Evaluating the Clinical Endpoint of Antibiotic Prophylaxis for Cirrhosis Patients Complicated with Upper Gastrointestinal Bleeding: An Updated Systematic Review and Meta-analysis

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ABSTRACT

Background and Objective. Antibiotic prophylaxis is used to prevent bacterial infections and rebleeding in cirrhosis patients with upper gastrointestinal bleeding (UGIB). However, the effects of various antibiotics on patients with UGIB are still being considered. This study aims to evaluate the effect of antibiotic prophylaxis on cirrhosis patients with UGIB.

Methods. The studies were searched through databases of PubMed, ScienceDirect, Wiley Online Library, and CENTRAL from 2013 to 2023. We used Revman 5.4 to perform a meta-analysis. I2 statistics measured the heterogeneity test. The odds ratio (OR) and 95% confidence interval (CI) were used to assess the effect of antibiotic prophylaxis.

Results. Twelve studies involving 14,825 cirrhosis patients were included in this study. Based on the meta-analysis, antibiotic prophylaxis significantly lowered the bacterial infection rate (OR: 0.29, 95%CI: 0.10 to 0.84, *P* = 0.02), and the incidence of serious adverse events (SAE) (OR: 0.50, 95%CI: 0.28 to 0.88, *P* = 0.02) in cirrhosis patients with UGIB.

Conclusions. Administration of antibiotics demonstrated a significant reduction in bacterial infection rates and SAEs. Broad-spectrum non-absorbable antibiotics can be used in cirrhosis patients with UGIB. The appropriate use of antibiotics is important to prevent resistance.

Keywords: antibiotic; prophylaxis, cirrhosis, variceal bleeding

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INTRODUCTION

Cirrhosis is a chronic disease characterized by various alterations in microcirculation, gross vascular anatomy, and the architecture of the liver. The escalation of portal hypertension severity triggers multiple pathophysiological pathways, culminating in the primary complications of cirrhosis, such as ascites, variceal hemorrhage, and hepatic encephalopathy. Liver cirrhosis was responsible for around 2% of global deaths in 2010, approximately one million.[1] The leading cause of mortality is the presence of portal hypertension characterized by increased hepatic venous pressure >10 mmHg.[2]

Liver cirrhosis has two main stages of disease - compensated and decompensated cirrhosis. In cases of compensated cirrhosis, the focus is to prevent recurrent variceal bleeding in those with a high risk of esophageal varices (EV) on endoscopy.[3] Esophageal varices are characterized by the

discovery of dilated veins in the esophagus, usually caused by portal hypertension. Esophageal varices prevalence is 40-95% in those with liver cirrhosis.[4]

Primary prevention of bleeding refers to treating EV before rupture and bleeding. In managing UGIB caused by variceal bleeding, various treatments can be performed, such as volume expansion, hemorrhage control, vasoconstriction, and short-term antibiotic prophylaxis.[5] However, current clinical guidelines recommend antibiotic prophylaxis in cirrhotic patients with UGIB. This therapy aims to prevent infection, but using inappropriate antibiotics raises the risk of resistance. Prophylaxis antibiotic stratification should be performed to choose the optimal prophylaxis antibiotic effect.[6]

This meta-analysis aims to assess the effect of antibiotic prophylaxis in cirrhotic patients experiencing UGIB by comparing mortality rates, bacterial infections, rebleeding rates, non-serious adverse events (NSAE), and serious adverse events (SAE) between patients receiving antibiotic prophylaxis and those given a placebo or no intervention.

MATERIALS AND METHODS

Registration

This study was based on Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol (PRISMA-P) guidelines. The protocol was registered (CRD42023441508) in the Prospective Register of Systematic Reviews (PROSPERO).

Data Sources and Searches

We performed a literature search for randomized control trials and observational studies using PubMed, PLoS, Scopus, Wiley-online, ScienceDirect, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from January 2013 to June 2023. The search strategy was primarily designed for the PubMed database using MeSH terms. We used ((Cirrhosis) OR (Liver cirrhosis) OR (Hepatic cirrhosis)) AND ((Antibiotic prophylaxis) OR (Antibiotic) OR (Antibacterial) OR (Quinolone) OR (Cephalosporin) OR (Beta-lactam)) AND ((Variceal bleeding) OR (Melena) OR (Gastrointestinal hemorrhage) OR (hemorrhage)) as a free-text term. The filter set for all types of articles except systematic review and review. We use the same method for the Wiley Online database except for publication type, we only included journals. The CENTRAL database is an exceptional setting for the Cochrane Protocol and Cochrane review. We combined the term PubMed for the ScienceDirect database and only selected research articles.

Definition of Variable

Antibiotic prophylaxis was defined as receiving oral or intravenous antibiotics at admission. The antibiotic types were classified based on each antibiotic's mechanism of action. The study that did not mention the type of antibiotic was grouped as "unclear" and the study using a combination of antibiotics was defined as "others". The control group was the sample who had not received antibiotics at admission. Upper gastrointestinal bleeding was defined by a sign of hematemesis, coffee-ground vomitus, and red/black aspiration of the nasogastric tube in cirrhosis patients. Rebleeding was defined as the new onset of the UGIB sign. The diagnosis of bacterial infection was made based on each study-owned reference. Mortality was defined as uncontrolled bleeding, multi-organ failure, septic shock, hypovolemic shock, hepatic encephalopathy, and other causes except trauma. The length of hospitalization was measured from day one of admission to discharge and presented in days. Non-serious adverse events (NSAE) were defined as non-life-threatening condition including mild ascites, fatigue, headache, nausea/vomiting, abdominal pain, malaise, dizziness, insomnia, pruritus, or diarrhea. Based on FDA, serious adverse events (SAE) occur when the patient outcome is: death, life-threatening, hospitalization, moderate to large ascites, hepatic encephalopathy, portal hypertensive bleeding, sepsis, liver failure, or HCC during the treatment period.

Inclusion and Exclusion Criteria

Studies of 14,825 patients with cirrhosis and UGIB were considered eligible for inclusion. The cirrhosis patients at least 18 years complicated with UGIB, there is no restriction for biological sex and cause of cirrhosis in the study. Inclusion criteria were defined using the PICOS principles: (P) population, cirrhosis patients with UGIB; (I) intervention and (C) control, patients with antibiotic prophylaxis and patients without antibiotic prophylaxis; (O) outcomes, overall mortality, bacterial infections, rebleeding, length of stay (LoS), serious adverse event (SAE), and non-serious adverse event (NSAE); (S) study design, randomized controlled trials (RCTs) and prospective or retrospective cohort studies.

Exclusion criteria were laboratory experiments or animal studies, studies with incomplete data or data that could not be extracted, supplement abstracts, case reports, literature reviews, meta-analyses, or dissertations. This review excluded studies that were published in other languages and did not have an official English translation.

Data Extraction and Quality Assessment

Data extraction was performed independently by five review authors (PISLD, KMNP, NLPYD, NGKD, NPGRS) and divided by the year of study from 2013 to 2023. Each reviewer read the study's full text then extracted the data on *Google Sheets* based on data availability. The following data extracted were study characteristics (author, year of study, country, design studies, total patients, age, gender, intervention, control, Child-Pugh score, Child-Pugh A/B/C, and study outcomes that consist of overall mortality, bacterial infection, rebleeding, SAE, NSAE). The studies were evaluated based on their quality using Critical Appraisal

Skills Programme Tools (CASP) (https://casp-uk.net/casp-tools-checklists) which consists of an 11-item checklist to assess included studies' validity, importance, and applicability. The quality of the studies was classified as Good, Fair, and Poor.

Risk of Bias Assessment

Five reviewers (PISLD, KMNP, NLPYD, NGKD, NPGRS) independently assessed the methodological quality and suitability of each study. The risk of bias assessments was assessed using the Risk of Bias 2 (RoB2) and Newcastle-Ottawa Scale (NOS) based on the type of study design. RoB2 was used to assess RCTs, and NOS was used to assess the Cohort Study. RoB2 included five domains: bias arising from the randomization process, bias due to deviation from intended interventions, bias due to missing outcomes, bias in the measurement of the outcome, and bias in the selection of the reported result. The risk of bias domain in RoB2 was rated as low, unclear, and high. Meanwhile, NOS included eight domains: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of the exposure, demonstration that outcome of interest was not present at study start, comparability of the cohort based on the design or analysis, assessment of outcome, follow-up length for the outcome occurs, and adequacy of follow-up of the cohort. The risk of bias domain in NOS was rated by score ≥7 as low risk, 4-6 as intermediate risk, and <4 as high risk. Differences in individual evaluations were resolved by reaching a consensus discussed with third parties (DAS and IKM).

Statistical Analysis

Statistical analysis was conducted using RevMan 5.4 and StataMP 17. Statistical heterogeneity was analyzed using chi-square and I^2 test with significance set at $P<0.1$. The random effect model was used in this study to evaluate size effects. The results were presented as OR with a 95%CI and P-value. We divided the analysis into two main domains, overall size effect, and subgroup size effect, to evaluate which regimen is superior. We did not perform subgroup analysis on outcome adverse events and length of hospitalization due to a lack of data.

RESULTS

Study Selections

2.901 articles were screened using PubMed, PLoS, Scopus, Wiley-online, ScienceDirect, and CENTRAL databases for the last ten years. A total of 16 articles were found after exclusions and duplicates were removed and assessed for eligibility. Four articles were excluded, mainly because the control group in those studies used antibiotic regimens. This meta-analysis comprised a total of 12 articles. Figure 1 shows the PRISMA flowchart detail of the study selection.

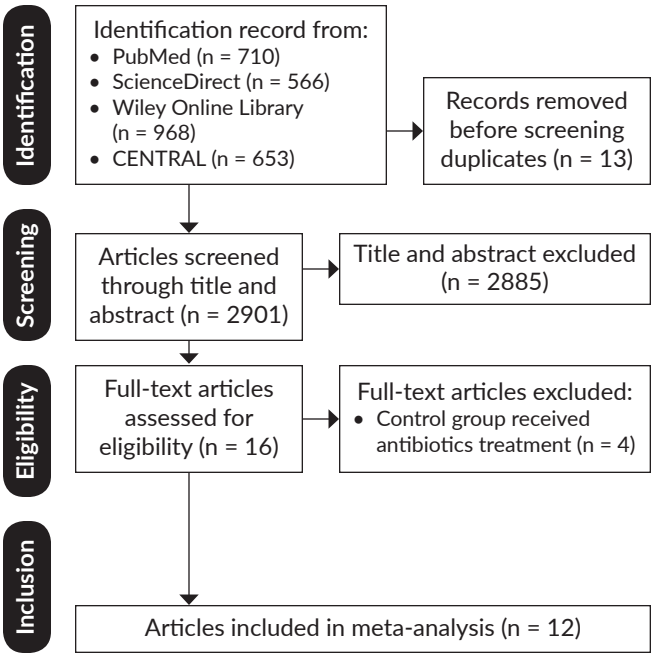

Figure 1. PRISMA flow chart of the study selection.

Characteristics of Studies

Twelve studies with 14,825 patients with hepatic cirrhosis were included in this study, with different antibiotic interventions (Table 1). Antibiotic groups include cephalosporins, cephalosporin combination with quinolone, macrolides, broad-spectrum non-absorbable, and others. This study's most commonly used interventional antibiotic was from the cephalosporin group (ceftriaxone, cefazolin, and cefuroxime).[7-11] Most study participants are male (68.3%). There are two randomized controlled trial studies, while the others are retrospective or prospective study designs. The longest study follow-up was six years,[7] and the shortest was 28 days[12].

Risk of Bias Assessment

All 10 cohort studies were at low risk of bias, with NOS score ≥7.One study had a high risk of bias, with NOS score of 6 due to the follow-up being not long enough; and on comparability domain, the highest NOS score was 9 as shown in Table 2.

There are three unclear domains of risk of bias in RCT studies by and Higuera et al.[12] and Ardakani et al.[13] Figure 2 demonstrates domains are bias in the measurement of the outcome, bias in the selection of the reported result, and bias due to deviation from the intended interventions.[14,15]

Publication Bias Assessment

The mean log odds ratio effect size based on the 12 observed studies showed no significant publication bias, with a 95% confidence interval (CI) of -0.04 to 0.225, $P = 0.115$. The hypothetical studies, K0=12-12=0, are estimated to be

Table 1. Characteristics of the Included Studies

Author, year	Country	Total	Intervention	Control	Child-Pugh score	Study Design	Outcome
Kuo, 2015[7]	Taiwan	235	Ceftriaxone, intravenous infusion, 1 gram per 12 hours	Without antibiotics	7.0 ± 1.6	Cohort	Length of hospital stay Rebleeding Infections In-hospital mortality
Tandon, 2015[8]	Canada	381	Ciprofloxacin in 50%, 3rd generation Cephalosporins in 41%, Others 9%	Without antibiotics	8.95 ± 2.05	Cohort	Bacterial infections Rebleeding within 6 weeks Overall mortality within 6 weeks
Chang, 2020[9]	Taiwan	913	Cefazolin, Cefazolin Gentamicin Cefuroxime, Ceftriaxone	Without antibiotics	7.34 ± 1.20	Cohort	4 days bacterial infection 4 days rebleeding 42 days mortality
Gan, 2023[10]	China	392	Oral Quinolones, Fluoroquinolones, IV 3rd generation Cephalosporin	Without antibiotics	NA	Cohort	In-hospital death Onset of the new infection
Ueno, 2020[11]	Japan	150	Cefazolin, Ceftriaxone for 5 to 7 days	Without antibiotics	8(7-9)	Cohort	In-hospital bacterial infection In-hospital mortality Rebleeding within 120 hours Emergency readmission within 30 days
Higuera, 2018[12]	Mexico	87	Lactulose 30 mL tid or LOLA 10 g IV or Rifaximin 400 mg PO 7 days	Placebo	NA	RCT	Hepatic Encephalopathy (HE) development Adverse event
Kang, 2017[13]	Korea	1042	Rifaximin 600 mg bid + Lactulose 30-60 mL tid	Lactulose 30-60 mL tid	8.0 - 11	Cohort	Overall survival Spontaneous Bacterial Peritonitis (SBP) Hepatorenal Syndrome (HRS) Variceal bleeding
Wu, 2019[14]	Taiwan	1205	Ceftriaxone, Cefotaxime, Ofloxacin, Ciprofloxacin, Levofloxacin, Imipenem, or Cephalosporin	Without antibiotics	NA	Cohort	Rebleeding All-cause mortality
Moon, 2016[15]	Seattle	8655	3rd generation Cephalosporin 54.5%, Fluoroquinolones 31.9%, Penicillins 2.9%, Aminoglycosides, Others	Without antibiotics	NA	Cohort	Length of hospital stay Weekend admission In-hospital mortality Crude 30-day mortality
Martinez, 2021[16]	Spain	1656	TGC 76.2%, Quinolones 19%, Amoxicillin/ Clavulanic 2.9%, Others 1.9%	Without antibiotics	NA	Cohort	Incidence of bacterial infection Predictive factors of bacterial and respiratory infection Antibiotic recommendation
Ardakani, 2013[17]	Iran	40	Erythromycin, intravenous, 3 mg/kg	Placebo	NA	RCT	Endoscopic yield Blood unit transfused LoS and mortality
Vlachogiannakos, 2013[18]	Greece	69	Rifaximin 400 mg tid	Without antibiotics	9.5 ± 1.9	Cohort	Survival variceal bleeding HE, SBP, HRS

NA – no data available, RCT – Randomized Controlled Trials, LoS – Length of stay

missing and imputed. The funnel plot showed no prominent asymmetry.

Mortality rate. The heterogeneity test showed that the difference was statistically significant (I^2 = 93%). The random-effects model analysis showed no difference in overall mortality between groups (OR: 0.82, 95%CI: 0.47 to 1.42, *P* = 0.47). In the subgroup analysis shown in Appendix A, the result showed that cephalosporin combined with quinolone (OR: 0.39, 95%CI: 0.25 to 0.60, *P*<0.0001) and broad-spectrum non-absorbable antibiotic (OR: 0.50, 95%CI: 0.38 to 0.66, *P*<0.00001) reduced the mortality rate of cirrhosis patients with UGIB.

Bacterial infections. The average occurrence of bacterial infection in patients who received antibiotic prophylaxis was lower than in the control group (OR: 0.29, 95%CI: 0.10 to 0.84, *P* = 0.02). Figure 3 showed that the antibiotic that provided stronger protection was the broad spectrum non-absorbable group (OR: 0.13, 95%CI: 0.09 to 0.20, *P*<0.00001).

Rebleeding. No significant difference is shown in Appendix B in the rebleeding rate (OR: 0.63, 95%CI: 0.33 to 1.21, *P* = 0.16). The use of broad-spectrum non-absorbable antibiotic (OR: 0.44, 95%CI: 0.29 to 0.66, *P*<0.0001) and cephalosporin combined with quinolone (OR: 1.99, 95%CI: 1.18 to 3.34, *P* = 0.010) lowered the rate of rebleeding.

Serious adverse events and Non-serious adverse events. The heterogeneity test showed I^2 = 78% and 82%, so the random effects model was applied. Five studies were included to analyze the incidence of SAE. Antibiotic prophylaxis significantly lowered the incidence of SAE in patients with UGIB (OR: 0.50, 95%CI: 0.28 to 0.88, *P* = 0.02), as shown in Figure 4. Four studies evaluated the incidence of NSAE (OR: 0.21, 95%CI: 0.03 to 1.37, *P* = 0.10).

Length of hospitalization. Antibiotic prophylaxis did not affect the length of hospitalization between the antibiotic and control groups (OR: 0.12, 95%CI: 2.51 to 2.27, *P* = 0.92).

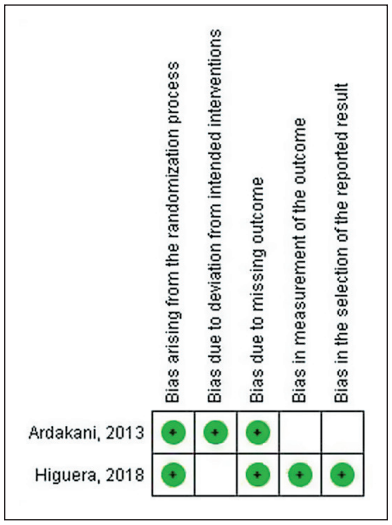

Figure 2. Risk of bias for RCT study.

Table 2. NOS Assessment for Risk of Bias Cohort Studies

Author, year	S					C		E/O				Total
	1	2	3	4	Sum	1	Sum	1	2	3	Sum	
Chang et al., 2020[9]	*	*	*	*	4	*	1	*	*	*	3	8
Gan et al., 2023[10]	*	–	*	*	3	**	2	*	*	*	3	8
Martinez et al., 2021[11]	*	*	*	*	4	*	1	*	–	*	2	7
Kang et al., 2017[12]	*	*	–	*	3	**	2	*	*	*	3	8
Wu et al., 2019[15]	*	*	*	*	4	*	1	**	*	*	4	9
Ueno et al., 2020[16]	*	*	*	*	4	*	1	*	–	*	2	7
Moon et al., 2016[17]	*	*	*	*	4	-	0	*	*	*	3	7
Kuo et al., 2015[7]	*	*	–	*	3	**	2	*	*	*	3	8
Tandon et al., 2015[8]	*	*	–	*	3	*	1	*	*	–	2	6
Vlachogiannakos et al., 2013[18]	*	*	–	*	3	*	1	*	*	*	3	7

S – selection; C – comparability; E – exposure; O – outcome

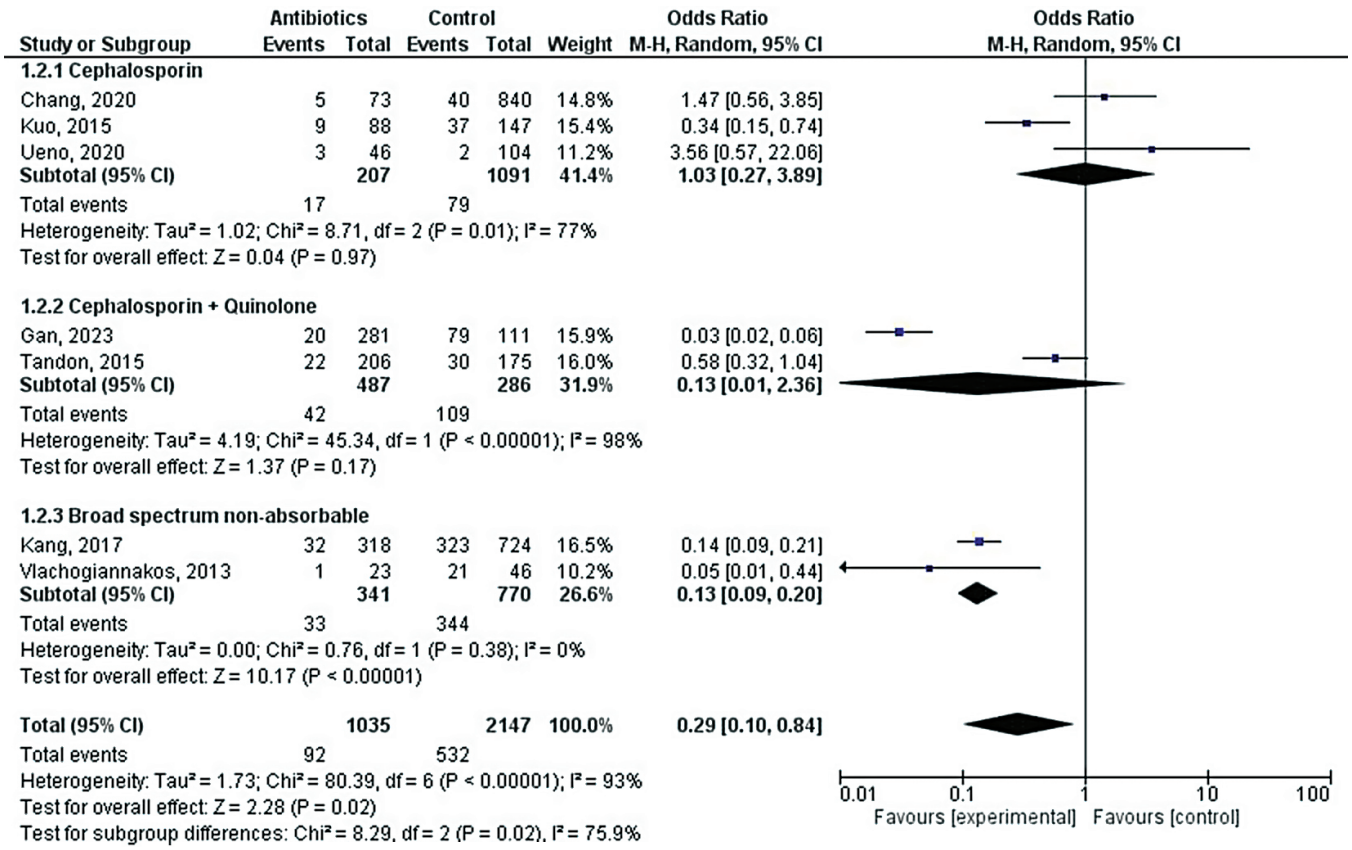

Figure 3. Forest plot for bacterial infection outcome.

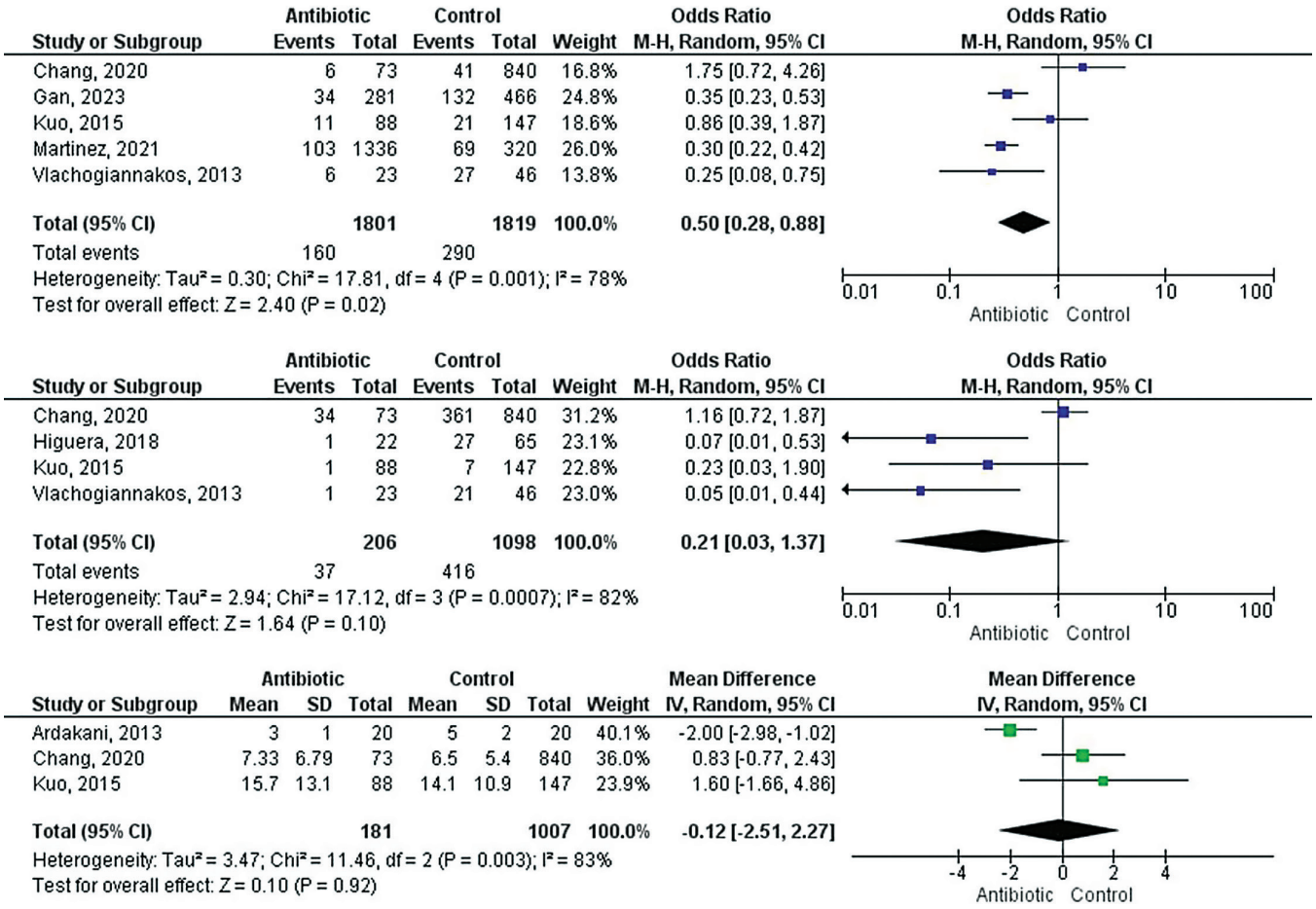

Figure 4. Forest plot for SAE, NSAE, and length of hospitalization outcome.

DISCUSSION

Antibiotic prophylaxis for cirrhosis patients with UGIB has been recommended in several guidelines. Whether antibiotic prophylaxis provides benefits for all cirrhosis patients is questionable. Recent studies revealed that administering antibiotic prophylaxis therapy can lower overall mortality, bacterial infections, and rebleeding rates. In addition, antibiotic prophylaxis is also related to the LoS.[5,6]

In the latest study, mortality rates were significantly lower in the antibiotic group than in the non-antibiotic group (6.41% vs. 17.12%, *P* = 0.001), and variceal bleeding (OR: 2.877, 95% CI: 1.043 to 7.933, *P* = 0.041) were risk factors for mortality.[10] Mortality rate in the previous study reached 4.3% in patients with antibiotic prophylaxis compared with 7.7% in the no prophylaxis group (*P* = 0.71).[11] In our subgroup analysis, the cephalosporin and quinolone combination significantly reduced the mortality rate in patients (p<0.0001). In the discussion related to the rebleeding rate, Wu et al. demonstrated that cirrhosis patients with UGIB without serious complications could benefit from antibiotic prophylaxis. The rebleeding rate within four weeks was significantly lower in patients with antibiotic prophylaxis (3.05% vs 6.03%, p = 0.0142).[14] Another study from Taiwan demonstrated that patients given antibiotic prophylaxis (ofloxacin 200 mg iv q12h for 2d followed by oral ofloxacin 200 mg q12h for 5d) reduced rebleeding rate.[19]

Infections are common in patients with UGIB, Bleichner et al. found that 22% of bacterial infections were diagnosed within 48 hours of admission.[20] Bernard et al. also defined early rebleeding as recurrent bleeding within seven days after admission.[21] Broad spectrum non-absorbable antibiotics such as Rifaximin significantly reduce bacterial infection and rebleeding rate. Nevertheless, the prevalence of antibiotic-resistant bacteria reduces the effectiveness of commonly used antibiotics. On the other hand, non-compliant prescription of antibiotics could increase multidrug-resistant bacteria (MDR) and medical expenses. Thereby, Tandon et al. suggested that patients with low bacterial infection and mortality rates, such as Child-Pugh A, seem unnecessary to receive antibiotic prophylaxis.[8] Those groups' risk of infection and mortality is relatively lower than CP-C. Hou et al. also recommended antibiotic prophylaxis effectively given to advanced cirrhosis (Child-Pugh B or C).[19]

The current study finds no difference in the LoS between the antibiotic and control groups. In contrast,

the current meta-analysis reported a significantly reduced hospitalization in the antibiotic group but not for the length of ICU stay.[6] LoS is influenced by factors such as disease severity, comorbidity, or hospital-acquired complication rather than prophylaxis.[7] A study by Kuo et al. describes the presence of comorbidity in their participants, primarily hypertension, DM, and CVD. Those diseases do not directly benefit from given antibiotics but may contribute to longer LoS.[7] Gao et al. showed that quinolone combination with beta-lactam shortened the LoS.[6] In our analysis, only three studies reported LoS. Antibiotic prophylaxis is not performed due to a lack of efficacy in preventing longer lengths of stay in inpatient CP-A/B with UGIB.[9] In our analysis, most participants had lower CP-class (CP-A/B).

A study by Ferrarese et al. reported that inappropriate antibiotic use was related to a 1.9 higher OR of death every hour in patients with cirrhosis and septic shock.[22] Therefore, the optimal selection, duration, and dosage of antibiotic treatment can save lives.[22,23] Regarding safety, physicians should consider the risk of drug-induced liver injury (DILI) or hepatic encephalopathy (HE).[22] Our analysis determined new onset HE as a serious adverse event (SAE). Since fluoroquinolone reported a significant cardiotoxicity effect,[24] we considered including new-onset myocardial infarction in our SAE analysis. This study identified a significant difference in the SAE between groups $P = 0.02$.

Additionally, there was no difference between antibiotic and control groups in NSAE. Komolafe et al. also reported no difference in SAE and NSAE between cirrhosis patients and control regarding antibiotic prophylaxis.[25] In our analysis, not all adverse events were considered drug-related. Most of our participants have low CP scores. In other words, a low degree of liver dysfunction is associated with a lower alteration of drug metabolism.[22]

Potential confounding variables may impact the findings of this meta-analysis. Endoscopy serves as the primary diagnostic and therapeutic approach for UGIB. Patients with cirrhosis who undergo endoscopic procedures to manage bleeding are notably vulnerable to infection.[26,27] However, research indicates that therapeutic endoscopy can significantly improve outcomes in patients with severe acute UGIB. Considering the recent progress in the management of UGIB through endoscopy, future research on prophylactic antibiotics in patients with cirrhosis and UGIB should consider the role of therapeutic endoscopy.[6,28]

This study has certain limitations that need to be acknowledged. Firstly, due to the restricted number of studies that discuss hospital stay, NSAE, and SAE, we could not conduct subgroup analyses. Secondly, few studies describe the dose of antibiotic prophylaxis, so we can't perform a dose-response analysis. Thirdly, more studies are needed to be included in each analysis, especially subgroup analysis, as this study only included two RCTs. This study outcome showed heterogeneity, which could be due to several factors such as differences in study designs, selective data processing, and varying levels of liver disease progression, all potentially diverging from the original study design. Further RCT studies assessing the effect of antibiotic prophylaxis on the different cirrhosis severity are needed.

CONCLUSION

This study confirmed the beneficial effects of antibiotic prophylaxis in cirrhotic patients with UGIB, demonstrating a reduction in bacterial infections and serious adverse events such as hepatic encephalopathy. Additionally, the study suggests that broad-spectrum non-absorbable antibiotics significantly improve survival, prevent rebleeding, and reduce bacterial infections in these patients. Notably, further prospective studies are necessary to appropriately and effectively evaluate the use of antibiotics in cirrhotic patients, as more research is needed to explore ways to improve the overall outcomes for cirrhotic patients with UGIB.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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None.

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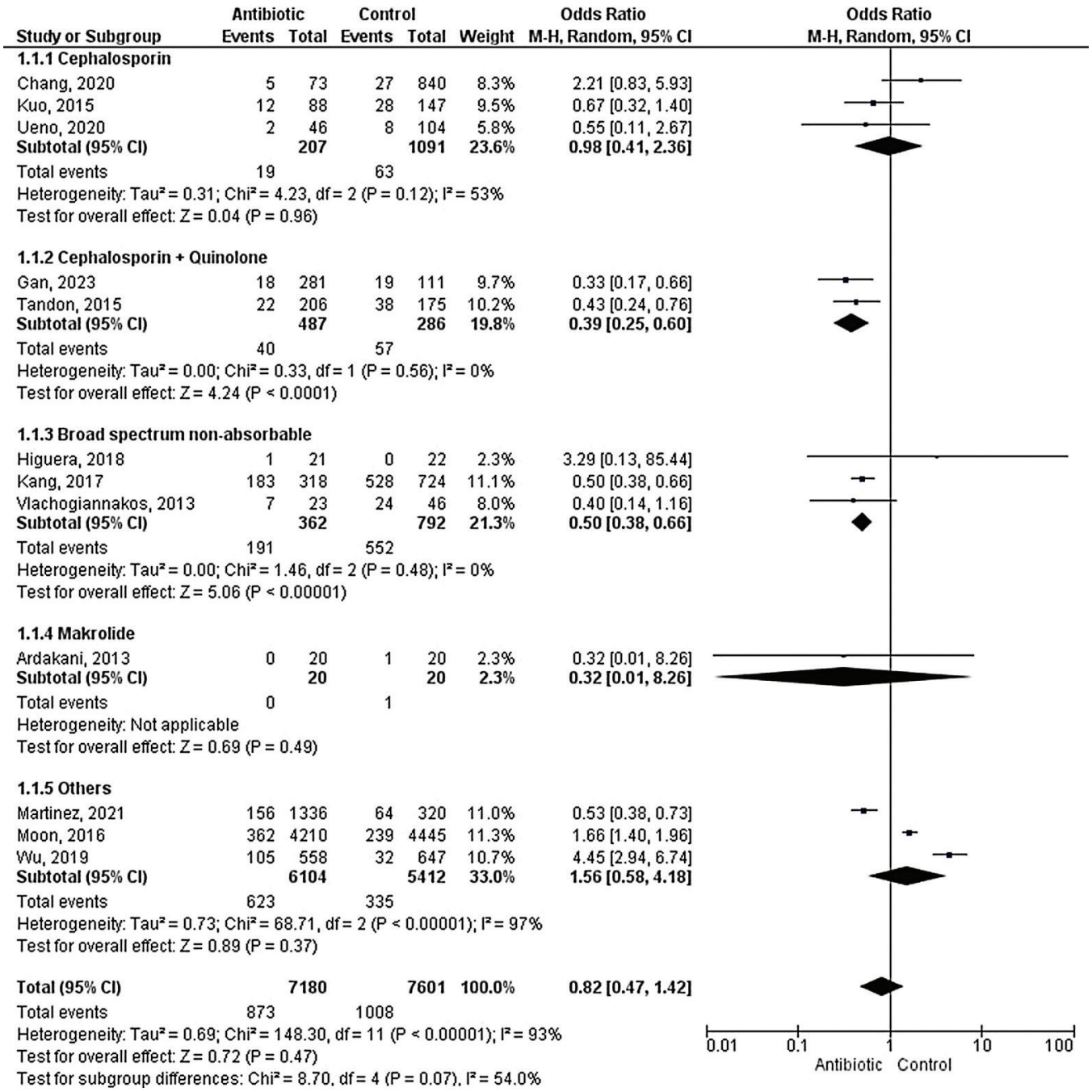
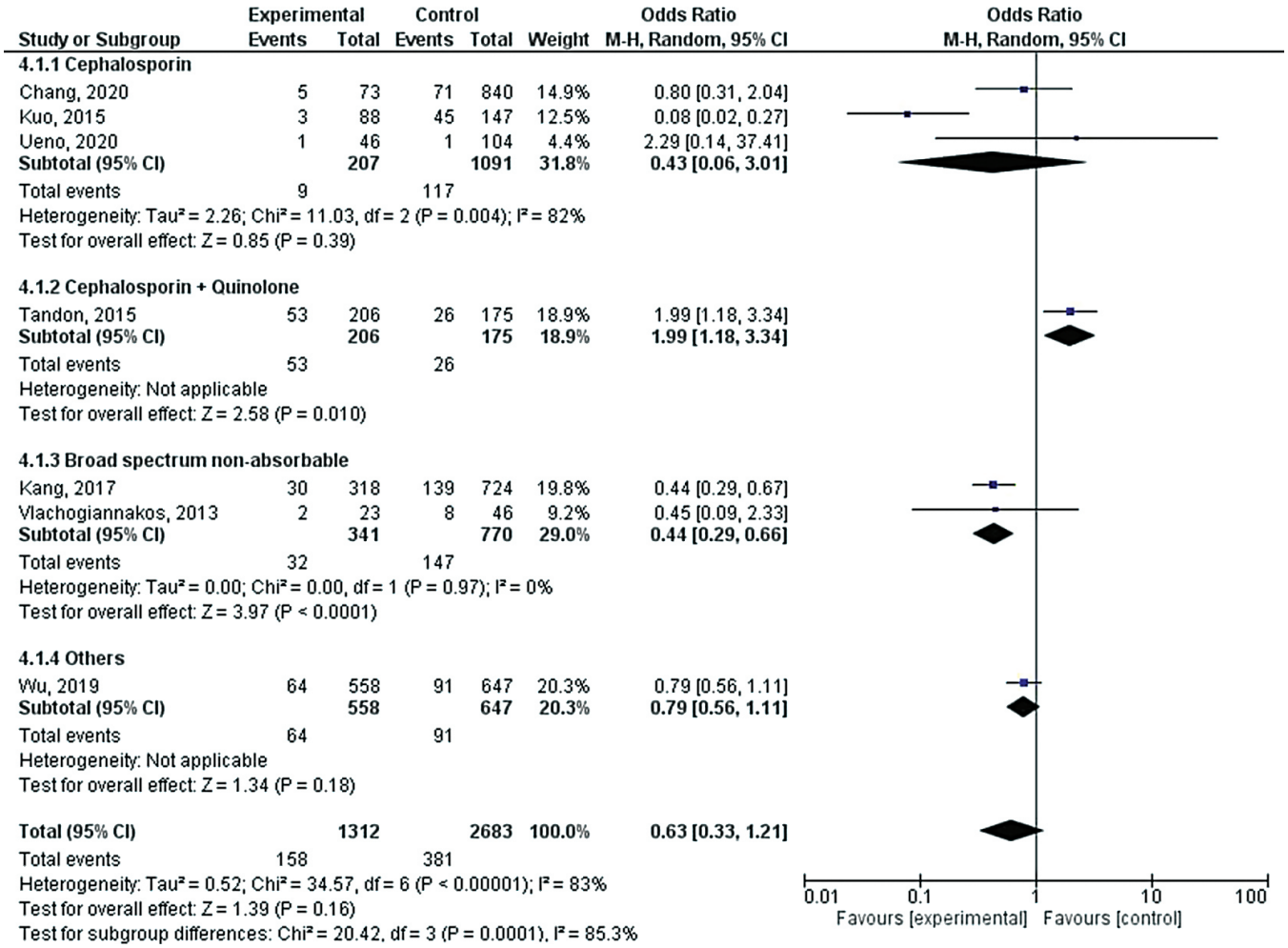
APPENDICES



Appendix A. Forest plot for mortality outcome.



Appendix B. Forest plot for rebleeding outcome.