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Efficacy and Safety of Azithromycin for the Treatment of COVID-19: A Systematic Review and Meta-analysis

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Background: The lack of effective medications for coronavirus disease 2019 (COVID-19) has led to a trend of drug repurposing such as the case of azithromycin which shows immunomodulatory and anti-viral effect. Several clinical trials have shown conflicting results. It is currently unclear whether the available evidence is in favor or against the use of azithromycin in COVID-19 patients. Thus, the aim of this study was to investigate the efficacy and safety of azithromycin in COVID-19 patients.

Methods: Four independent reviewers selected relevant studies from PubMed, ScienceDirect, EBSCO, and ProQuest published prior to March 2021. The protocol used in this study has been registered in PROSPERO (CRD42020224967).

Results: We included 17 studies and found that the mortality rate (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.76–1.19), need of respiratory support (OR, 1.30; 95% CI, 0.98–1.73), hospitalization rate (standardized mean difference, 0.12; 95% CI, –0.02 to 0.27), and intensive care unit transfer (OR, 1.21; 95% CI, 0.79–1.86) of azithromycin-treated group did not differ significantly (p>0.05) from those of the control group. Azithromycin treatment did not significantly increase the risk of getting secondary infection (OR, 1.23; 95% CI, 0.83–1.82), hypoglycemia (OR, 0.73; 95% CI, 0.38–1.40), gastrointestinal problems (OR, 1.03; 95% CI, 0.73–1.45) or electrocardiogram abnormalities (OR, 1.16; 95% CI, 0.94–1.42). The overall quality of evidence ranged from low to very low.

Conclusion: Azithromycin did not result in a superior clinical improvement in COVID-19 patients, although it was well-tolerated and safe to use.

Keywords: Azithromycin; COVID-19; Meta-analysis; Systematic Review; Treatment

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Introduction

Coronavirus disease 2019 (COVID-19) pandemic has infected more than 138 million people with a devastating impact on global health. It has caused more than 2.9 million deaths across 223 countries in the world as of April 16, 2021[1]. While the majority of people with COVID-19 only develop mild symptoms, about 10%–15% people develop severe illness requiring hospitalization and intensive care unit (ICU) admission[2]. There is an immense pressure to find a therapy to improve the prognosis and minimize the mortality rate of COVID-19 patients.

The lack of effective medications for the management of COVID-19 has led to a trend of drug repurposing for an indi-

cation different from what was initially marketed. One of such cases is the use of macrolide azithromycin, a broad-spectrum antibiotic commonly used to treat respiratory infections[3], for COVID-19 patients. Besides its bacteriostatic activity, azithromycin has been shown to possess immunomodulatory, anti-inflammatory, and anti-viral effect[3-5]. Azithromycin can also lead to a significant improvement of patients with acute respiratory distress syndrome (ARDS)[6]. These findings have served as a rationale for clinical use of azithromycin in COVID-19 treatment, especially for those with moderate-to-severe stage of the disease, although there is a concern on the potential torsadogenic effect of this drug that could lead to cardiac arrest[7,8]. The widespread use of azithromycin in COVID-19 might also be driven by the intention to decrease the risk of bacterial superinfections in patients with a more severe disease[9]. However, several clinical trials have shown conflicting results. Currently it is unclear whether the available evidence is in favor or against the use of azithromycin in COVID-19 patients[10-26]. Existing literature only provided a brief hypothetical explanation on the potential benefit of azithromycin for COVID-19[27]. However, results were not quantitatively measured. Therefore, the objective of this study was to perform a systematic review and meta-analysis of existing clinical studies to further investigate the efficacy and safety of azithromycin in COVID-19 patients.

Materials and Methods

1. Study registration and methodology

This study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[28]. The protocol used in this study had been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020224967).

2. Eligibility criteria

The following criteria were considered for studies' eligibility: type of study, population, intervention, comparison, and outcome.

1) Type of study

All types of clinical studies (randomized or non-randomized controlled trials, cohort, case control, cross-sectional) evaluating the role of azithromycin in COVID-19 treatment were included in this study. Reviews, commentaries, conference abstracts, case reports, and case series were excluded.

2) Population

Patients diagnosed with COVID-19 and admitted to the hospital were included in this study. The severity of COVID-19 ranged from mild to critical conditions based on staging from

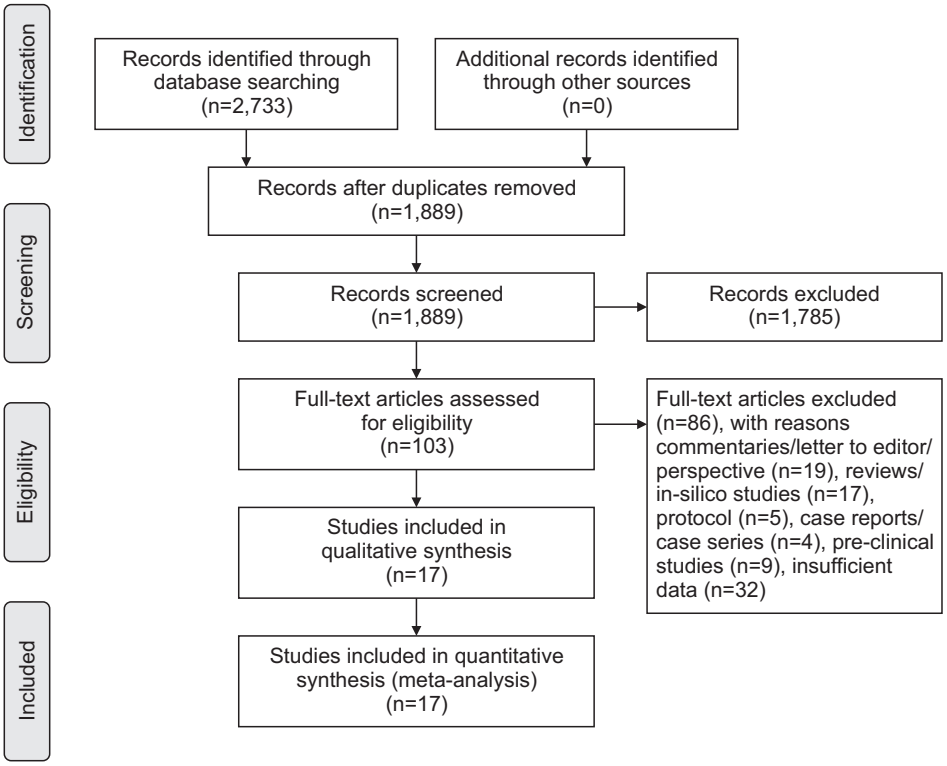

Figure 1. PRISMA Flow Diagram showing the search strategy and the selection process applied to include articles eligible for this meta-analysis.

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Table 1. Characteristics of included studies

Study	Region	Study design	Sample size	Sample characteristics*	COVID-19 severity	Intervention	Control	Follow-up
Albani et al., 2020[10]	Italy	Single-center, retrospective cohort	Intervention: AZM (421/1,403) Control: BAT (605/1,403) Intervention: AZM (+HCQ) (166/1,403) Control: BAT (+HCQ) (211/1,403)	Age AZM: 71 (59–79) Control: 72 (60–81) AZM (+HCQ): 70 (62–75) Control (+HCQ): 68 (59–74) Sex Male: 924/1,403 Female: 479/1,403 BMI AZM: 26 (23–29) Control: 26 (23–29) AZM (+HCQ): 26 (24–29) Control (+HCQ): 26 (24–29)	Moderate to severe	AZM 500 mg QD for 5 days	BAT	12 weeks
Arshad et al., 2020[11]	United States	Multi-center, retrospective cohort	Intervention: AZM (147/2,541) Control: BAT (409/2,541) Intervention: AZM (+HCQ) (783/2,541) Control: BAT (+HCQ) (1,201/2,541)	Age AZM: 64 (52–76) Control: 71 (56–83) AZM (+HCQ): 62 (51–74) Control (+HCQ): 64 (53–74) Sex Male: 1,298/2,541 Female: 1,243/2,541 BMI AZM: 29 (25–36) Control: 28 (23–33) AZM (+HCQ): 32 (27–37) Control (+HCQ): 30 (26–36)	Moderate to severe	AZM 500 mg QD on day 1, 250 mg QD on day 2–5	BAT	Median days (IQR): 28.5 (3–53)
Bernardini et al., 2021[12]	Italy	Single-center, retrospective cohort	Intervention: AZM (+HCQ) (53/93) Control: BAT (+HCQ) (40/93)	Age Group 1: 66.8±13.6 Group 2: 67.3±12.2 Sex Male: 66/93 Female: 27/93 BMI AZM (+HCQ): 26.1±5.2 Control (+HCQ): 28.1±6.5	Moderate to severe	AZM 500 mg QD on day 1, 250 mg QD onward	BAT	Mean days (SD): 13.6±7.4
Cavalcanti et al., 2020[13]	Brazil	Multi-center, open-label, randomized controlled trial	Intervention: AZM (+HCQ) (217/438) Control: BAT (+HCQ) (221/438)	Age AZM (+HCQ): 49.6±14.2 Control (+HCQ): 51.3±14.5 Sex Male: 265/438 Female: 173/438	Mild to moderate	AZM 500 mg QD for 7 days	BAT	15 days

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Table 1. Continued

Study	Region	Study design	Sample size	Sample characteristics*	COVID-19 severity	Intervention	Control	Follow-up
Furtado et al., 2020[14]	Brazil	Multi-center, open-label, randomized controlled trial	Intervention: AZM (214/397) Control: BAT (183/397)	Age Intervention: 59.4 (49.3–70.0) Control: 60.2 (52.0–70.1) Sex Intervention Male: 140/214 Female: 74/214 Control Male: 122/183 Female: 61/183 BMI Intervention: 26.4 (23.5–31.8) Control: 27.2 (23.7–31.7)	Severe	AZM 500 mg QD for 10 days, PO/nasogastric/IV	BAT	15 days
Lagier et al., 2020[15]	France	Multi-center, retrospective cohort	Intervention: AZM (137/3,737) Control: BAT (162/3,737) Intervention: AZM (+HCQ) <3 days (218/3,737) Intervention: AZM (+HCQ) ≥3 days (3,119/3,737) Control: BAT (+HCQ) (101/3,737)	Age: 45.3±16.8 Sex Male: 1,704/3,737 Female: 2,033/3,737	Moderate to severe	AZM 500 mg QD on day 1, 250 mg QD on day 2–5	BAT	10 days
Lauriola et al., 2020[16]	Italy	Single-center, retrospective cohort	Intervention: AZM (+HCQ) (297/314) Control: BAT (+HCQ) (17/314)	Age: 71.8±13.4 Sex Male: 248/377 Female: 129/377	Moderate to severe	AZM 500 mg QD for 10 days	BAT	40 days
Mercuro et al., 2020[17]	United States	Single-center, retrospective cohort	Intervention: AZM (+HCQ) (53/90) Control: BAT (+HCQ) (37/90)	Age Intervention: 60.6±17.4 Control: 59.5±15.9 Sex Male: 46/90 Female: 44/90 BMI Intervention: 32.3±6.9 Control: 30.4±6.1	Moderate to severe	AZM 250–500 mg QD	BAT	4 weeks
Omrani et al., 2020[18]	Qatar	Prospective, randomized controlled trial	Intervention: AZM (+HCQ) (152/304) Control: BAT (+HCQ) (152/304)	Age Group 1: 40 (31–47) Group 2: 42 (38–48) Control: 41 (31–47) Sex Male: 150/152 Female: 2/152	Mild to no symptoms	AZM 500 mg QD on day 1, 250 mg QD on day 2–5	BAT	14 days

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Table 1. Continued

Study	Region	Study design	Sample size	Sample characteristics*	COVID-19 severity	Intervention	Control	Follow-up
Ozdemir et al., 2021[19]	Turkey	Single-center, retrospective cohort	Intervention: AZM (+HCQ) (56/101) Control: BAT (+HCQ) (45/101)	Age Intervention: 53.5±19 Control: 46.0±16 Sex Male: 55/101 Female: 46/101 BMI Intervention: 27.02±2.95 Control: 28.12±3.65	Moderate to severe	AZM 500 mg QD (loading dose), 250 mg QD (maintenance dose) for 5 days	BAT	7 days
RECOVERY Collaborative Group, 2021[20]	United Kingdom	Multi-center, open-label, randomized controlled trial	Intervention: AZM (2,582/7,763) Control: BAT (5,181/7,763)	Age Intervention: 65.4±15.6 Control: 65.2±15.7 Sex Male: 4,819/7,763 Female: 2,944/7,763	Moderate to severe	AZM 500 mg QD for 10 days or until discharge, if sooner	BAT	28 days
Rodriguez-Molinero et al., 2020[21]	Spain	Retrospective cohort	Intervention: AZM (29/58) Control: BAT (29/58)	Age Intervention: 63 Control: 63.1 Sex Male: 42/58 Female: 16/58	Moderate to severe	AZM 500 mg on day 1, 250 mg QD on day 2–5	BAT	Median days (IQR): 8 (5–12)
Rosenberg et al., 2020[22]	United States	Multi-center, retrospective cohort	Intervention: AZM (211/1,438) Control: BAT (221/1,438) Intervention: AZM (+HCQ) (735/1,438) Control: BAT (+HCQ) (271/1,438)	Age (median): 63 Sex Male: 858/1,438 Female: 580/1,438	Moderate to severe	AZM 200–500 mg single dose/ QD/ BID	BAT	1 month
Saleh et al., 2020[23]	United States	Multi-center, prospective cohort	Intervention: AZM (+HCQ) (119/201) Control: BAT (+HCQ) (82/201)	Age: 58.5±9.1 Sex Male: 115/201 Female: 86/201	Moderate to severe	AZM 500 mg QD for 5 days	BAT	-
Sekhavati et al., 2020[24]	United States	Open label, randomized controlled trial	Intervention: AZM (56/111) Control: BAT (55/111)	Age Intervention: 54.38±15.92 Control: 59.89±15.55 Sex Male: 51/111 Female: 60/111	Moderate to severe	AZM 500 mg QD for 5 days	BAT	30 days

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Table 1. Continued

Study	Region	Study design	Sample size	Sample characteristics*	COVID-19 severity	Intervention	Control	Follow-up
Seyhan et al., 2020[25]	Turkey	Retrospective cohort	Intervention: AZM (+HCQ) (93/144) Control: BAT (+HCQ) (51/144)	Age: 55.81±19.32 Sex Male: 74/144 Female: 70/144	Moderate to severe	AZM 250 mg QD for 5 days	BAT	-
Tanriverdi et al., 2021[26]	Turkey	Retrospective cohort	Intervention: AZM (+HCQ) (26/56) Control: BAT (+HCQ) (30/56)	Age Intervention: 51.65±13.41 Control: 46.30±17.07 Sex Male: 39/56 Female: 17/56	Mild to severe	AZM 500 mg QD on day 1, 250 mg QD on day 2–5	BAT	-

COVID-19: coronavirus disease 2019; AZM: azythromycin; BAT: best available therapy; HCQ: hydroxychloroquine; BMI: body mass index; IQR: interquartile range; SD: standard deviation; QD: once daily; PO: by mouth; IV: intravenous; BID: twice daily.
*Number, median (IQR), or mean±SD.

World Health Organization. There was no restriction for age, races, occupation, economy/social status, religion, country, or underlying condition.

3) Intervention

Studies evaluating all types of azithromycin for the treatment of COVID-19 were included in this study. Azithromycin was given in any dosage regimen either alone or in combination with the best available therapy (BAT).

4) Comparison and outcome

Comparators included patients treated with placebo and/or only given BAT. Outcomes of interest were efficacy and safety of azithromycin in COVID-19 treatment. Efficacy included clinical improvement, hospitalization period, and mortality. Safety included toxicity and serious adverse events occurring during treatment.

3. Search strategy and study selection

Literature search was carried out with multiple electronic databases such as PubMed, ScienceDirect, EBSCO, and ProQuest from inception to March 2021. No time and language restriction were applied. This study only included peer-reviewed articles of clinical trials evaluating the efficacy and safety of azithromycin in COVID-19 patients. The search was performed by three independent reviewers (GM, G, and N).

Articles were identified using keywords ("COVID-19" OR "COVID-19" OR "2019 novel coronavirus disease" OR "Coronavirus disease 2019" OR "COVID19" OR "2019 nCoV disease" OR "SARS-CoV-2 infection") AND ("azithromycin") with their respective Medical Subject Headings (MeSH) terms, if applicable. After removing duplicates using EndNote program, retrieved articles were screened based on their titles and abstracts. Thereafter, potentially eligible full-text articles were thoroughly assessed using the eligibility criteria described above. Any emerging discrepancies were resolved by consensus among the three reviewers.

4. Data extraction

The following data were extracted from these studies: (1) first author, (2) publication year, (3) region, (4) study design, (5) sample characteristics and size, (6) COVID-19 severity, (7) intervention (dose, route of administration, duration, other treatments besides azithromycin) and control, (8) follow-up period, if any, and (9) efficacy and safety of azithromycin.

5. Quality assessment and reliability of data

Version 2 of the Cochrane Risk of Bias tool (RoB-2) was used to assess the quality of included randomized trials[29]. Newcastle-Ottawa Scale was used to evaluate the quality of

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Table 2. Methodological quality: cohort studies

Study	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohort
Albani et al., 2020[10]	★	★	★	☆	★★	★	★	★
Arshad et al., 2020[11]	★	★	★	★	★★	★	★	★
Bernardini et al., 2020[12]	★	★	★	☆	★★	★	★	★
Lagier et al., 2020[15]	★	★	★	★	★☆	★	★	★
Lauriola et al., 2020[16]	★	★	★	☆	★★	★	★	★
Mercuro et al., 2020[17]	★	★	★	☆	★★	★	★	★
Ozdemir et al., 2021[19]	★	★	★	☆	★★	★	★	★
Rodriguez-Molinero et al., 2020[21]	★	★	★	☆	★☆	★	★	★
Rosenberg et al., 2020[22]	★	★	★	☆	★★	★	★	★
Saleh et al., 2020[23]	★	★	★	☆	★☆	★	★	★
Seyhan et al., 2020[25]	★	★	★	☆	★☆	★	★	★
Tanriverdi et al., 2021[26]	★	★	★	☆	★☆	★	★	★

★: 1 point; ☆: 0 point.

Note: The study is rated either as "good" (3 or 4 points in selection, 1 or 2 points in comparability, and 2 or 3 points in outcomes), "fair" (2 points in selection, 1 or 2 points in comparability, and 2 or 3 points in outcomes) or "poor" (0 or 1 point(s) in selection, or 0 point in comparability, or 0 or 1 point(s) in outcomes).

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non-randomized study design for the included study[30]. Three researchers (G, GM, and N) independently evaluated whether a study had low or some concerns or high risk of bias. Any discrepancies were resolved through discussion. Trial sequential analysis (TSA) was performed to determine the required sample size and confirm whether the meta-analysis was conclusive. TSA generated thresholds for declaring significance of the result to avoid an overestimation of intervention effects and prevent spurious results. A two-sided trial of the sequential monitoring boundary type was used in our TSA. The required information size was calculated with α=0.05. TSA was performed using TSA version 0.9.5.10 beta[31].

6. Data synthesis and statistical analysis

Either odds ratio (OR) or weighted mean difference with a

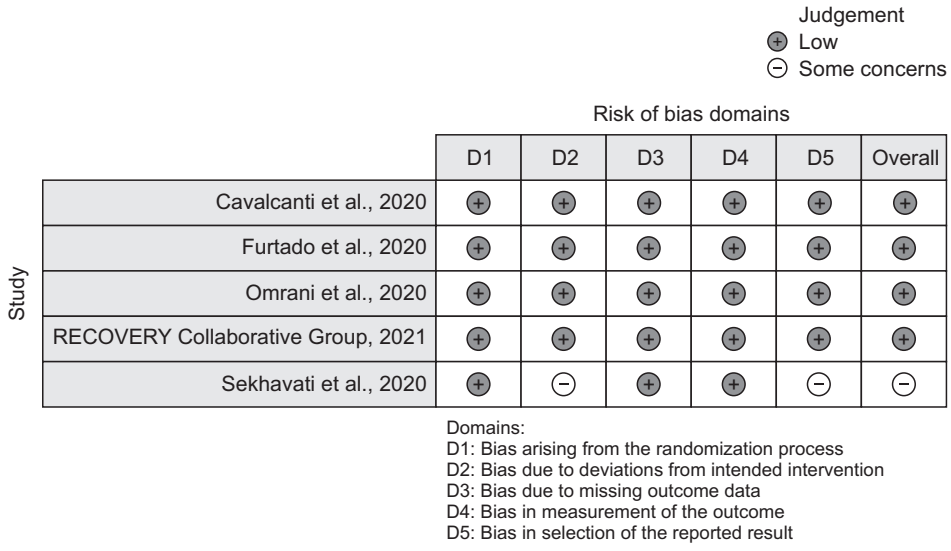


Figure 2. Methodological quality: randomized controlled trials.

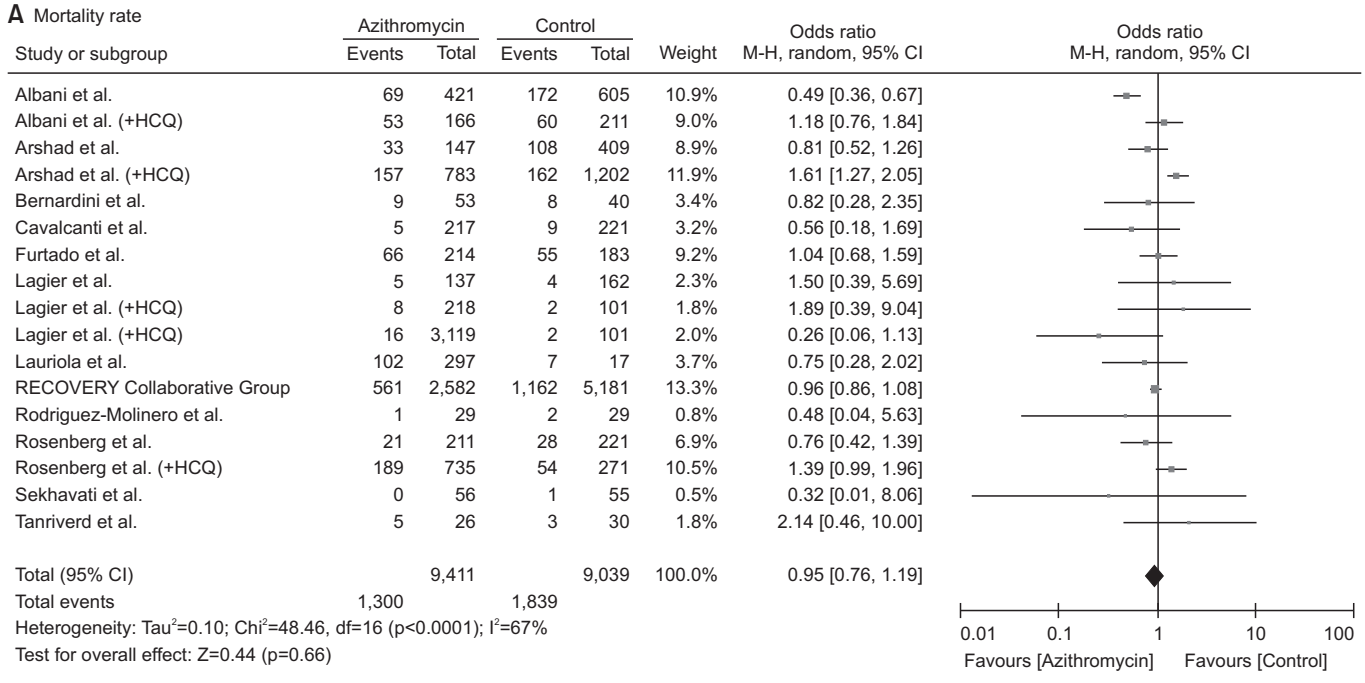


Figure 3. (A–D) Efficacy of azithromycin. The horizontal line indicates 95% CI of the study. The square represents the result of each individual study. The size of the square varies according to the weight of a particular study. The diamond at the bottom of the plot represents pooled analysis of all included studies. Outer edges of the diamond indicate CIs. CI: confidence interval; df: degree of freedom; I^2: test of heterogeneity; M-H: Mantel-Haenszel.

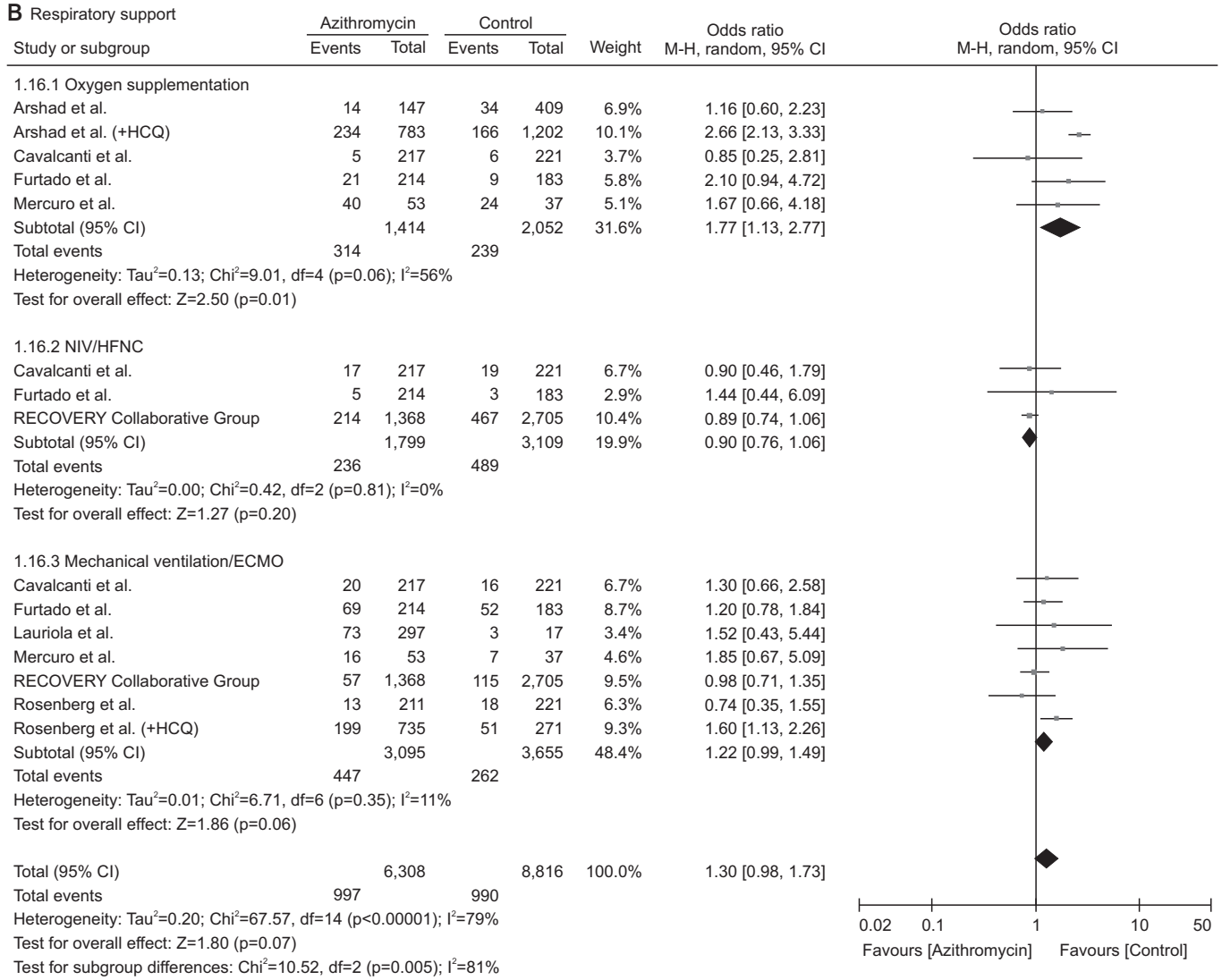


Figure 3. Continued.

confidence interval (CI) of 95% was used to determine the efficacy and safety of azithromycin in COVID-19 patients. Either fixed-effects or random-effects model was used depending on the study heterogeneity. Heterogeneity of included studies was assessed using Cochrane's Q test of homogeneity and Higgins I^2 statistics. Subgroup analysis was conducted to find the possible cause of heterogeneity.

Funnel plot was used to assess publication bias visually. Asymmetric funnel plot indicated possible publication bias. Begg and Mazumdar rank correlation test and Egger's test of the intercept were used to determine the presence of publication bias statistically. All statistical tests were performed using Review Manager (RevMan) 5.3 and MedCalc version 19.5.1[32,33].

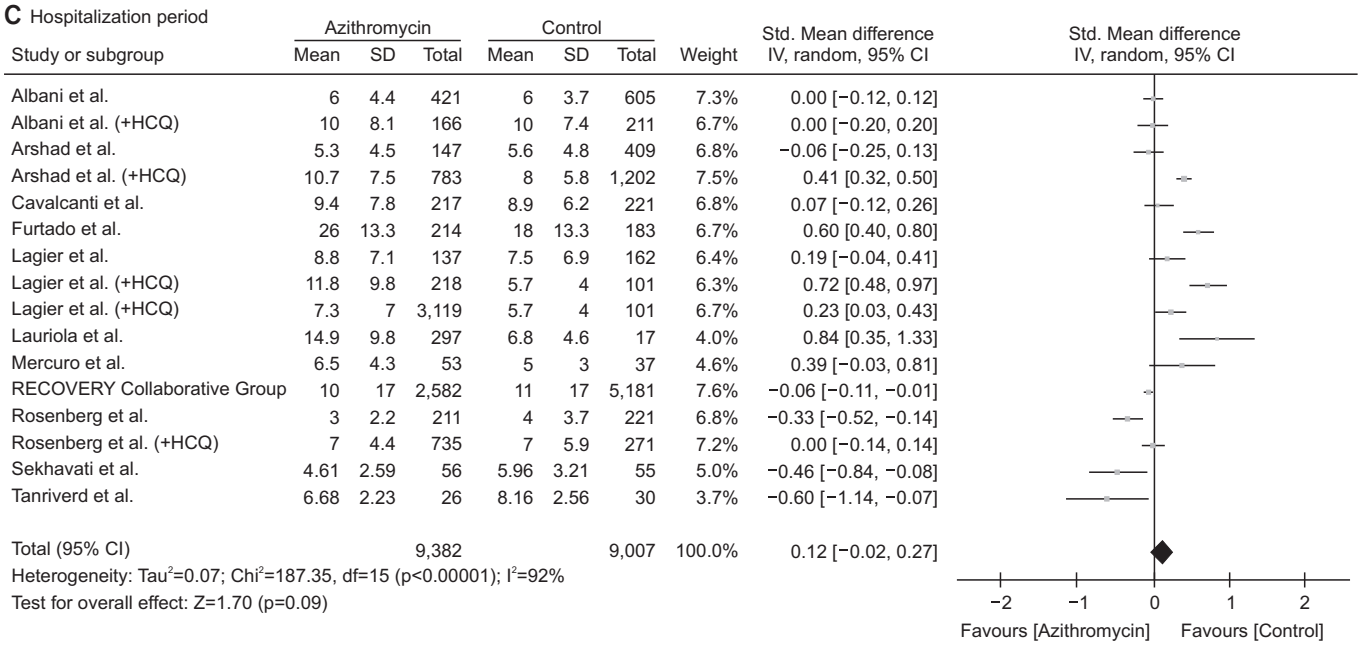
7. Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was performed to determine the confidence in cumulative evidence. Judgement was made considering the presence of study limitations, consistency, directness, imprecision, and/or reporting bias. Overall certainty of evidence was shown as high, moderate, low, or very low.

Results

1. Search results

After searching electronic databases, 2,733 studies were found. After screening titles and abstracts, 1,889 articles were



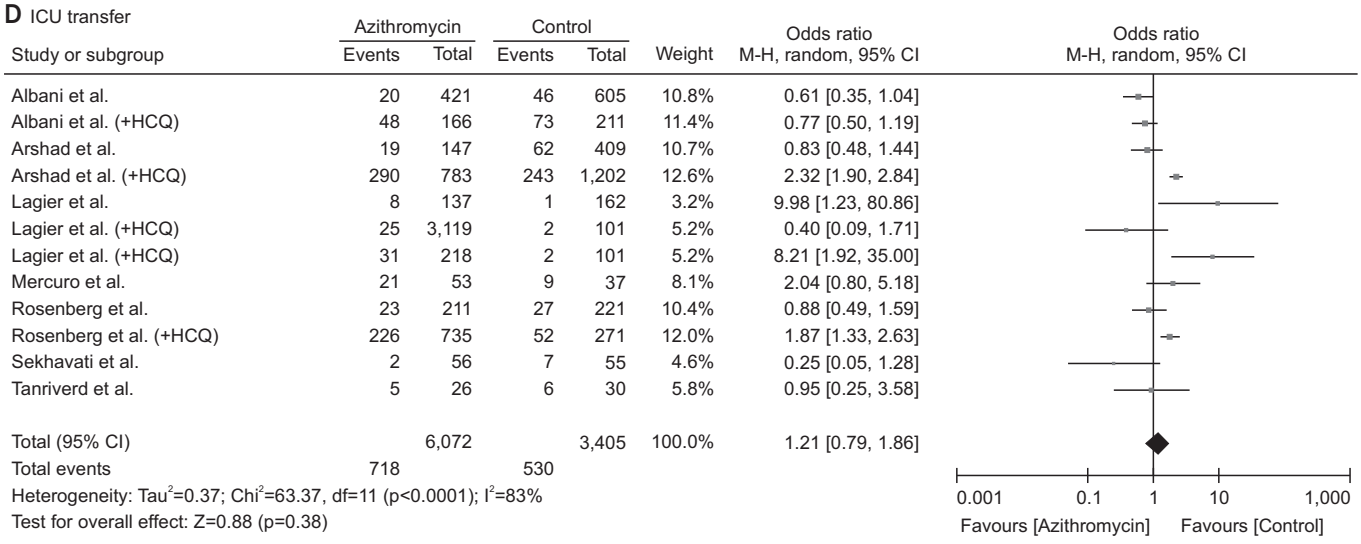


Figure 3. Continued.

found, of which 104 were assessed for eligibility. A total of 17 studies were included in the meta-analysis finally[10-26]. Search flowchart and selection methods used in this study are summarized in Figure 1.

2. Characteristics of included studies

Included studies were conducted in various regions, including America[11,13,14,17,22-24], Europe[10,12,15,16,20,21], and Middle East[18,19,25,26]. All studies recruited adults aged 45 to 83 years. Included patients had common underlying conditions such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and cardiovascular disease. The severity of COVID-19 ranged from mild to severe. Overall, azithromycin was given as much as 250–500 mg daily for 5–10 days. Other treatments besides azithromycin that the majority of patients received were glucocorticoids, hydroxychloroquine, diuretics, and anticoagulants. All four randomized controlled trials had low risk of bias except that one study showed some concerns of bias in classifying the interventions and measurements of outcomes[24]. Twelve cohort studies showed good quality in terms of selection, comparability, and outcomes. Characteristics of included studies are summarized in Tables 1, 2 and Figure 2.

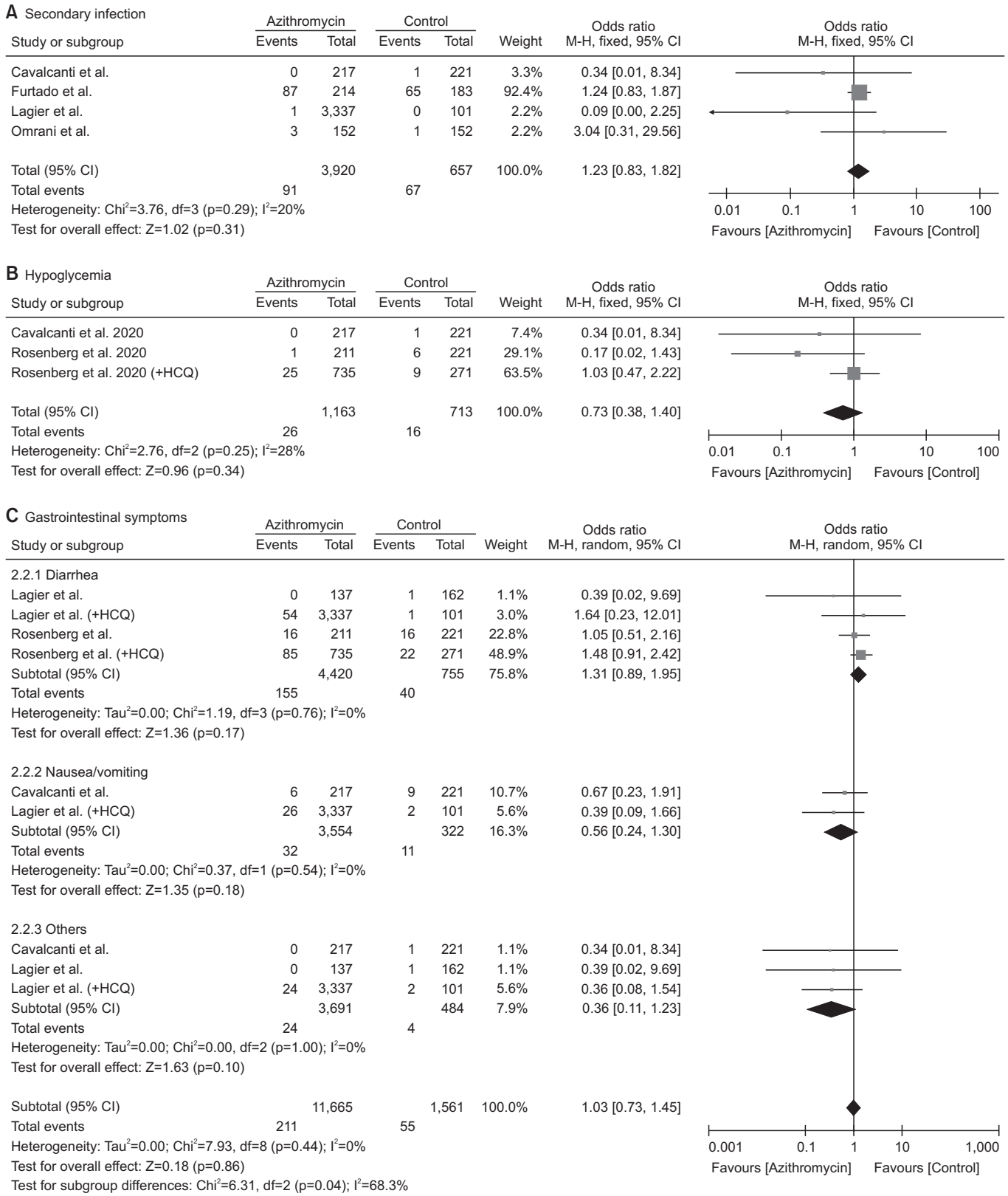


Figure 4. (A–D) Safety of azithromycin. The square represents the result of each individual study. The size of the square varies according to the weight of a particular study. The diamond at the bottom of the plot represents pooled analysis of all included studies. Outer edges of the diamond indicate CIs. CI: confidence interval; df: degree of freedom; I^2: test of heterogeneity; M-H: Mantel-Haenszel.

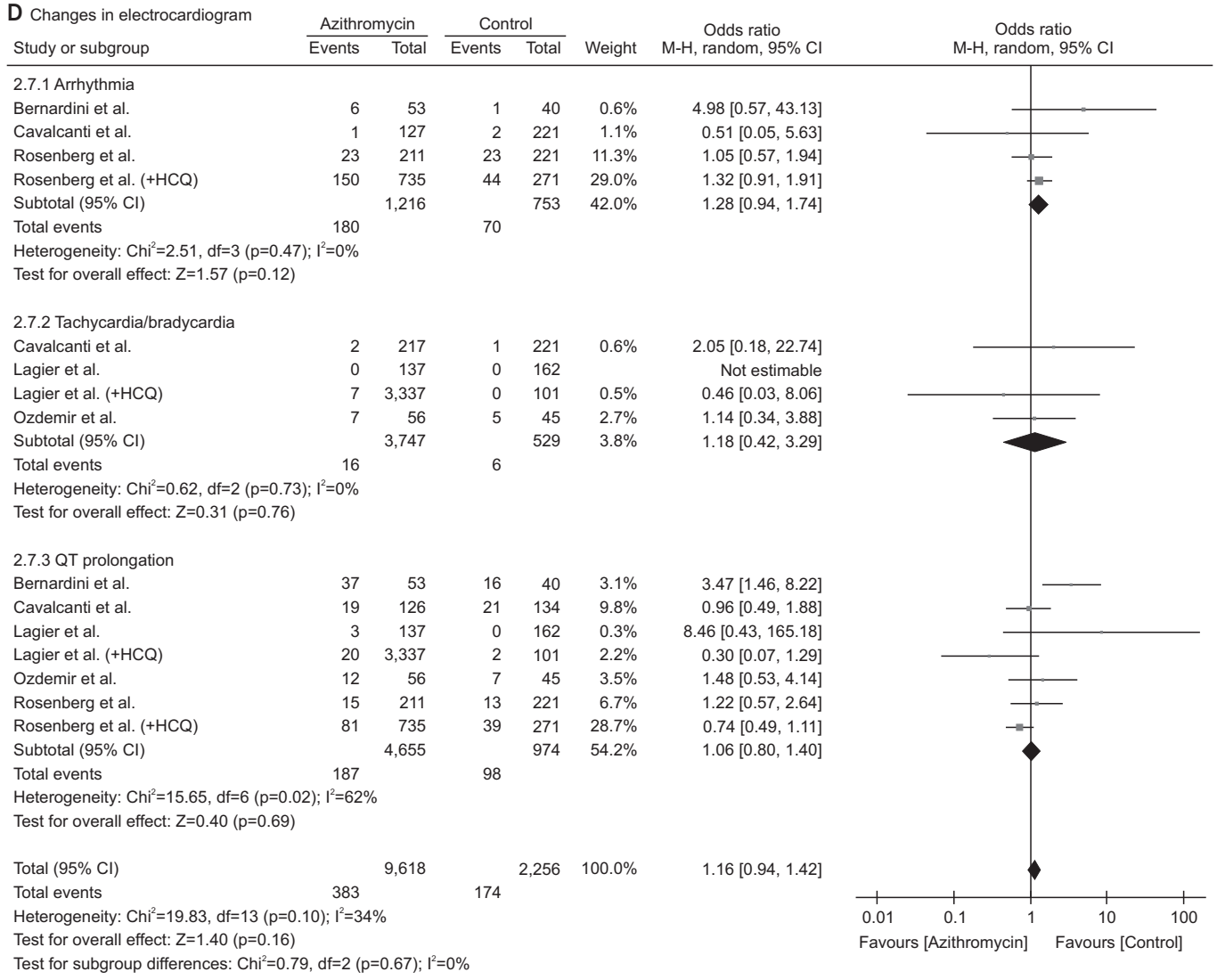


Figure 4. Continued.

3. Meta-analysis: efficacy and safety of azithromycin in COVID-19 patients

COVID-19 patients treated with azithromycin showed lower mortality rate than controls, although the difference between the two was not statistically significant (OR, 0.95; 95% CI, 0.76–1.19; p=0.66; I^2=67%) (Figure 3A). Needs for oxygen supplementation (OR, 1.77; 95% CI, 1.13–2.77) and mechanical ventilation/extracorporeal membrane oxygenation (OR, 1.22; 95% CI, 0.99–1.49) were higher for patients treated with azithromycin, although the overall need for respiratory support did not significantly differ between the two groups (OR, 1.30; 95% CI, 0.98–1.73; p=0.07; I^2=79%) (Figure 3B). Azithromycin-treated patients showed a longer hospitalization period (standardized mean difference, 0.12; 95% CI, –0.02 to 0.27; p=0.09; I^2=92%) (Figure 3C) and a higher ICU transfer (OR, 1.21; 95% CI, 0.79–1.86; p=0.38; I^2=83%) (Figure 3D) compared to the control group, although differences between the two groups were not statistically significant. Interestingly, this meta-analysis showed that patients receiving both azithromycin and hydroxychloroquine had a higher mortality rate (p=0.03) and more likely to need respiratory support (p=0.01) compared to those receiving azithromycin only (OR, 1.21; 95% CI, 0.92–1.59 vs. OR, 0.80; 95% CI, 0.61–1.05 and OR, 1.59; 95% CI, 1.13–2.24 vs. OR, 0.98; 95% CI, 0.84–1.15, respectively).

Azithromycin treatment did not significantly increase the risk of getting secondary infection (OR, 1.23; 95% CI, 0.83–1.82; p=0.31; I^2=20%) (Figure 4A) or hypoglycemia (OR, 0.73; 95% CI, 0.38–1.40; p=0.34; I^2=28%) (Figure 4B). No significant difference was observed in gastrointestinal symptoms between the two groups (OR, 1.03; 95% CI, 0.73–1.45; p=0.86; I^2=0%) (Figure 4C), such as diarrhea (OR, 1.31; 95% CI, 0.89–1.95; p=0.17) or

nausea/vomiting (OR, 0.56; 95% CI, 0.24–1.30; p=0.18). There was no significant difference in change of electrocardiogram (OR, 1.16; 95% CI, 0.94–1.42; p=0.16; I^2=34%) (Figure 4D), incidence of arrhythmia (OR, 1.28; 95% CI, 0.94–1.74; p=0.12), bradycardia/tachycardia (OR, 1.18; 95% CI, 0.42–3.29; p=0.76), or QT prolongation (OR, 1.06; 95% CI, 0.80–1.40; p=0.69) either between the two groups (patients treated with azithromycin and control).

This meta-analysis found no evidence of publication bias (Figure 5) except for the assessment of gastrointestinal symptoms occurring in azithromycin-treated patients compared to those in the control. The rest of outcomes showed a symmetrical funnel plot which was further confirmed statistically (p>0.1) by Begg and Mazumdar rank correlation test and Egger's test of the intercept. Sensitivity analysis was conducted with or without exclusion of a study that cause some concerns

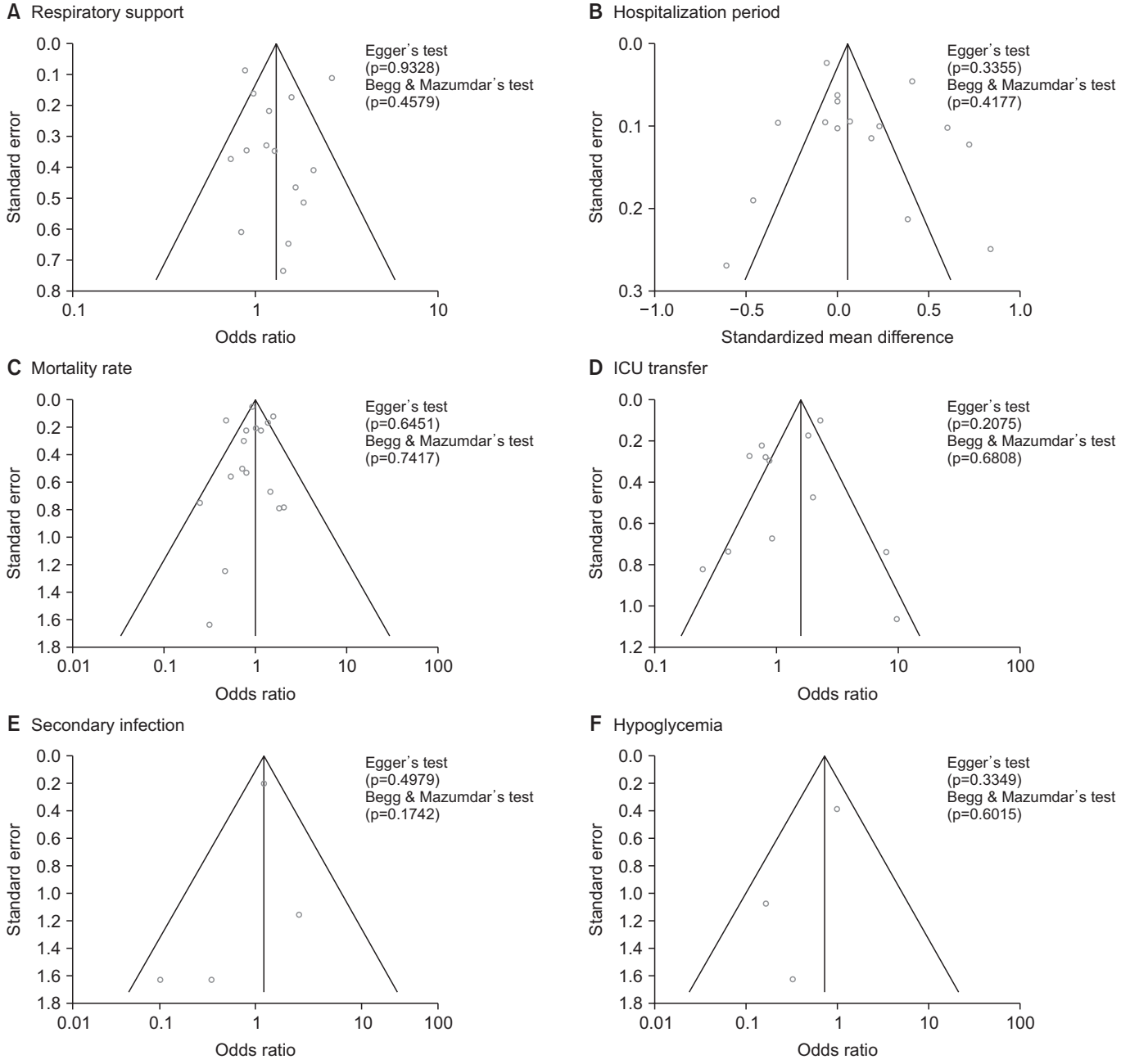


Figure 5. (A–H) Publication bias. Funnel plot presented the distribution of included studies. Asymmetrical plot indicated that publication bias was present. This was confirmed by Begg and Mazumdar rank correlation test and Egger's test of the intercept to determine the presence of publication bias statistically (p<0.1). ICU: intensive care unit.

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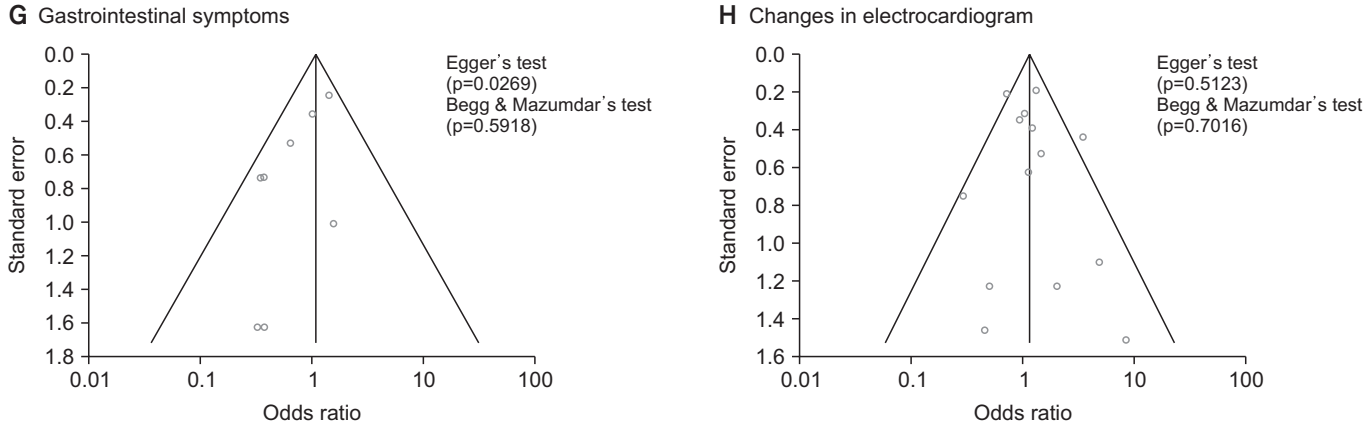

Figure 5. Continued.

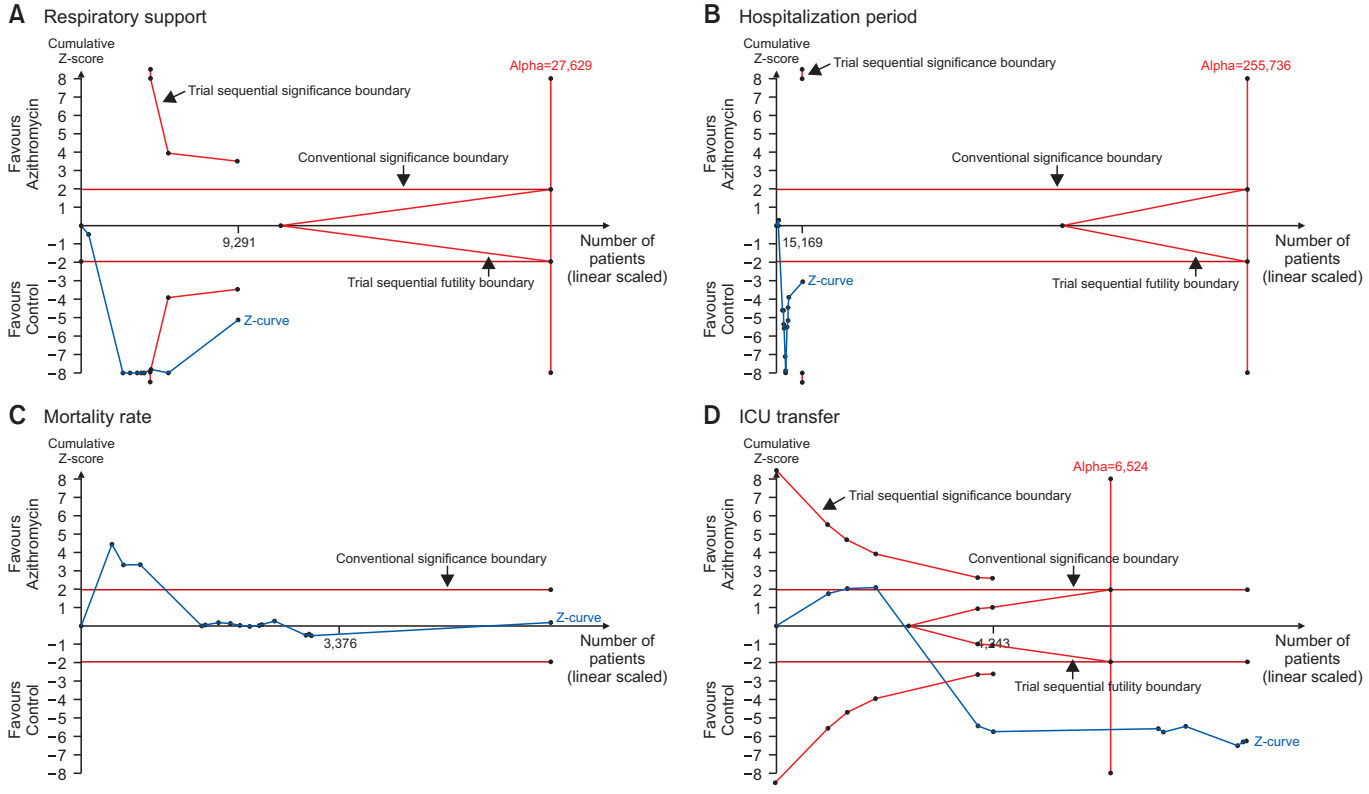

Figure 6. (A–H) Trial sequential analysis. Findings are represented by cumulative Z-curves. When Z-curves surpass the futility boundary, the level of evidence is adequate and further trials will be judged as futile. The level of evidence was judged to be adequate and conclusive if the Z-curves surpassed the conventional and trial sequential significance boundaries. On the contrary, when Z-curves did not cross any boundaries or only surpassed the conventional boundary, the level of evidence was inadequate and more trials would be needed to clarify the conclusion. The blue line represents the cumulative Z-curve. The horizontal red line at Z=+1.96 and Z=−1.96 indicates the conventional meta-analysis boundary. The diagonal red line at the top and the bottom of the plot indicates the trial sequential significance boundary. The triangular red line on the right represents the trial sequential futility boundary. The vertical red line on the right indicates the required sample size for the meta-analysis.

of bias. Findings did not show any meaningful differences, indicating the stability of results from this meta-analysis.

TSA was performed to further investigate and confirm results from this meta-analysis (Figure 6). All pooled analyses did not exceed the required sample size except in the assessment of ICU transfer. However, TSA confirmed that results

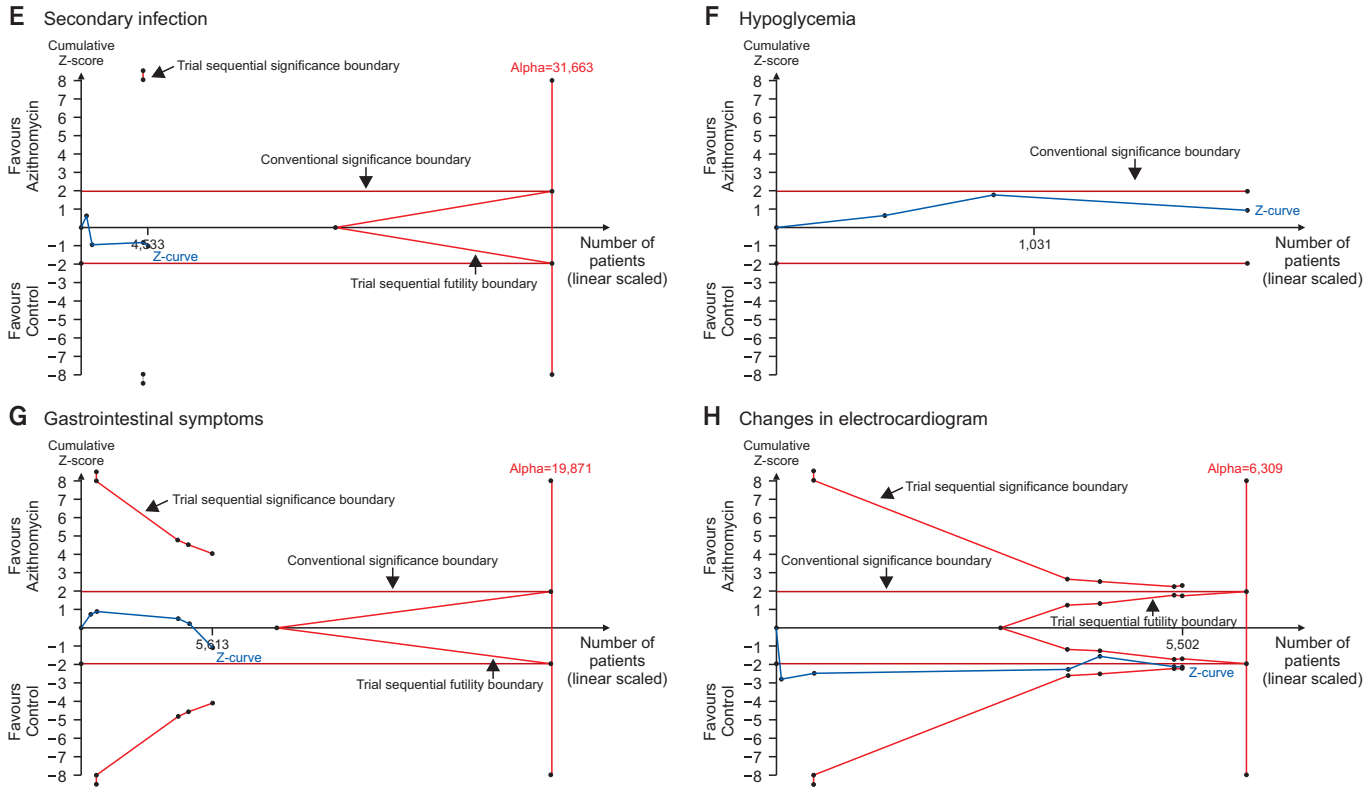

Figure 6. Continued.

of this meta-analysis evaluating the need of ICU transfer and respiratory support were conclusive as the cumulative Z-curve of outcomes surpassed both conventional and trial significance boundaries, indicating that type I and type II errors were avoided. On the contrary, pooled analysis evaluating the rest of outcomes was inconclusive as the cumulative Z-curve either surpassed the conventional boundary (but not the trial sequential significance boundary) or surpassed neither boundaries. Therefore, more clinical studies are needed to confirm these results.

4. Confidence in cumulative evidence

Studies included in this meta-analysis were randomized controlled trials (RCTs) and cohorts that indicated initial moderate-quality evidence in the GRADE system. The majority of RCTs were judged to have a low risk of bias according to RoB2 except in one study. Meanwhile, all included cohort studies were judged to have a good quality. Sensitivity analysis did not show any meaningful differences either when one study with some concerns of bias was omitted. Therefore, it could be concluded that results were unlikely to be affected by bias. No serious indirectness was found in this study that could affect study results. Publication bias was not present except in the meta-analysis evaluating gastrointestinal symptoms that occurred after azithromycin treatment. There were substantial inconsistencies in results evaluating the efficacy of azithromycin due to high heterogeneity of studies caused by differences in the population. Although the CI of each outcome was unlikely to pose a problem, the majority of results from this meta-analysis caused some concerns regarding the precision of data as TSA was inconclusive. Overall, these included studies were had a low-to-very low quality of evidence. GRADE evidence profile is summarized in Table 3.

Discussion

COVID-19 patients who received azithromycin treatment were unlikely to have better outcomes than those who did not receive it. This meta-analysis demonstrated that azithromycin treatment was not significantly associated with a lower mortality, a shorter hospitalization period, a lower ICU transfer, or a less need for respiratory support. Azithromycin is a broad-spectrum antibiotic widely used to treat lower respiratory tract infections[3]. The rationale for using azithromycin in COVID-19 treatment was probably due to its potential immunomodulatory, anti-inflammatory, and anti-viral properties[3-5,34]. It has been reported that patients with moderate-to-severe ARDS have significant clinical improvement after they are treated

Table 3. GRADE evidence profile: azithromycin compared to control for COVID-19 treatment

Outcome	No. of participants (studies)	Quality assessment						Summary of findings		
		Risk of Bias (RoB-2 and NOS)	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Estimated risk with azithromycin	Estimated risk with control	Relative effect (95% CI)
Efficacy: Mortality rate	18,450 (4 RCTs, 8 cohorts)	Not serious	Serious*	Not serious	Serious†	Not serious	⊕◯◯◯ VERY LOW	1,300/9,411	1,839/9,039	OR 0.95 (0.76–1.19)
Efficacy: Respiratory support	15,124 (3 RCTs, 4 cohorts)	Not serious	Serious*	Not serious	Not serious	Not serious	⊕⊕◯◯ LOW	997/6,308	990/8,816	OR 1.30 (0.98–1.73)
Efficacy: Hospitalization period	18,389 (4 RCTs, 7 cohorts)	Not serious	Serious*	Not serious	Serious†	Not serious	⊕◯◯◯ VERY LOW	The hospitalization period in the azithromycin groups was on average 0.12 SDs (–0.02 to 0.27) higher than in the control groups		
Efficacy: ICU Transfer	9,477 (1 RCT, 6 cohorts)	Not serious	Serious*	Not serious	Not serious	Not serious	⊕⊕◯◯ LOW	718/6,072	530/3,405	OR 1.21 (0.79–1.86)
Safety: Secondary infection	4,577 (3 RCTs, 1 cohort)	Not serious	Not serious	Not serious	Serious†	Not serious	⊕⊕◯◯ LOW	91/3,920	67/657	OR 1.23 (0.83–1.82)
Safety: Hypoglycemia	1,876 (1 RCT, 1 cohort)	Not serious	Not serious	Not serious	Serious†	Not serious	⊕⊕◯◯ LOW	26/1,163	16/713	OR 0.73 (0.38–1.40)
Safety: Gastrointestinal symptoms	13,226 (1 RCT, 2 cohorts)	Not serious	Not serious	Not serious	Serious†	Serious‡	⊕◯◯◯ VERY LOW	211/11,665	55/1,561	OR 1.03 (0.73–1.45)
Safety: Changes in ECG	9,905 (1 RCT, 4 cohorts)	Not serious	Not serious	Not serious	Serious†	Not serious	⊕⊕◯◯ LOW	203/8,402	104/1,503	OR 1.07 (0.81–1.40)

COVID-19: coronavirus disease 2019; RoB-2: Cochrane Risk of Bias tool; NOS: Newcastle-Ottawa Scale; CI: confidence interval; RCT: randomized controlled trial; OR: odds ratio; ICU: intensive care unit; ECG: electrocardiogram.

*There was a substantial heterogeneity among included studies. †Trial sequential analysis was inconclusive. ‡There was an indication of publication bias through Egger's test.

with azithromycin[7]. The widespread use of azithromycin in COVID-19 patients might be driven by the risk of bacterial superinfections in patients with a more severe disease[9]. However, this meta-analysis of subjects with mostly moderate-to-severe COVID-19 showed no meaningful clinical benefits from azithromycin treatment. This might be due to a low rate of secondary infection among subjects included in this study or due to the fact that the effect of azithromycin was partially masked by the use of other antibiotics or standard COVID-19 treatment.

In terms of safety, azithromycin has a relatively safe profile. This meta-analysis suggested that the number of patients in the azithromycin group experiencing adverse events such as hypoglycemia, diarrhea, nausea/vomiting, arrhythmia, and secondary infections were similar to those in the control group. The risk of QT prolongation was not statistically significant either compared to previous studies showing a potential torsadogenic effect of azithromycin[7,8].

The evidence generated from this study confirmed that azithromycin was not associated with a significant clinical improvement in COVID-19 patients. The lack of clinical benefits suggested that routine use of azithromycin should be ceased except in cases with evident bacterial pneumonia for which a combination of a beta-lactam and macrolide antibiotics is recommended[35]. However, it was unclear whether the quality of evidence from this meta-analysis was sufficient. Although overall pooled results were stable, effects were inconclusive for the majority of cases. Additional data are needed to confirm results of this study. There were substantial inconsistencies observed across studies, especially in the analysis evaluating the efficacy of azithromycin. It might be due to the heterogeneous nature of study subjects and the timing of outcome measurement. Despite some imprecision and heterogeneity in outcomes, this meta-analysis suggested a weak recommendation for using azithromycin as one treatment for COVID-19.

Azithromycin did not result in a superior clinical improvement for COVID-19 patients, although it was well-tolerated and safe to use. Due to a low quality of evidence presented in this meta-analysis, more clinical studies are needed to clearly elucidate the benefit of azithromycin for COVID-19 patients.

Authors' Contributions

Conceptualization: Glenardi, Mangkuliguna G, Natalia. Methodology: Glenardi, Mangkuliguna G, Natalia, Pramono LA. Formal analysis: Glenardi, Mangkuliguna G, Natalia, Pramono LA. Data curation: Glenardi, Mangkuliguna G, Natalia, Pramono LA. Software: Glenardi, Mangkuliguna G, Natalia. Validation: Glenardi, Mangkuliguna G, Natalia, Pramono LA. Investigation: Glenardi, Mangkuliguna G, Natalia, Pramono LA. Writing - original draft preparation: Glenardi, Mangkuliguna G, Natalia. Writing - review and editing: Glenardi, Mangkuliguna G, Natalia, Pramono LA. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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