Outcomes in meningitis-ventriculitis treated with intravenous or intrathecal plus intravenous colistin: A meta-analysis

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Abstract. The aim of the present meta-analysis was to provide further evidence on the management of bacterial ventriculitis or meningitis (BVM) and to compare the efficacy of intravenous (IV) or intravenous plus intrathecal (IV/ITH) treatment with colistin. The present meta-analysis included full-text articles published between 1980 and 2020 that compared outcomes in meningitis-ventriculitis treated with IV or IV/ITH colistin. The collected variables included the first author's name, country, study period covered, publication year, the total number of patients and follow-up, Glasgow Coma Scale score upon admission, treatment duration, Acute Physiological and Chronic Health Evaluation II score, the length of intensive unit (ICU) stay, treatment efficacy and mortality for both groups. To avoid publication bias, the final aim was to collect a homogenous pool of manuscripts, including only articles that compared only two modalities. After applying all exclusion and inclusion criteria, seven of 55 articles were left in the final article pool. The total number of patients in those seven articles was 293, divided into two groups (186 in the IV and 107 in the IV/ITH group). As regards ICU stay and mortality, the findings illustrated a statistically significant difference between the two groups. On the whole, the findings of the present study support the addition of ITH colistin to its IV administration for the effective treatment of BVM.

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Key words: meningitis-ventriculitis, intravenous, intraventricular plus intravenous, colistin, multi-drug resistant bacteria

Introduction

Bacterial ventriculitis or meningitis (BVM) is a comparatively unusual, yet life-threatening complication that often follows the treatment of acute hydrocephalus with external ventricular drainage (EVD) (1). The prevalence of BVM ranges between 1 and 18% (2-5), and the diagnosis is frequently difficult to establish due to its often insidious onset and uncommon symptoms (1).

BVM may be caused by Gram-negative (GRn) or Gram-positive (GRp) bacteria. Still, there is a predominance in more recent years of GRn infections (6,7), and considering Gram-negative multi-drug resistant (GRn-MDR) bacteria, BVM is associated with severe underlying disease and a worse prognosis (8).

The mortality rate among patients with GRn bacteria ventriculitis or meningitis (GRn-BVM) has been 8-70% (1-8). Furthermore, the most commonly identified microbes (98%) of GRn are *Pseudomonas aeruginosa* and *Acinetobacter baumannii* MDR, which demonstrate resistance in antibiotic classes and are considered to be selective mediators for central nervous system (CNS) infections, such as carbapenems. On this basis, older therapeutic agents, such as colistin are being researched again as a potential treatment (9).

Due to the poor infiltration of colistin in the CNS, with ~10% of its concentration in serum even when meninges are contaminated, the intrathecal (ITH) use of colistin has been proposed as an alternative therapy to the intravenous (IV) administration for disease management (10,11).

In the present meta-analysis, the authors aimed to provide further evidence on the management of BVM compared to the efficacy of IV or IV plus IT (IV/ITH) treatment with colistin.

Data and methods

Literature search strategy. The study searched the comparative articles involving IV and IV/ITH colistin treatment in patients with meningitis or ventriculitis through electronic databases, including the Cochrane Library, Medline (1983-August, 2020), PubMed (1983-August, 2020), and EMBASE (1983-August, 2020). Preferred reporting items for systematic reviews and meta-analyses (PRISMA) were applied for establishing protocol and manuscript design (12). The key words 'meningitis', 'intravenous intraventricular antibiotics' and 'intrathecal colistin' were used in the MeSH list.

Procedures. The intrathecal infusion of colistimethate sodium was administered in a standard manner through an EVD system at a mean dose of 170,000±400 IU (range, 50,000-250,000 IU) or (13.6±0.03 mg), which was then closed for 1 h.

Inclusion and exclusion criteria. The literature was included in the present meta-analysis if the article met the following criteria, as determined by PICOS: i) Population: Limited to patients with meningitis or ventriculitis; ii) intervention: For meningitis and ventriculitis, the IV-strict and IV/ITH-colistin treatments were used; iii) comparison: The outcomes were compared; iv) outcome measures: One of the primary outcomes, such as the Glasgow Coma Scale (GCS) score upon admission, treatment duration, Acute Physiological and Chronic Health Evaluation II (APACHE II), the length of intensive unit (ICU) stay, treatment efficacy and mortality, were all included. To avoid publication bias, the final aim was to collect a homogenous pool of manuscripts, including only articles that compare only two modalities. The articles that were excluded were editorials, reviews, case reports, articles focusing on the pediatric population, comorbidities, unrelated outcomes, experimental techniques, or one of the two treatment modalities, and all those that demonstrated mixed or unclear results, being separated between IV and IV/ITH treatment.

Data extraction and outcome definition. Two of the authors (GF and VEG) independently extracted data from the included articles, following the guidelines of the epidemiology of meta-analysis. The following essential information was captured: The main authors, year of publication, total case number in the IV and IV/ITH groups, study type, outcome indicator, etc. The extracted data were input into a designed, standardized Table according to the Cochrane Handbook (https://training.cochrane.org/handbook). When there was disagreement, another author with authority made the final decision.

Data regarding one of the primary outcomes, including treatment efficacy [patients discharged from the ICU who had three negative cerebrospinal fluid (CSF) CSF or blood cultures]; length of ICU stay, mortality, treatment duration, the GCS score upon admission and the severity of the clinical condition according to the APACHE II scoring system were retrieved from patients' records and documented. The APACHE II score is a severity-of-disease classification system that is applied within 24 h of a patient's admission: An integer score from 0 to 71 is calculated based on numerous measurements; higher scores correspond to more severe disease and a higher risk of mortality (6). Post-operative outcomes mentioned in the included articles were evaluated at least 6 months following treatment (IV or IV/ITH). Additionally, in order to decrease the risk of bias in the articles, a quality assessment tool (the Newcastle-Ottawa Scale) was utilized Table I (13). Additionally, the patients were divided into two groups as follows: Those receiving therapy with IV colistin (IV group) and those receiving therapy with IV/ITH colistin (IV/ITH group).

Statistical analysis. All analyses were carried out using STATA, version 16 (Stata Corporation, College Station, TX, USA). Heterogeneity across trials was assessed using I^2 statistics; considering I^2 >50% as high heterogeneity, a meta-analysis was performed using a random-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). Otherwise, the fixed-effect model was performed. The continuous outcomes (GCS of admission, APACHE II) were expressed as a weighted mean difference with 95% confidence intervals (CIs). For discontinuous variables (treatment duration, ICU stay, cure rate and mortality), odds ratios (ORs) with 95% CIs were applied for the assessment. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

Studies in the final pool. Following the initial search, 14 articles were eligible for further analysis. Applying all exclusion and inclusion criteria, seven articles remained in the final article pool (Fig. 1) (11,14-19). The detailed data on these articles are presented in Table II. The total number of patients included in these seven articles was 293 (186 in the IV group and 107 in the IV/ITH group).

GCS score at admission. In total, three articles (11,14,17) provided information on GCS at the time of admission. In the total group of patients, there were 89 patients: 41 in the IV group and 48 in the IV/ITH group. The pooled results demonstrated no statistically significant difference between the IV and IV/ITH groups [OR, 0.05; 95% CI, -0.69 to 0.79; P=0.89] with a low heterogeneity (P=0.55 and I^2=-65.86%) (Fig. 2).

Treatment duration. Information regarding treatment duration was available in five articles (11,15,16,18,19). There were 238 patients (156 in the IV group and 82 in the IV/ITH group), and there was no statistically significant difference between treatments (OR, -0.30; 95% CI, -0.76 to 0.15; P=0.19); however, there was heterogeneity (P=0.05 and I^2=74.51%) (Fig. 3A). While evaluating the sensitivity, one study was removed at a time. After removing the article by Wang *et al* (2012) (18), there was additionally no statistically significant superiority over the groups (OR, 0.17; 95% CI, -0.37 to 0.70; P=0.55), with no heterogeneity (P=0.60 and I^2=-62.32%) (Fig. 3B). When examining the funnel plot of the same parameter, it was observed that the study results without the study by

Table I. Newcastle-Ottawa scale quality assessment of the final article pool.

		Newcastle-Ottawa scale				
Trial, year	Study design	Selection	Comparability	Exposure	Total scores	(Refs.)
Chusri *et al*, 2018	Retrospective	3	3	3	9	(14)
Fotakopoulos *et al*, 2016	Retrospective	3	3	3	6	(11)
Shoftly *et al*, 2015	Retrospective	3	3	3	9	(15)
De Bonis *et al*, 2015	Retrospective	3	2	2	7	(16)
Moon *et al*, 2013	Retrospective	3	2	2	7	(17)
Wang *et al*, 2012	Retrospective	3	3	3	9	(18)
Tangden *et al*, 2011	Retrospective	3	3	3	9	(19)

IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group.

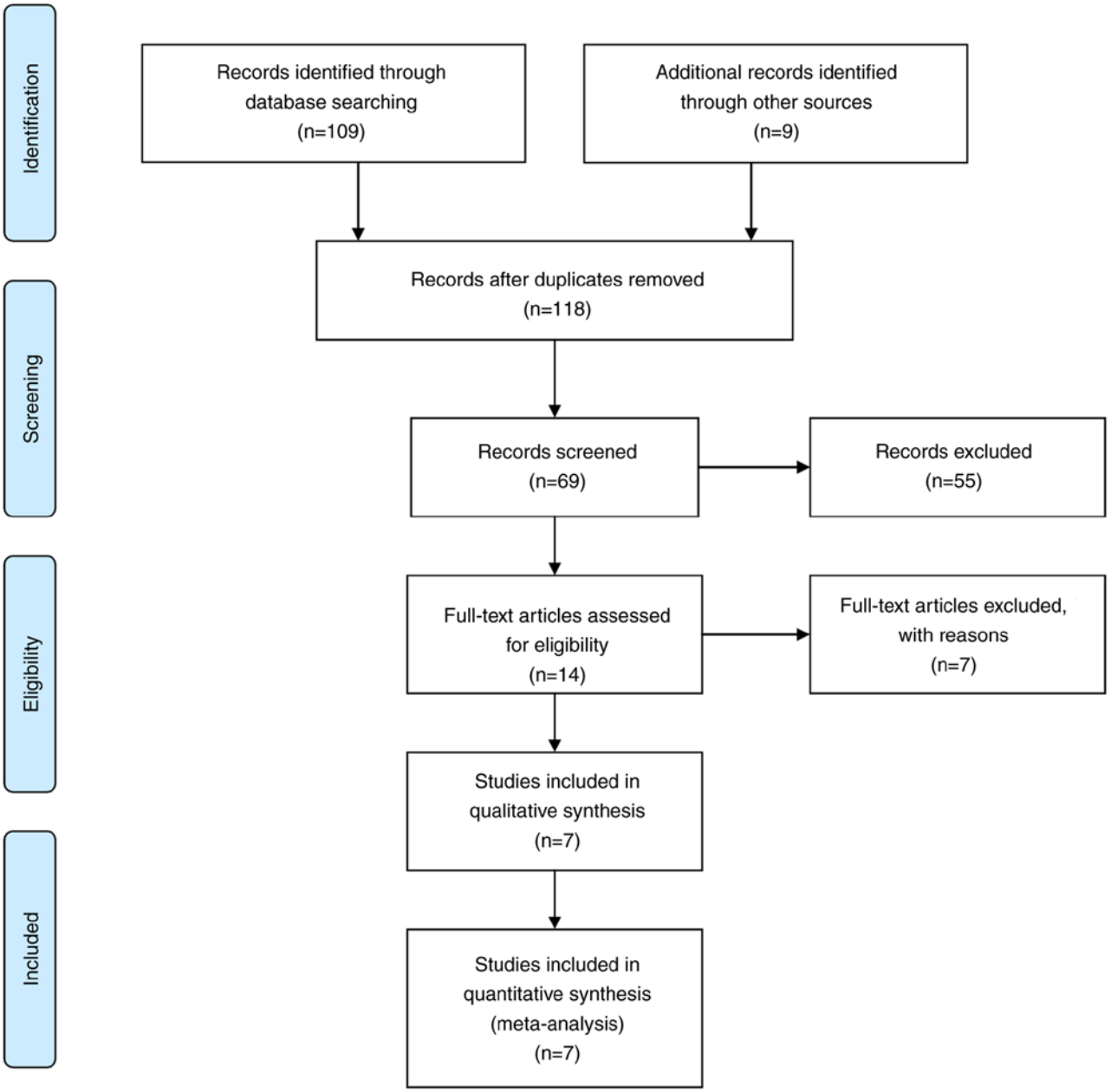

Figure 1. Flowchart of the study selection process.

Table II. Design and baseline characteristics of the included study trials.

	Sample size		Mean age (years)		No.of males		GCS at admission		Colistin dose		Treatment duration (days)		APACHE II		Duration of ICU stay (days)		Cured		Mortality		
Trial, year	IV	IV/ITH	IV	IV/ITH	IV	IV/ITH	IV	IV/ITH	IV (mg)	IV/ITH (UI)	IV	IV/ITH	IV	V/ITH	IV	V/ITH	IV	V/ITH	IV	V/ITH	(Refs)
Chusri *et al*, 2018	17	16	42	42	10	9	8	9	NR	175,000	-	-	15	15	11	3	8	11	9	5	(14)
Fotakopoulos *et al*,2016	11	23	44.5	53.5	5	8	7	8	9	20,000	16	16	15	16	41	20	3	20	8	3	(11)
Shoftly *et al*, 2015	27	23	55	49.1	16	15	-	-	NR	50,000	9	9	-	-	-	-	18	21	9	2	(15)
De Bonis *et al*, 2015	9	9	52	52	5	5	-	-	240	30,000	26	26	-	-	41	20	2	6	7	3	(16)
Moon *et al*, 2013	13	9	56	56	9	6	5	5	240	300,000	-	-	-	-	-	-	11	3	2	6	(17)
Wang *et al*, 2012	95	14	53.8	48.9	62	10	-	-	NR	NR	13	13	13	13	-	-	61	10	34	4	(18)
Tangden *et al*, 2011	14	13	54	49	-	-	-	-	NR	80,000	8	8	-	-	-	-	15	10	3	3	(19)

IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group, APACHE II, Acute Physiological and Chronic Health Evaluation II; ICU, intensive care unit; NR, not reported.

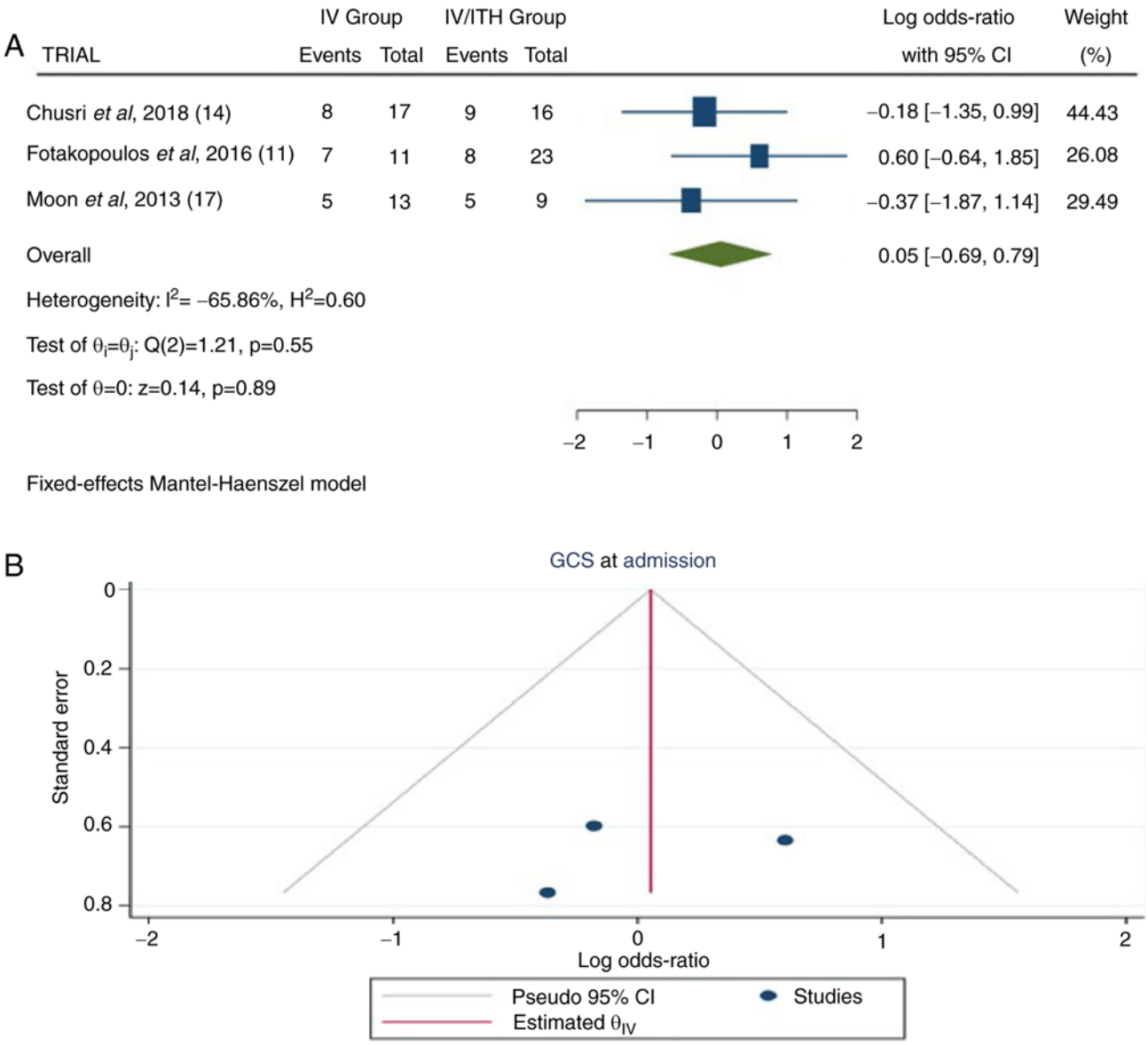

Figure 2. (A) Forest plot GCS of admission. The results demonstrated no statistically significant difference between the IV and IV/ITH group (OR, 0.05; 95% CI, -0.69 to 0.79; P=0.89). (B) Funnel plot, testing the sensitivity for GCS of admission; there was no statistically significant superiority between groups, with no heterogeneity (P=0.55 and I^2=-65.86%). IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; GCS, Glasgow Coma Scale.

Wang *et al* (2012) (18) exhibited better dispersion, with no publication bias, in contrast to the same analysis including this article (Fig. 3C and D). This was expected as the patients in the study by Wang *et al* (18) represented 45.7% (109/238) of the patients in the included articles.

APACHE II score. Information regarding APACHE II scores was available in three articles (11,14,18). There were 176 patients (123 in the IV group and 53 in the IV/ITH group), with no statistically significant difference between treatments (OR, -0.42; 95% CI, -0.96 to 0.12; P=0.13); however, there was heterogeneity (P=0.05 and I^2=86.23%) (Fig. 4A). While evaluating the sensitivity, one study was removed at a time. After removing the study by Wang *et al* (2012) (18), there was no statistically significant superiority over the groups (OR, 0.30; 95% CI, -0.40 to 1.00; P=0.40), with no heterogeneity (P=0.31 and I^2=3.73%) (Fig. 4B). When examining the funnel plot of the same parameter, it was observed that the results without the study by Wang *et al* (2012) (18) exhibited better dispersion with no publication bias, in contrast with the same analysis including this article (Fig. 4C and D). This was expected, given that in the study by Wang *et al* (18), the patients accounted for 61.9% (109/176) of all patients.

Length/duration of stay in ICU. Information regarding the duration of ICU stay was available in three articles (11,14,16). In the total group of patients, there were 95 patients, 37 in the IV group and 48 in the IV/ITH group. The pooled results demonstrated a statistically significant difference between the IV and IV/ITH groups (OR, 1.17; 95% CI, 0.56 to 1.79; P<0.05] with no heterogeneity (P=0.58 and I^2=-83.76%) (Fig. 5).

Cure rate. Information on cure rate was available in seven articles (11,14-19). In the total group of patients, there were 293 patients: 186 in the IV group and 107 in the IV/ITH group.

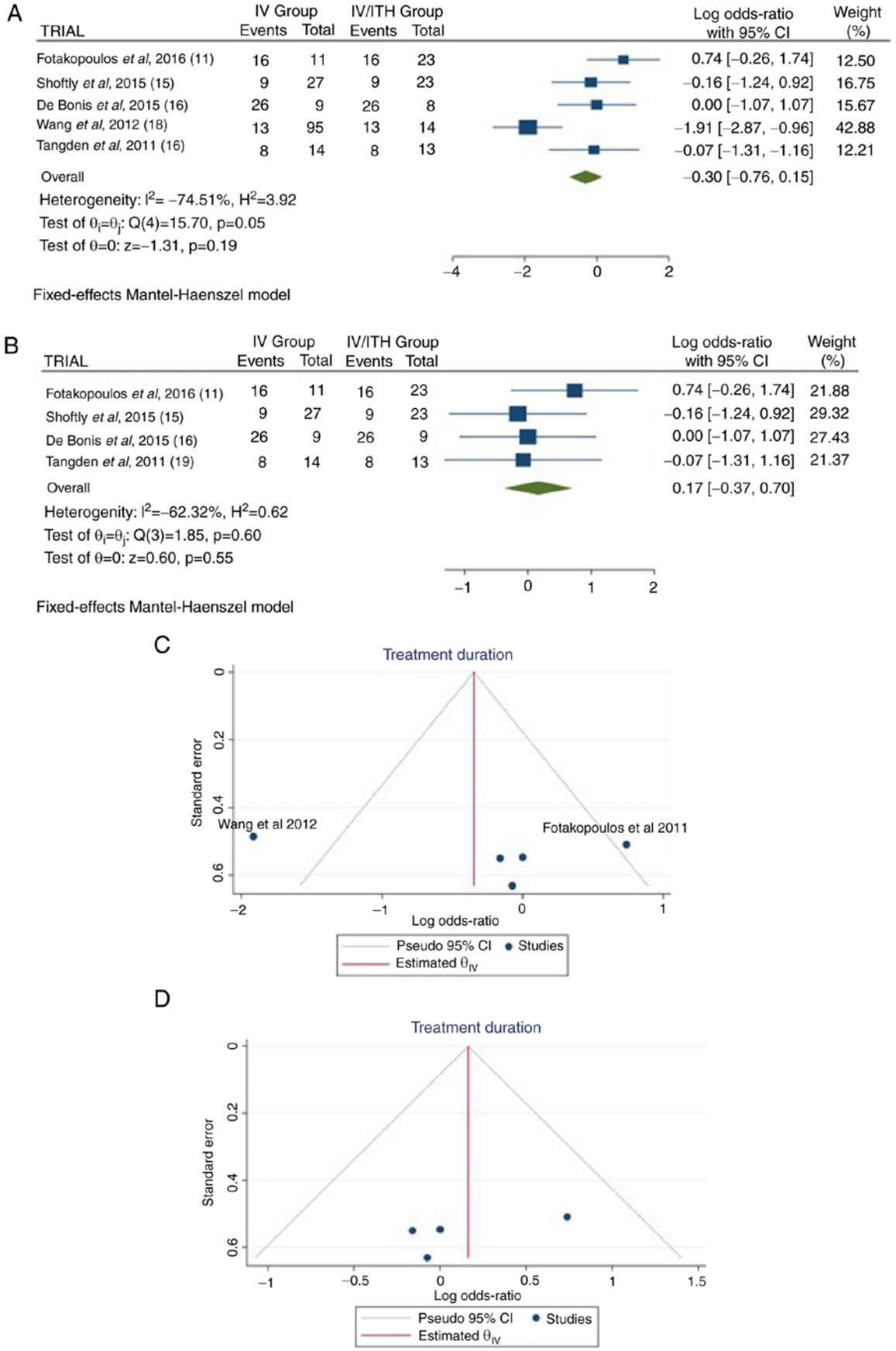

Figure 3. (A) Forest plot for treatment duration. The results demonstrated no statistically significant difference between the two groups (OR, -0.30; 95% CI, -0.76 to 0.15; P=0.19), but with heterogeneity (P=0.05 and I^2=74.51%). (B) Forest plot for treatment duration without the study by Wang *et al* (2012) (18). The results demonstrated an additionally no statistically significant difference between the two groups (OR, 0.17; 95% CI, -0.37 to 0.70; P=0.55). (C and D) Funnel plots for treatment duration in the groups, with (left) or without (right) the study by Wang *et al* (2012) (18), and with a high (left) heterogeneity (P=0.01 and I^2=74.51%) or with no (right) heterogeneity (P=0.60 and I^2=-62.32%). IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group; I^2, percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

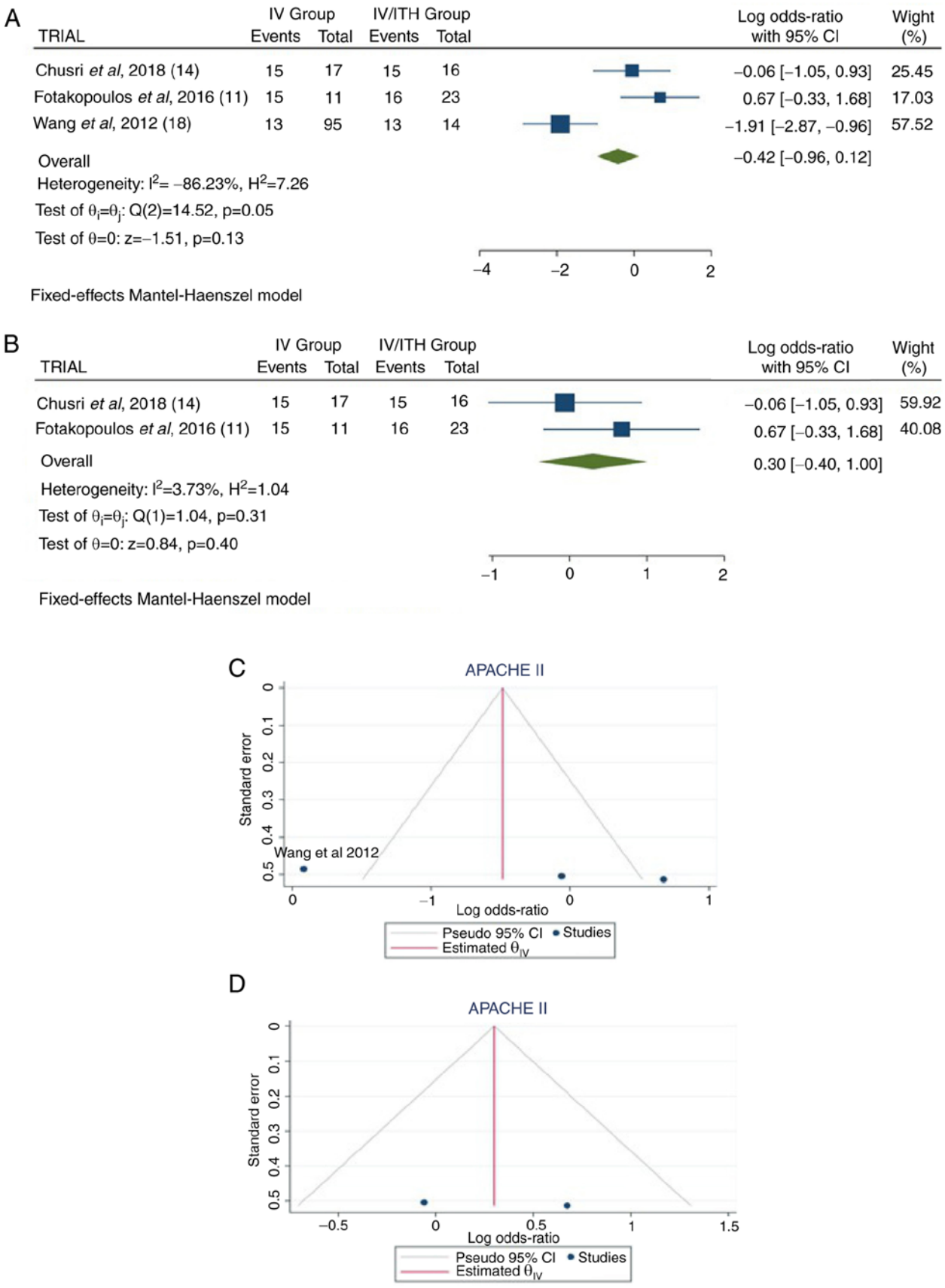

Figure 4. (A) Forest plot for APACHE II. The results demonstrated no statistically significant difference between the two groups (OR, -0.42; 95% CI, -0.96 to 0.12; P=0.13), but with heterogeneity (P=0.05 and I^2=86.23%). (B) Forest plot for APACHE II without the study by Wang *et al* (2012) (18). The results demonstrated an additionally no statistically significant difference between the two groups (OR, 0.30; 95% CI, -0.40 to 1.00; P=0.40); (C and D) Funnel plots for APACHE II in the groups, with (left) or without (right) the study by Wang *et al* (2012) (18), and with high (left) heterogeneity (P=0.05 and I^2=86.23%) or with no (right) heterogeneity (P=0.31 and I^2=3.73%). IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; APACHE II, Acute Physiological and Chronic Health Evaluation II.

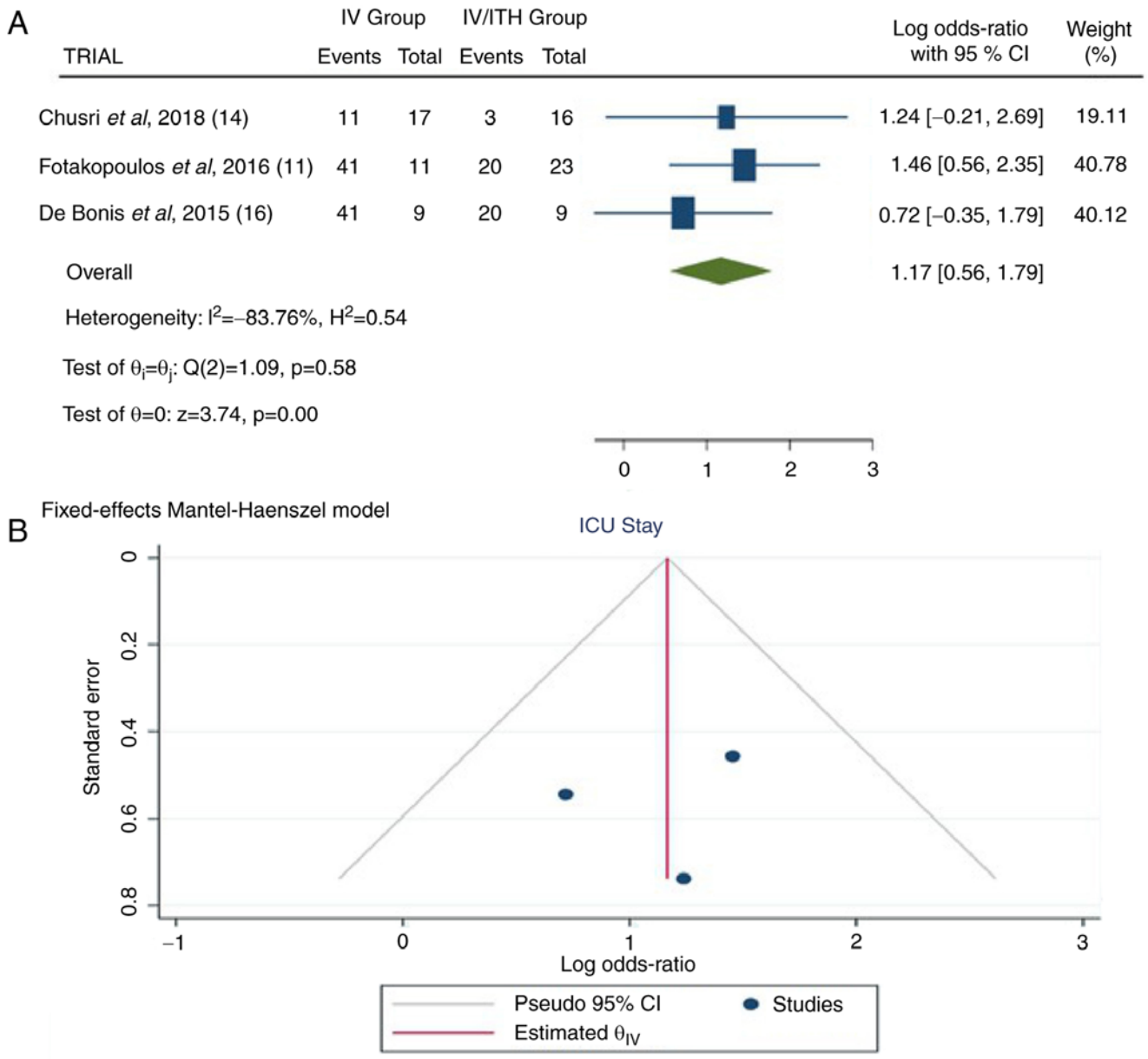

Figure 5. (A) Forest plot for duration of stay in ICU. The results demonstrated a statistically significant difference between the IV and IV/ITH groups (OR, 1.17; 95% CI, 0.56 to 1.79; P<0.05). (B) Funnel plot, testing the sensitivity with funnel plot for length of stay in the ICU. There was a statistically significant superiority between the groups, with no heterogeneity (P=0.58 and I^2=-83.76%). ICU, intensive care unit; IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

The combined results revealed no statistically significant difference between the IV and IV/ITH groups (OR, -0.21; 95% CI, -0.62 to 0.20; and P=0.32), as well as no heterogeneity (P=0.44 and I^2=-1.93%) (Fig. 6).

Mortality rate. Information was available in seven articles (11,14-19). In the total group of patients, there were 293 patients, 186 from the IV group and 107 from the IV/ITH group, showing a statistically significant difference between the IV and IV/ITH groups (OR, 0.50; 95% CI, -1.04 to 1.03; P=0.05) with very low heterogeneity (P=0.18 and I^2=32.17% (Fig. 7).

A summary of the results of the present meta-analysis is presented in Table III.

Discussion

The present meta-analysis suggests that IV/ITH colistin administration is associated with the increased survival of patients with BVM caused by GRn-MDR bacteria compared to those treated with IV colistin alone. More precisely, the length of stay in the ICU was a statistically significant parameter in patients with BVM treated with colistin, exhibiting the superiority of IV/ITH over IV colistin administration. In addition, mortality was also another statistically significant factor, demonstrating the advantage of IV/ITH colistin management more than the IV treatment alone. The findings of the present meta-analysis indicate that this treatment may benefit the management of GRn-MDR CNS infections.

Table III. A summary of the results of the present meta-analysis.

		Groups		Overall effect			Heterogeneity	
Outcomes	Trial, n=7	IV	IV/ITH	Effect estimate	95% CI	P-value	I^2 (%)	P-value
GCS at admission	3	41	48	0.50	-0.69 to 0.79	0.89	-65.86	0.55
Treatment duration (days)	5	203	82	0.17	-0.37 to 0.70	0.55	-62.32	0.60
APACHE II	3	123	53	0.30	-0.40 to 1.00	0.40	3.73	0.31
Duration of ICU stay (days)	3	37	48	1.17	0.56 to 1.79	**0.01**	-83.76	0.58
Cured	7	186	107	-0.21	-0.62 to 0.20	0.32	-1.93	0.44
Mortality	7	186	107	0.50	-0.04 to 1.03	**0.05**	32.17	0.18

IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group; APACHE II, Acute Physiological and Chronic Health Evaluation II; ICU, intensive care unit; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; GCS, Glasgow Coma scale. Data in bold font indicate a statistically significant difference.

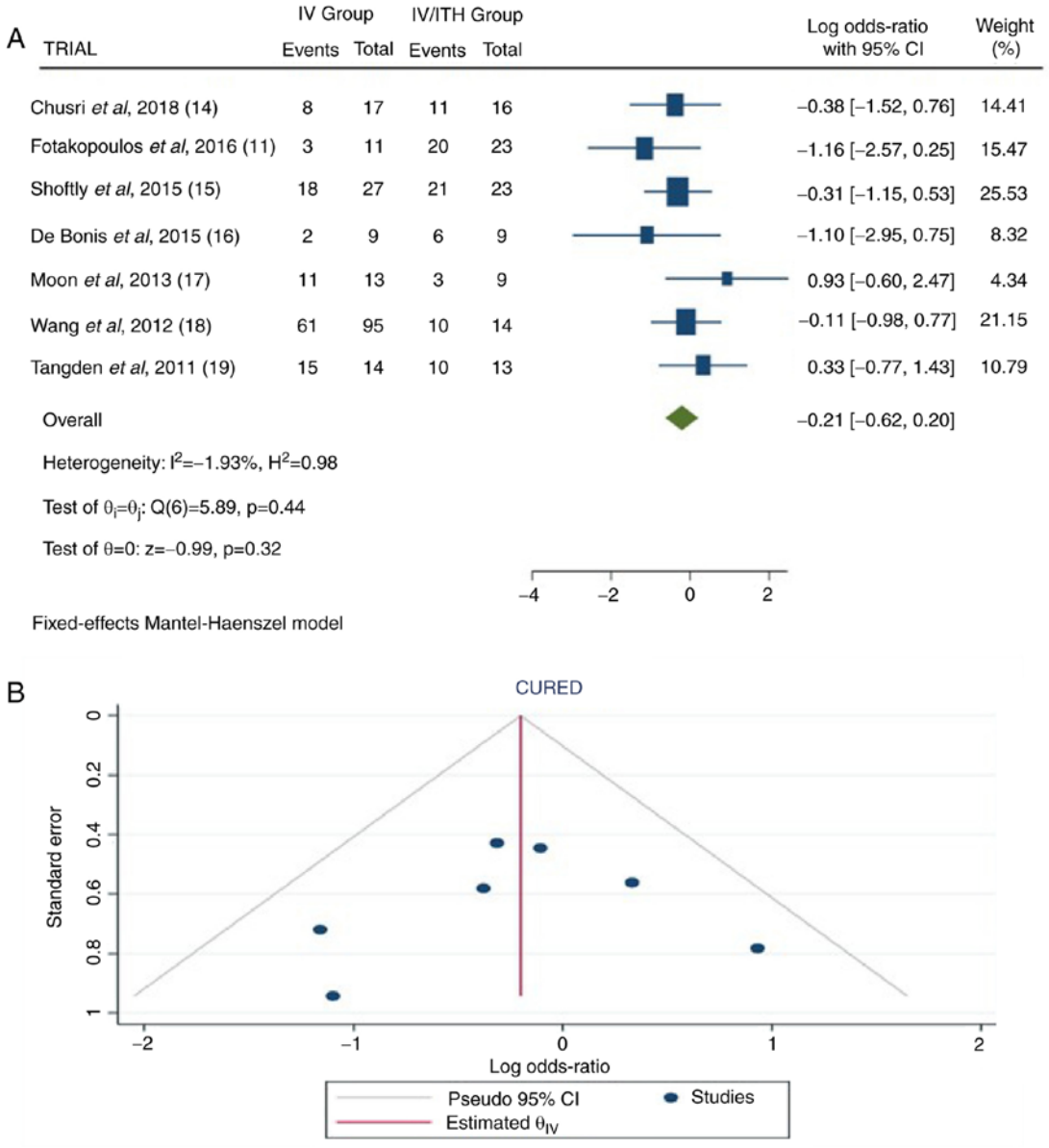

Figure 6. (A) Forest plot for the cured rate. The results demonstrated no statistically significant difference between the IV and IV/ITH groups (OR, -0.21; 95% CI, -0.62 to 0.20; P=0.32). (B) Funnel plot, testing the sensitivity with funnel plot for the cured rate. There was no statistically significant superiority between groups, with no heterogeneity (P=0.44 and I^2=-1.93%). IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

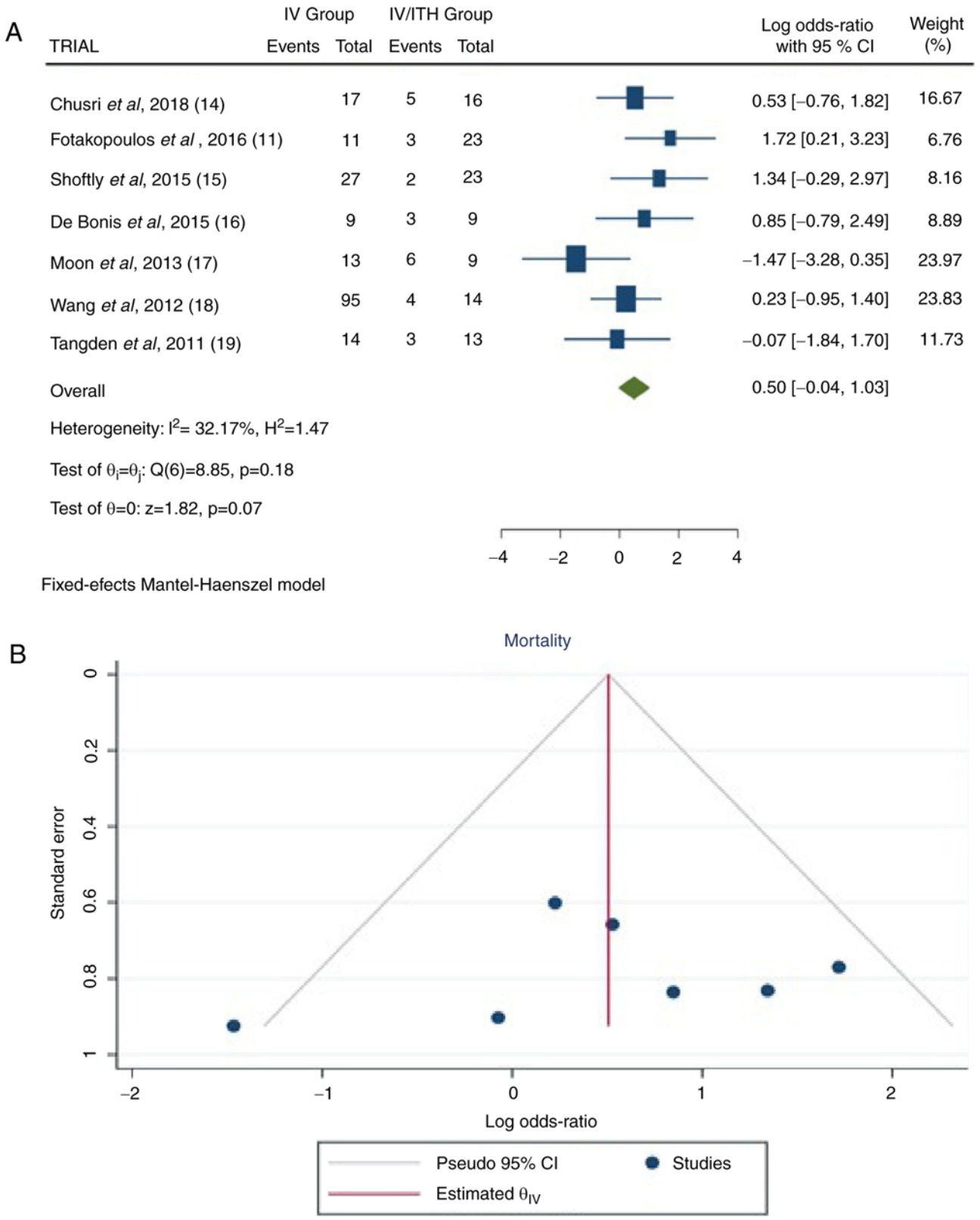

Figure 7. (A) Forest plot for mortality. The results demonstrated a statistically significant difference between the IV and IV/ITH groups (OR, 0.50; 95% CI, -1.04 to 1.03; P=0.05). (B) Funnel plot, testing the sensitivity with funnel plot for mortality there was a statistically significant superiority between groups, with very low heterogeneity (P=0.18 and I^2=32.17%). IV, intravenous treatment group; IV/ITH, intravenous combined with intrathecal treatment group; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

BVM is one of the most severe complications in patients with EVD, accounting for 8% of cases, with MDR bacteria, such as *Acinetobacter baumannii* in the majority (11). ITH treatment with colistin is used as the band of activity of colistin consists of GRn bacteria, and particularly as it is effective against *Acinetobacter baumannii*, which has appeared

over the past few years as an endo-nosocomial infection agent. However, colistin has a reduced infiltration through the blood-brain barrier, and of note, with intravenous monotherapy, it can reach the CSF at only 5-10% of the levels in the blood (20). The present meta-analysis revealed an improved clinical outcome in cases with BVM caused by GRn-MDR bacteria using combined IV/ITH colistin therapy.

ITH management with colistin is a well-established treatment modality; however, the treatment conditions for this are not yet concrete due to some aversion to its use (11). In addition, there have been mentions of fears concerning the efficiency of ITH colistin, the threat of secondary infections or chemical meningitis/ventriculitis due to the manipulations during the colistin placement via the EVD, as well as the length of its treatment (11). In the present meta-analysis, the length of ICU stay and mortality rates yielded statistically significant results, exhibiting the privilege of IV/ITH use over IV colistin administration. However, there were no data regarding brain magnetic resonance imaging that could provide an indication of a possible unfavorable outcome of ITH treatment in the epithelium of the brain ventricle, as well as the risk of chemical meningitis.

Clinical studies have mentioned an increased risk of nephrotoxicity associated with colistin (21,22), mostly by its IV management (23). However, no severe nephrotoxic effect was mentioned in the eligible articles of the present meta-analysis by the ITH colistin placement, most likely due to an adequately managed fluid-electrolyte balance and other potential risks for renal damage during treatment (11). Although colistin has been proposed as an alternative for treating neurosurgical meningitis, further data are required in order to be able to draw firm conclusions about the role of intrathecal antibiotic therapy, apart from pharmacokinetic data demonstrating that colistin reaches bactericidal concentrations in CSF (20).

In conclusion, considering the low number of studies, the results of the present meta-analysis support the addition of ITH colistin to its IV administration, which is an effective treatment for BVM caused by GRn-MDR bacteria. Furthermore, colistin is a viable and safe option for the systemic antimicrobial treatment of these severe neurointensive care infections.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GF and VEG conceptualized the study. VEG, DAS, IT, PP, AG, EA, AAF, GF and NT analyzed the data, and wrote and prepared the draft of the manuscript. DAS and GF provided critical revisions. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. GF and VEG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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