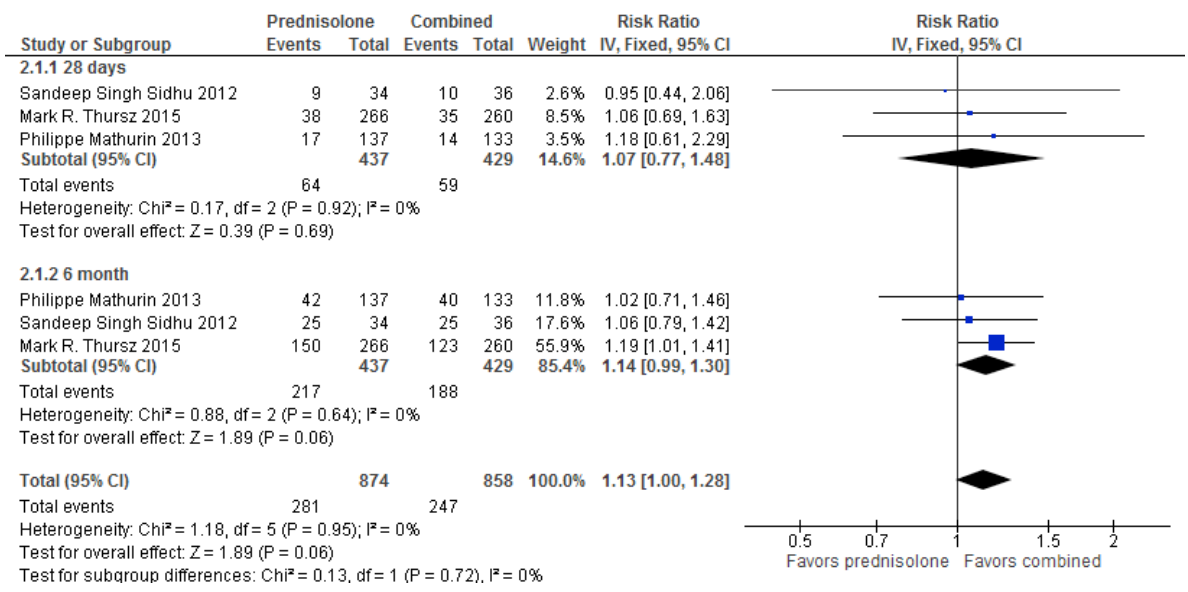

Figure 4. Forest plot of comparison prednisolone versus prednisolone plus pentoxifylline, outcome: 28-day and 6-month mortality

PENTOXIFYLLINE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

28-day mortality

The meta-analysis of 28 days mortality showed that pentoxifylline alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.47; 95% CI, 1.00 to 2.18, fixed-effect model) (Figure 5). The heterogeneity was measured as having I^2 equal to 0%.

1-year mortality

The meta-analysis of 1-year mortality showed that pentoxifylline alone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 0.99; 95% CI, 0.88 to 1.12, fixed-effect model) (Figure 5). The heterogeneity was measured as having I^2 equal to 23%.

ADVERSE REACTIONS

PREDNISOLONE VS. PENTOXIFYLLINE

Hepatorenal syndrome

The meta-analysis on data of hepatorenal syndrome showed that pentoxifylline did not significantly increase the rate of hepatorenal syndrome in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.75; 95% CI, 0.29 to 1.94, random-effect model) (Figure 6). The heterogeneity was measured as having I^2 equal to 52%.

This pattern was also observed in our sensitivity analysis suggested that pentoxifylline

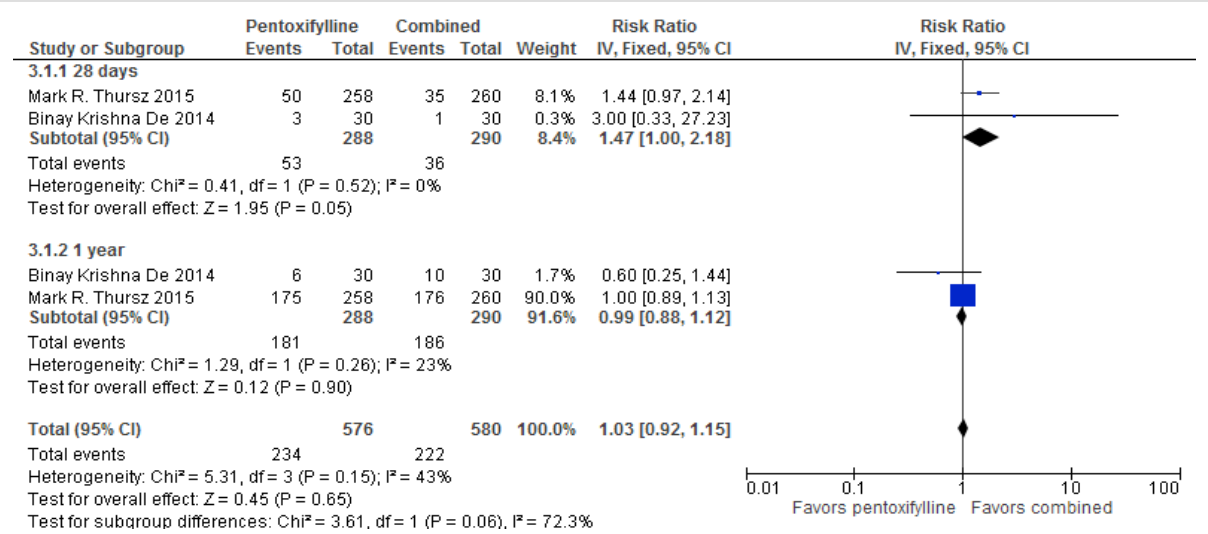

Figure 5. Forest plot of comparison pentoxifylline versus pentoxifylline plus prednisolone, outcome: 28-day and 1-year mortality

did not significantly increase the rate of hepatorenal syndrome in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.45; 95% CI, 0.03 to 7.44, random-effect model) (Figure S-2). The heterogeneity was measured as having I^2 equal to 73%.

Infection

Our meta-analysis showed that pentoxifylline did not significantly increase the rate of infection in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.55; 95% CI, 0.29 to 1.06, random-effect model) (Figure 6). The heterogeneity was measured as having I^2 equal to 64% but after we performed the sensitivity analysis, it suggested that pentoxifylline significantly reduced the rate of infection in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.38; 95% CI, 0.25 to 0.58, random-effect model, I^2 equal to 0% (Figure S-2).

Gastrointestinal bleed

Our meta-analysis showed that pentoxifylline did not significantly decrease the rate of gastrointestinal bleed in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.14; 95% CI, 0.65 to 2.00, random-effect model) (Figure 6). The heterogeneity was measured as having I^2 equal to 0%. This pattern was also observed in our sensitivity analysis suggested that pentoxifylline did not significantly increase the rate of gastrointestinal bleed in participants with severe alcoholic hepatitis compared to prednisolone (RR, 1.11; 95% CI, 0.60 to 2.05, random-effect model) (Figure S-2). The heterogeneity was measured as having I^2 equal to 0%.

Encephalopathy

Our meta-analysis showed that pentoxifylline did not significantly increase the rate of encephalopathy in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.72; 95% CI, 0.44 to 1.18, random-effect model)

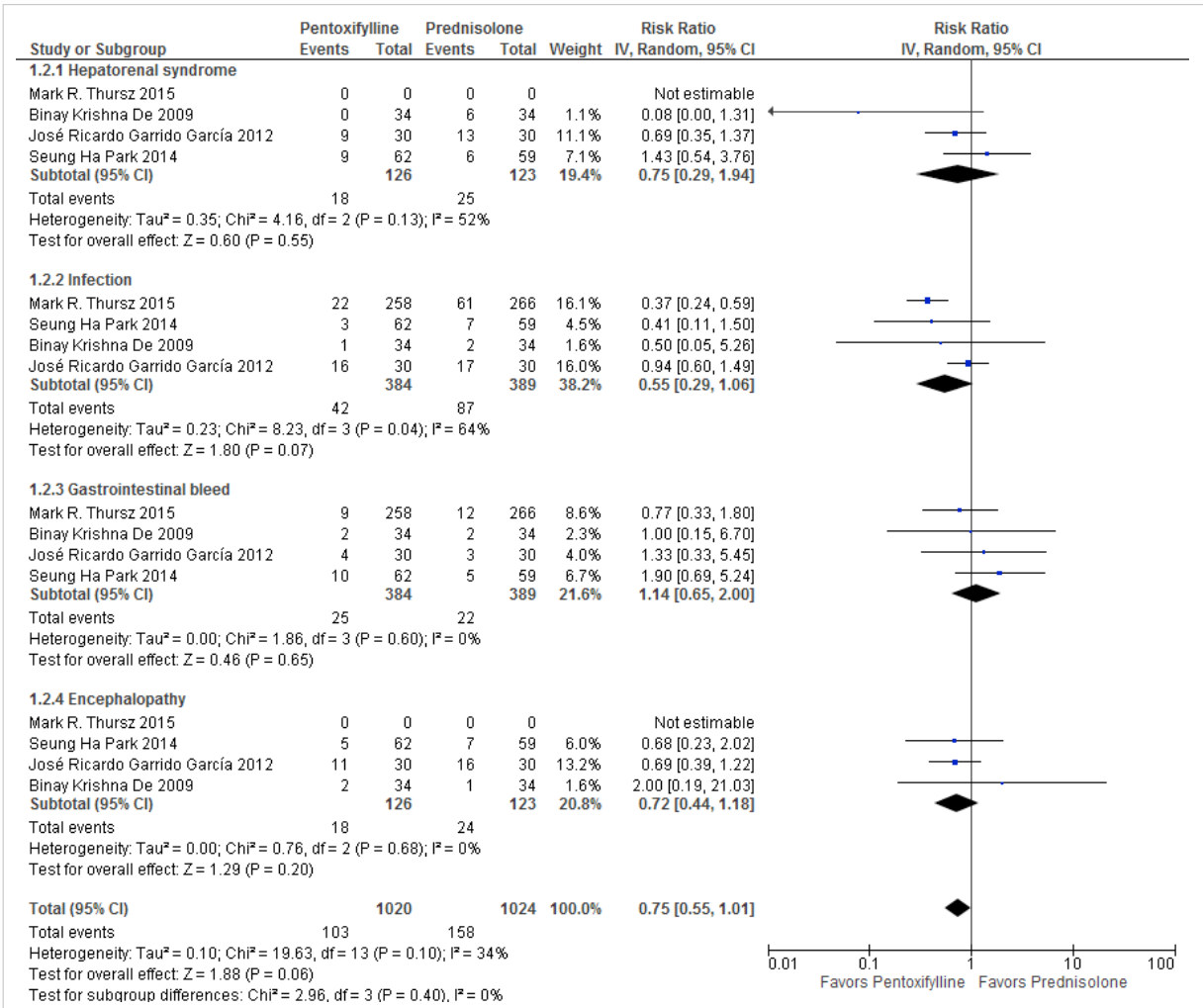

Figure 6. Forest plot of comparison prednisolone versus pentoxifylline, outcome: adverse effect

(Figure 6). The heterogeneity was measured as having I^2 equal to 0%. This pattern was also observed in our sensitivity analysis suggested that pentoxifylline did not significantly increase the rate of encephalopathy in participants with severe alcoholic hepatitis compared to prednisolone (RR, 0.82; 95% CI, 0.31 to 2.21, random-effect model) (Figure S-2). The heterogeneity was measured as having I^2 equal to 0%.

PREDNISOLONE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

Encephalopathy

Our meta-analysis showed that prednisolone did not significantly increase the mortality rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 1.57; 95% CI, 0.85 to 2.89, fixed-effect model, I^2=0%) (Figure 7).

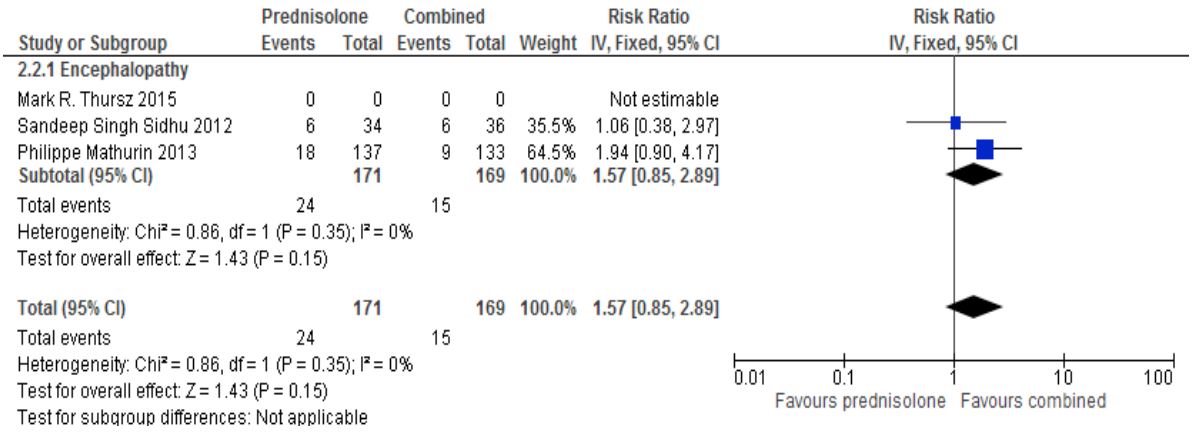

Figure 7. Forest plot of comparison prednisolone versus prednisolone plus pentoxifylline, outcome: adverse effect

PENTOXIFYLLINE VS. PREDNISOLONE PLUS PENTOXIFYLLINE

Gastrointestinal bleed

Our meta-analysis showed that pentoxifylline did not significantly decrease the rate of gastrointestinal bleeding in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR, 0.82; 95% CI, 0.40 to 1.69, fixed-effect model) (Figure 8), The heterogeneity was measured as having I^2 equal to 0%.

Infection

Our meta-analysis showed that pentoxifylline significantly decreased the infection rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline (RR 0.45; 95% CI, 0.28 to 0.72, fixed-effect model) (Figure 8). The heterogeneity was measured as having I^2 equal to 0%.

PUBLICATION BIAS

The funnel plots show symmetry in Figure S-3. Hence, we have no evidence to suggest publication bias in these analyses. The results should be considered with carefulness because the number of included studies in each group was relatively small.

DISCUSSION

PRINCIPAL FINDINGS

In our systematic review, a meta-analysis of seven RCTs, the primary outcome suggested that pentoxifylline did not reduce 28-day mortality compared to prednisolone. Prednisolone plus pentoxifylline did not reduce the 28-day and 6-month mortality compared to prednisolone alone and pentoxifylline plus prednisolone also did not reduce 28-day mortality compared to pentoxifylline alone.

For the secondary outcomes, hepatorenal syndrome, infection and encephalopathy were not found less common in pentoxifylline group than that of in prednisolone group. Pentoxifylline did not increase GI bleeding than prednisolone. The incidence of encephalopathy in prednisolone plus pentoxifylline group was not similar to that of

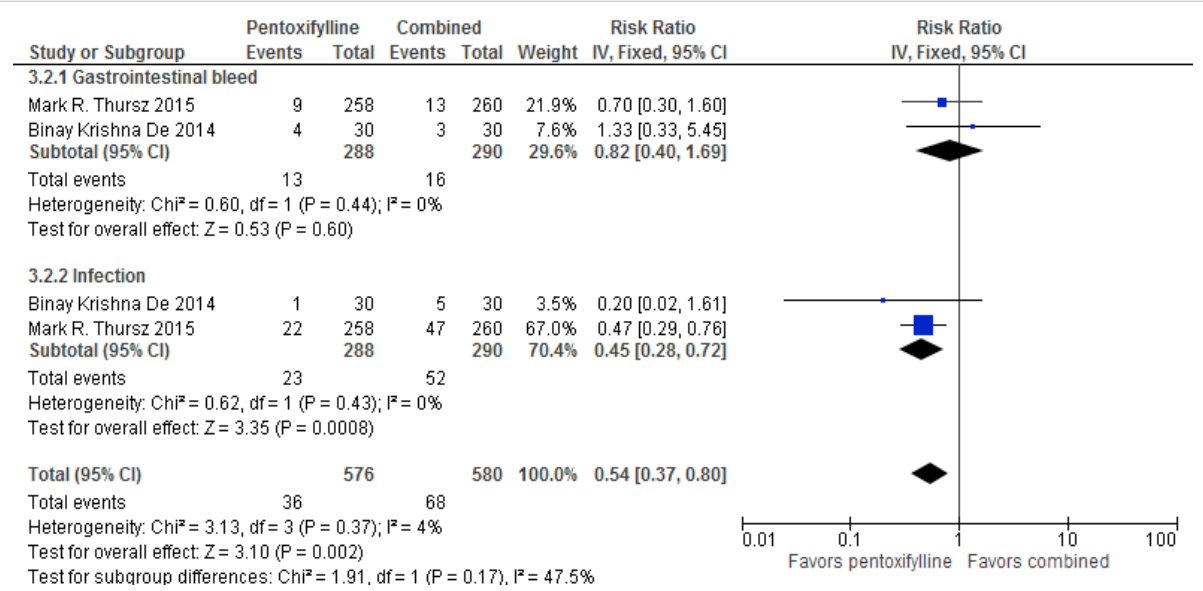

Figure 8. Forest plot of comparison pentoxifylline versus pentoxifylline plus prednisolone, outcome: adverse effect

prednisolone alone group, pentoxifylline alone caused less GI bleeding than pentoxifylline plus prednisolone. Pentoxifylline alone was significantly reduced the infection rate than that of pentoxifylline plus prednisolone.

COMPARISON WITH OTHER STUDIES

There have two meta-analysis[17,18] that compared pentoxifylline and placebo and showed that pentoxifylline had benefit in relation to mortality reduction from hepatorenal syndrome but not survival rate. Our systematic review, however, found no superiority of pentoxifylline over prednisolone because our study is the first systematic review included all RCTs relevant to three trials, pentoxifylline vs. prednisolone, prednisolone alone vs. prednisolone plus pentoxifylline and pentoxifylline alone vs. prednisolone plus pentoxifylline in the patient with severe alcoholic hepatitis.

LIMITATIONS OF THE REVIEW

This meta-analysis is based on the trials with limit sample sizes. Our pool effects of the interventions seemed to be similar, thus, we suggest to have another larger RCT to make the results more clearly. Another limitation of this systematic review is based on many included studies with unclear allocation concealment. We also suggest having a new RCT which free from selection bias.

CONCLUSION

For short-term treatment, there was no difference in 28 days mortality rate between pentoxifylline compared to prednisolone, prednisolone compared to prednisolone plus pentoxifylline and pentoxifylline compared to prednisolone plus pentoxifylline. For long-term treatment, there was also no difference between prednisolone compared to prednisolone plus pentoxifylline and pentoxifylline compared to prednisolone plus

pentoxifylline. For adverse effects between prednisolone compared to pentoxifylline there was no difference in the rates of hepatorenal syndrome, infection rate, gastrointestinal bleed, and encephalopathy but after we performed the sensitivity analysis it suggested that pentoxifylline significantly decreased infection rate in participants with severe alcoholic hepatitis compared to prednisolone. Comparing prednisolone to prednisolone plus pentoxifylline, there was no difference in encephalopathy. Pentoxifylline significantly decreased the infection rate in participants with severe alcoholic hepatitis compared to prednisolone plus pentoxifylline but not for the gastrointestinal bleeding rate. Conducting new RCT to see the precise effects of these various combinations of the interventions is still suggested.

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COMPETING INTERESTS: This study has no competing on interest.

FUNDING: None

REFERENCES

1. Singal AK, Kamath PS, Gores GJ, et al. Alcoholic hepatitis: current challenges and future directions. Clin Gastroenterol Hepatol. 2014;12:555–564
2. Neff GW, Duncan CW, Schiff ER. The current economic burden of cirrhosis. Gastroenterol Hepatol (N Y). 2011;7: 661–671.
3. Williams R. The pervading influence of alcoholic liver disease in hepatology. Alcohol Alcohol. 2008;43:393–397
4. Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000; 119:1637.
5. Mathurin P. Corticosteroids for alcoholic hepatitis–what's next? J Hepatol. 2005;43:526–533.
6. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med. 2009;360:2758–2769.
7. Taieb J, Mathurin P, Elbim C, et al. Blood neutrophil functions and cytokine release in severe alcoholic hepatitis: effect of corticosteroids. J Hepatol. 2000;32:579–586.
8. Han J, Thompson P, Beutler B. Dexamethasone and pentoxifylline inhibit endotoxin-induced cachectin/tumor necrosis factor synthesis at separate points in the signaling pathway. J Exp Med. 1990;172:391–394.
9. Park SH, Kim DJ, Kim YS, et al. Pentoxifylline vs corticosteroid to treat severe alcoholic hepatitis: a randomised, non-inferiority, open trial. J Hepatol 2014; 61:792.
10. Sidhu SS, Goyal O, Singla M, et al. Pentoxifylline in severe alcoholic hepatitis: a prospective randomized trial. Trop Gastroenterol. 2009;30:S21–S22.
11. De BK, Gangopadhyay S, Dutta D, et al. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World J Gastroenterol. 2009;15:1613–1619.
12. Garcõa JRG, Hernandez GS, Lopez AM, et al. Pentoxifilina versus esteroide en la sobrevivencia a corto plazo en hepatitis aguda alcoholica severa. Medicina Interna de Mexico 2012; 28: 228.
13. M.R. Thursz et al. Prednisolone or Pentoxifylline for Alcoholic Hepatitis. N Engl J Med 2015;372:1619-28.
14. Sidhu SS, Goyal O, Singla P, et al. Corticosteroid plus pentoxifylline is not better than corticosteroid alone for improving survival in severe alcoholic hepatitis (COPE trial). Dig Dis Sci 2012; 57: 1664–71.
15. Mathurin P, Louvet A, Duhamel A, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. JAMA 2013; 310:1033.
16. De B, Mandal S, Sau D et al. Pentoxifylline Plus Prednisolone versus Pentoxifylline Only for Severe Alcoholic Hepatitis: A Randomized Controlled Clinical Trial. Annals of Medical & Health Sciences Research 4:810-816.
17. Whitfield K, Rambaldi A, Wetterslev J, Gluud C. Pentoxifylline for alcoholic hepatitis. Cochrane Database Syst Rev 2009; 4: CD007339.
18. Parker R, Armstrong MJ, Corbett C, Rowe IA, Houlihan DD. Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther 2013; 37: 845-54.

SUPPLEMENT FIGURES & TABLES

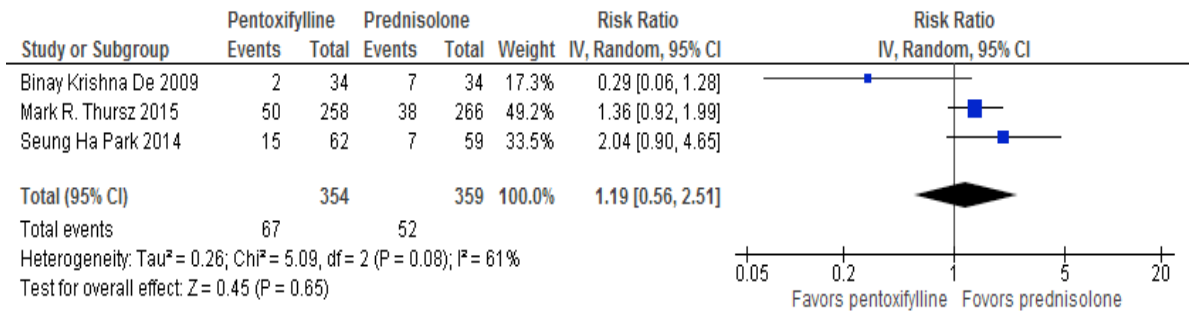

Figure S-1. Forest plot of comparison prednisolone versus pentoxifylline, outcome: 28-day mortality (sensitivity analysis)

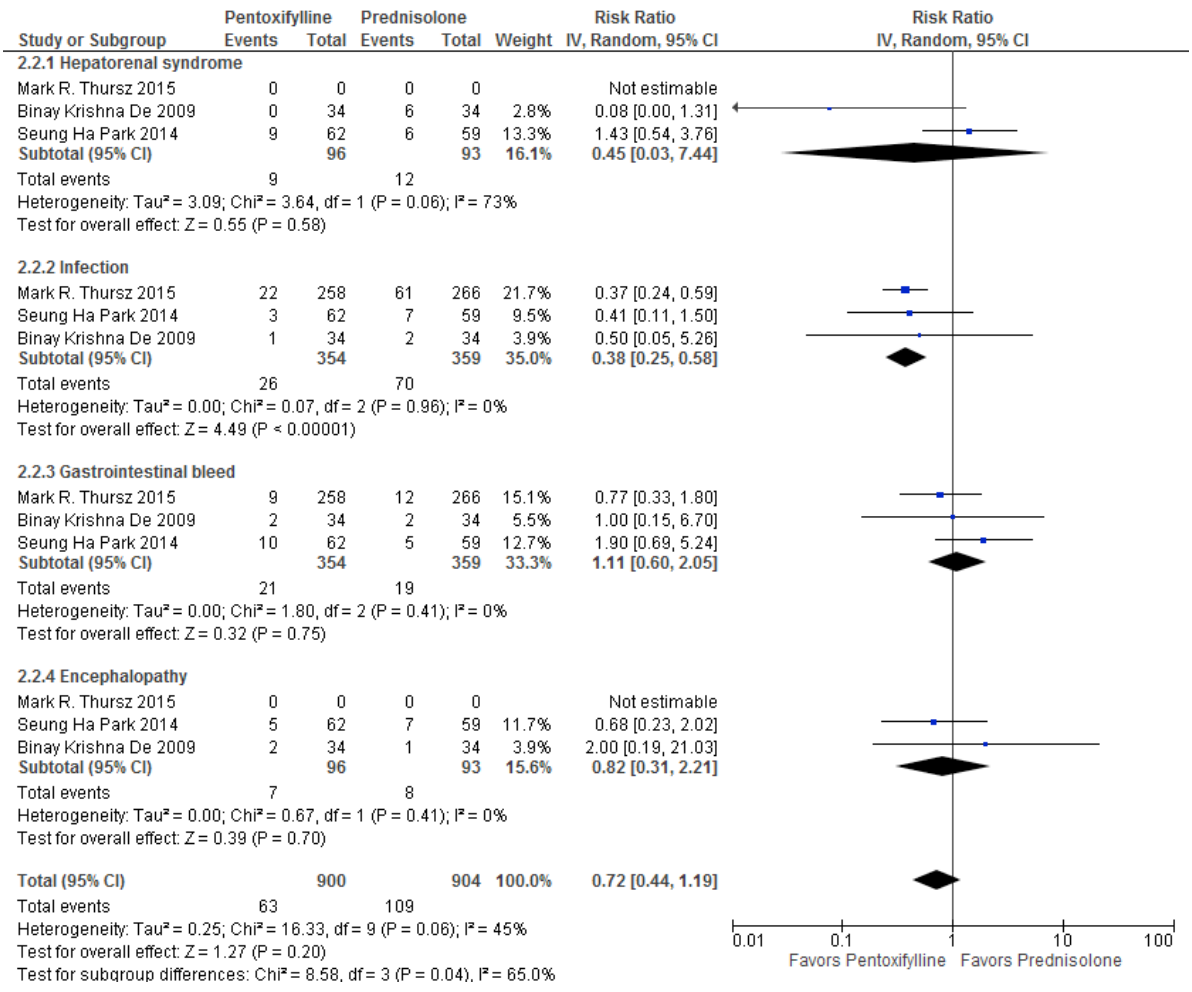

Figure S-2. Forest plot of comparison prednisolone versus pentoxifylline, outcome: adverse effect (sensitivity analysis)

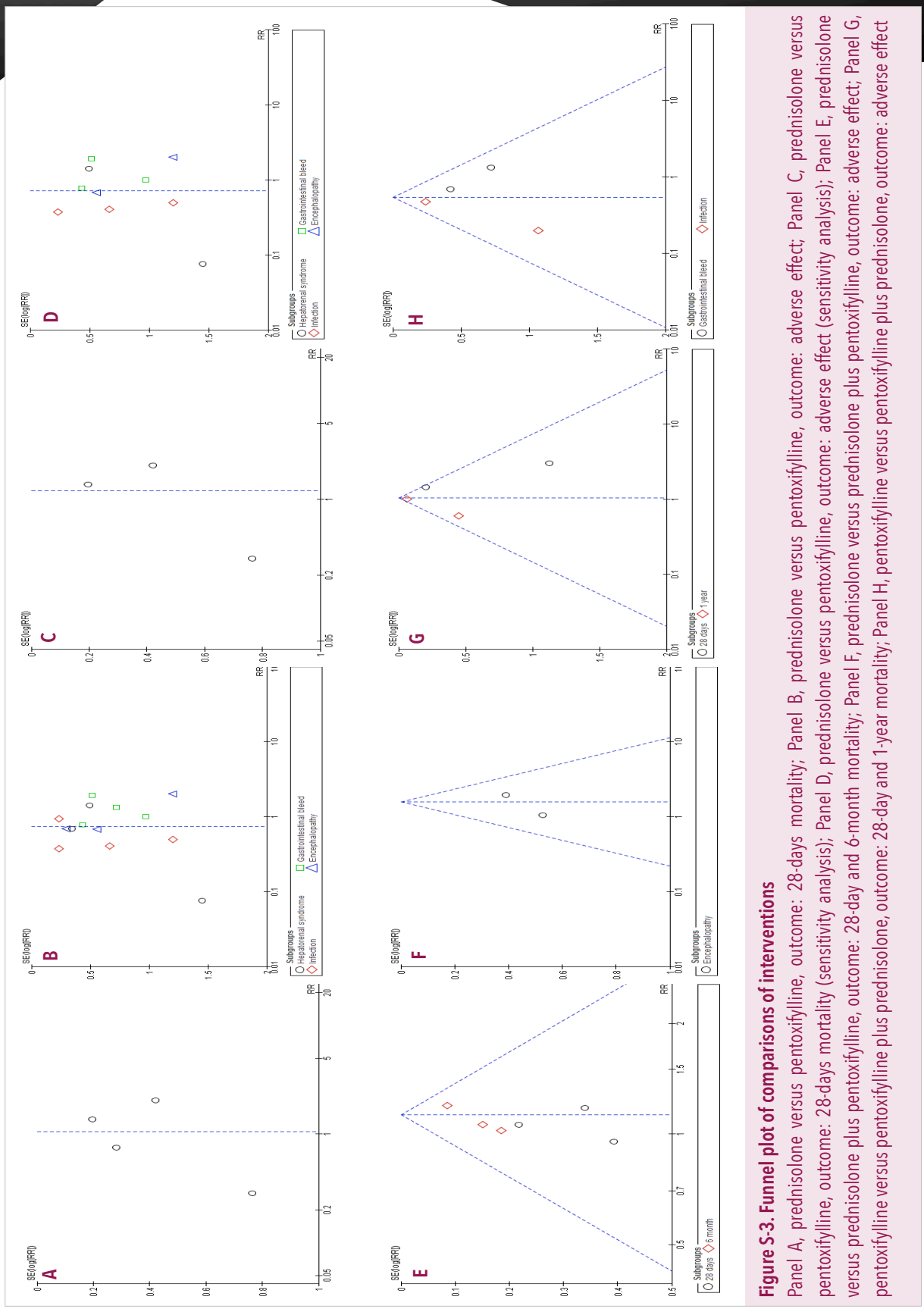

Figure S-3. Funnel plot of comparisons of interventions

Panel A, prednisolone versus pentoxifylline, outcome: 28-days mortality; Panel B, prednisolone versus pentoxifylline, outcome: adverse effect; Panel C, prednisolone versus pentoxifylline, outcome: 28-days mortality (sensitivity analysis); Panel D, prednisolone versus pentoxifylline, outcome: adverse effect (sensitivity analysis); Panel E, prednisolone versus prednisolone plus pentoxifylline, outcome: 28-day and 6-month mortality; Panel F, prednisolone versus prednisolone plus pentoxifylline, outcome: adverse effect; Panel G, pentoxifylline versus pentoxifylline plus prednisolone, outcome: 28-day and 1-year mortality; Panel H, pentoxifylline versus pentoxifylline plus prednisolone, outcome: adverse effect