Association between Prior Calcium Channel Blocker use and Mortality in Septic Patients: A Meta-Analysis of Cohort Studies

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Research

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Abstract

Background: To comprehensively review the literature and synthesize evidence concerning the relationship between preadmission calcium channel blocker (CCB) use and mortality in patients with sepsis.

Methods: The MEDLINE, EMBASE, and Cochrane CENTRAL databases were searched from their inception to April 9, 2020. Cohort studies that related to prior CCB use in patients with sepsis were analysed. Pairs of reviewers independently screened studies, extracted data, and assessed the risk of bias. Two primary outcomes related to mortality, namely, 30-day mortality and 90-day mortality, were analysed; heterogeneity between studies was assessed using I^2 and was considered moderate if I^2 was equivalent to 50–75% and high if $I^2 \geq 75\%$. Fixed and random-effects models were used to calculate the pooled odds ratios (ORs) and 95% confidence intervals (CIs). The quality of outcomes was evaluated with the Newcastle-Ottawa Scale (NOS). Sensitivity analyses were performed to examine the robustness of the results.

Results: 552 potentially relevant studies were identified, and the full texts of 25 articles were reviewed. Ultimately, five cohort studies involving 280,982 patients were confirmed to have a low risk of bias and were included. Preadmission CCB use was associated with a significantly lower 30-day mortality in septic shock (OR, 0.61 [0.38-0.97]; $P = 0.035$; $I^2 = 62.4\%$), not in sepsis (OR, 0.83 [0.66-1.04]; $P = 0.103$; $I^2 = 95.4\%$). Moreover, prior CCB use could significantly reduce 30-day mortality in sepsis (OR, 0.90 [0.85-0.95]; $P < 0.001$; $I^2 = 31.9\%$).

Conclusions: This meta-analysis suggests that preadmission CCB use is significantly associated with improving long-term prognosis of sepsis, and also short-term survival of septic shock patients. This finding may provide an attractive direction for sepsis management.

Background

Sepsis is defined as a life-threatening disorder of organ function caused by dysregulated host responses to infection (1). Global epidemiological data suggest that sepsis is a major public health issue and remains a primary reason for mortality and critical illness; sepsis affects millions of people worldwide each year (2-4), and its incidence is not declining (5). Currently, the pathophysiological basis of sepsis is thought to involve a disorder of pro- and anti-inflammatory responses, which offers a new method for the treatment of this deadly disease (6). The prognosis is associated with not only the virulence of the pathogens but also the septic patient's age and coexisting diseases, such cardiovascular dysfunction (7).

Calcium channel blocker (CCB) is widely administered for cardiovascular disease therapy in conditions such as hypertension and ischaemic heart disease (8, 9). These drugs can inhibit Ca^{2+} channels in the myocardium and vascular smooth muscle cells, resulting in the inhibition of myocardial contractions, the pulse conduction system (anti-arrhythmias), and vasodilation (10). Cardiovascular disease is well known to be one of the most common coexisting conditions in septic patients and is independently related to an increased risk of death during hospitalization (11, 12). Sepsis is related to an overload of Ca^{2+} levels in many cell types (13) and can lead to disordered cellular processes, cytotoxicity or even cell death via a variety of mechanisms, such as metabolic manifestations, vascular smooth muscle tone dysregulation, mitochondrial dysfunction, nuclear damage, cytoskeletal breakage, production of nitric oxide and pro-inflammatory cytokines, and apoptosis (14, 15). However, CCB can restore such disrupted cellular processes to normal through calcium channel-dependent calcium ion homeostasis. Furthermore, CCB shows pleiotropic effects, such as antioxidant properties (16)，decreasing immunodepression and anti-inflammatory activity (17), in sepsis. Therefore, CCB use may benefit patients with sepsis.

Recently, Wiewel et al (18) reported that previous CCB use had an obvious survival benefit compared with non-CCB use in patients with sepsis. However, several studies (19-21) have indicated that preadmission CCB use was not related to lower mortality in septic patients. In addition, Hsieh et al (21) reported that CCB had a decreased 30-day mortality in septic shock patients. But Roquetaillade et al (22) indicated that CCB using was not associated with lower mortality of septic shock patients. So the relationship between previous CCB use and prognosis is controversial in sepsis. Thus, a synthesis of obtainable data was performed to evaluate whether CCBs are helpful for reducing mortality in septic patients.

Methods

The study protocol is registered on the PROSPERO website (http://www.crd.york.ac.uk/PROSPERO) with the registration number CRD42019127112, which can be found online at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=127112.

Search Strategy

The methodology followed the Observational Studies in Epidemiology guidelines for meta-analysis. A comprehensive literature search for cohort studies on CCB use and mortality of septic patients published from database inception to April 9, 2020, was performed using the MEDLINE (www.ncbi.nlm.nih.gov/pubmed), EMBASE (www.embase.com), and Cochrane CENTRAL (https://www.cochranelibrary.com/central) databases. A combination of MeSH/Emtree, title, abstract or keyword terms was used. The search terms were "calcium channel blockers", "calcium channel blocking agent", "calcium antagonist", "sepsis", and "septic shock". The detailed retrieval strategy can be seen in **Supplemental Table 1**. The search was restricted to English. Furthermore, we reviewed references of eligible articles to identify other potentially relevant studies. Literature searches were conducted independently by Xianfei Ding, Yuqing Cui and Yanhui Zhu.

Eligibility Criteria

Studies were considered eligible for inclusion in the meta-analysis if they met the following population, intervention, comparators, outcomes and study design (PICOS) criteria: 1) the population included adult septic patients, 2) the intervention involved preadmission use of CCB, 3) the comparison intervention

consisted of non-CCB use, 4) the outcome was mortality, and 5) the study design was an observational cohort study. We excluded relevant studies that did not report outcome data. In addition, we also excluded literature for which full texts could not be searched and summarized and review articles.

Study Selection and Data Extraction

Xianfei Ding, Yuqing Cui and Yanhui Zhu independently screened the titles and/or abstracts of all retrieved studies to determine whether they potentially met the eligibility criteria and noted the cause for excluding each article. Key data explications were performed independently by Huoyan Liang and Lifeng Li. All disputes were settled by discussions with Dong Wang, Quancheng Kan and Lexin Wang. The following characteristics were extracted from all the included studies: first author, year (publication), country, study design, CCB and non-CCB use in patients with sepsis, sex composition of patients, study duration, and unadjusted or adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for primary outcomes.

Assessment of Risk of Bias

The risk of bias of eligible studies was evaluated by the Newcastle-Ottawa Scale (NOS) for cohort studies (23). A maximum of nine points could be obtained: four points as the maximum for selection, two points as the maximum for design and analysis comparability, and three points as the maximum for assessment of outcomes. High-quality studies received a score ≥ 7, whereas moderate- and low-quality studies received scores of 4–6 and ≤ 4, respectively.

Statistical Analysis

For binary data, we used ORs and their 95% CIs to estimate the effect sizes of our outcome of interest. The pooled ORs of the included studies were calculated by fixed-effects model with inverse-variance or a random-effects model with I-V heterogeneity method to generate forest plots. Heterogeneity among studies was evaluated by I^2; I^2 values of 0–25% represented no heterogeneity, values of 25–50% represented mild heterogeneity, values of 50–75% represented moderate heterogeneity, and values of 75–100% represented high heterogeneity. A fixed-effects model was used to calculate pooled ORs when no or mild heterogeneity existed in the included studies; otherwise, a random-effects model was used. Begg's funnel plot (24) was constructed and Egger's linear regression (25) was performed to evaluate potential publication bias. Funnel plots were visually evaluated for dissymmetry. One-way sensitivity analysis was applied to evaluate the robustness of the results. All statistical analyses were performed by Stata 14.0 (College Station, Texas, 77845, USA, Serial number: 401406267051).

Results

Study Selection

The initial literature search yielded 552 potentially relevant publications, and 457 records remained after removing duplicates. We then excluded 432 records after preliminary title and abstract screening. After evaluating the full texts of the remaining 25 records, we identified 5 cohort studies (18–22) for inclusion in this meta-analysis (Fig. 1).

Study Characteristics

An in-depth detailed description of the 5 included studies is shown in Table 1. In total, 280,982 septic patients were included in this meta-analysis. All included studies were multi-centre cohort studies that involved septic patients who reported preadmission use of CCB (18–22). All included studies reported 30-day or 90-day mortality as the primary outcomes. We extracted the adjusted or propensity-matched ORs and 95% CIs from the primary outcome data. Otherwise, the data were calculated from the raw data from each included study.

Table 1
Summary of identified studies

First Author	Year	Country	Study Design	Multi/ Single Centre	Number of Patients in CCB Use	Number of Patients in non-CCB Use	Female/ Male of Patients in CCB Use	Female/ Male of Patients in non-CCB Use	Study Duration	Primary Outcome (OR, 95		
										30-day Mortality in sepsis#	30-day Mortality in septic shock	9 M i s
Wiewel 2017 (18)	2017	Netherlands	PC	Multi	197	863	79/118	341/522	01/2011-07/2013	0.48 (0.31–0.74)	0.31 (0.14–0.65)	0 (0
Lee 2017 (19)	2017	Taiwan	RC	Multi	19742	31336	8999/10743	11904/19432	2000–2011	0.92 (0.85–0.99)	NA	0 (0
Kim 2019 (20)	2019	South Korea	RC	Multi	1287	3262	626/661	1702/1560	2003–2013	0.83 (0.72–0.95)	NA	0 (1
Hsieh A 2020 (21)	2020	Taiwan	RC	Multi	NA	NA	NA	NA	1999–2013	1.21 (1.17–1.26)*	NA	N
Hsieh B 2020 (21)	2020	Taiwan	RC	Multi	NA	NA	NA	NA	1999–2013	NA	0.64 (0.53–0.77)	N
Roquetaillade 2020 (22)	2020	French	RC	Multi	103	632	NA	NA	2008–2016	0.95 (0.52–1.74)	0.95 (0.52–1.74)	N

Abbreviations: PC prospective cohort, RC retrospective cohort, CCB calcium channel blockers, OR odds ratio, CI confidence interval. #, 30-day Mortality in seps included septic shock; *, 30-day Mortality in sepsis that not included septic shock.

Risk of Bias Assessment

The risk of bias assessment of the included studies is shown in **Supplemental Table 2**. The five eligible studies (18–22) that had a point value ≥ 8 were observational cohort studies and were considered to have a low risk of bias on the basis of the NOS.

Effects of CCB on Septic Patients

The results of the primary outcomes in this meta-analysis are shown in Figs. 2–4. A random-effects model was used to perform in this meta-analysis for 30-day mortality due to high or moderate heterogeneity (I^2 = 95.4%, 62.4%, respectively), and fixed-effects model was used to perform in this meta-analysis for 90-day mortality due to mild heterogeneity (I^2 = 31.9%) between studies. In the five included cohort studies, preadmission CCB use was associated with a significantly lower 30-day mortality in septic shock (OR, 0.61 [0.38–0.97]; P = 0.035; I^2 = 62.4%), not in sepsis (OR, 0.83 [0.66–1.04]; P = 0.103; I^2 = 95.4%) (Figs. 2, 3). Moreover, prior CCB use was also associated with a significantly lower 90-day mortality in sepsis (OR, 0.90 [0.85–0.95]; P < 0.001; I^2 = 31.9%) (Fig. 4).

Sensitivity Analysis

As the included studies were observational cohort studies with a low risk of bias (**Supplemental Table 2**), a sensitivity analysis of the methodological criteria was not conducted. A sensitivity analysis was conducted to evaluate the effect of any one study on the pooled ORs and 95% CIs by removing one individual study at a time. The sensitivity analysis findings indicated that the results were robust and reliable ((**Supplemental Fig. 1–3**).

Publication Bias

Because the number of included studies that reported the effects of CCB use on septic patients was small (< 10), we did not generate a funnel plot, as it may not have discovered publication bias (26).

Discussion

This meta-analysis involving 280,982 patients indicated that compared with non-CCB use, preadmission CCB use was related to reduced 90-day mortality rate in patients with sepsis and 30-day mortality rate in patients with septic shock. To our knowledge, this is the first meta-analysis to explore and evaluate the relationship between preadmission CCB use and mortality in septic patients. These findings indicate that CCB administration is associated with significant effects on long-term prognosis of sepsis and also short-term survival of septic shock patients.

Currently, the outcome of preadmission CCB use on mortality of septic patients remains inconsistent (18–22). Several animal studies (27, 28) have suggested that CCB could reduce mortality in endotoxaemic mouse models. And, verapamil improved the survival rate of dogs with endotoxin shock (29). However clinical researches are not consistent with this animal studies (19–21). This meta-analysis may provide supporting evidence that preadmission CCB use may be associated with decreased mortality among patients with sepsis.

The potential mechanism underlying the association of CCB use and mortality in septic patients remains unclear. CCB may ameliorate cardiac dysfunction (29, 30) among septic survivors with cardiovascular complications (31). Several studies reported that CCB differentially inhibited the generation of pro-inflammatory factors, such as interleukin-12 (IL-12), interferon-gamma (IFN-γ) (28), and TNF-alpha (32) in sepsis. Additionally, CCB could inhibit nuclear transcription factor, NF-κB, and activated PI3K/Akt passage (33–36), which reducing LPS-induced acute inflammatory reaction (37). Moreover, CCB has been shown lower oxidative burst and inducible nitric oxide synthase (iNOS) protein expression to regulate inflammatory response (38), and ameliorates cellular injury and cardiac dysfunction. Most importantly, sepsis disrupts intracellular calcium homeostasis which lead to endothelial injury and destroyed subcelluar structures (39, 40). CCB, which is involved in targeting and blocking calcium ions overload (41, 42), can reduce intracellular Ca^{2+} levels and prevent cytotoxicity. As a result, CCB use with sepsis may lead to improved cardiovascular function and anti-inflammatory effect. It may be the explanation why CCB users had lower mortality among patients with sepsis. However, the relationship between CCB administration and sepsis prognosis needs clincial trial to further confirmation.

A meta-analysis was used to systematically and statistically analyse a variety of studies on the same topic. The summarized meta-analysis results present statistical heterogeneity when the difference among outcomes in the included individual studies is greater than expected. In the present meta-analysis, the assessment for risk of bias in eligible studies showed a low risk of bias; thus, methodological heterogeneity did not exist.

This meta-analysis has a few advantages. First, the sample of included septic patients was large, suggesting that the results may be stable. And the large population was sufficient to conduct propensity matching, which could reduce the effects of deviations and confounding variables between the CCB use and the non-CCB use group. Second, the NOS was used to assess risk of bias. The result indicated that this meta-analysis had a low risk of bias among the studies that met the inclusion criteria. Third, we extracted the adjusted or propensity-matched ORs and 95% CIs to calculate the pooled ORs for the effect of CCB use on mortality in an unbiased manner. Fourth, the sensitivity analysis suggested that the results were robust and reliable.

However, this meta-analysis has several limitations. Although we conducted an overall search of the pertinent literature as far back as possible, only five studies were included; more researches may be needed to confirm this conclusion. Nevertheless, the robustness of the conclusion was supported by the sensitivity analysis. Besides, the studies included in this meta-analysis were only observational studies, not randomized controlled trials. The effectiveness of prior CCB treatment in severely ill patients need to be further elucidated in high-quality clinical trials. However, a certain limitation exists even if all the included cohort studies show a low risk of bias.

Conclusions

This is the first systematic review and meta-analysis to report the association between preadmission CCB use and mortality in septic patients. This meta-analysis suggests that preadmission CCB use is significantly associated with improving long-term prognosis of sepsis, and also short-term survival of septic shock patients. However, this finding should be evaluated in future RCT studies, as CCB remain an attractive intervention for future investigations aiming to improve sepsis-related mortality.

Abbreviations

CCB, calcium channel blocker; CIs, confidence intervals; NOS, Newcastle-Ottawa Scale; PICOS, population, intervention, comparators, outcomes and study design; LPS, lipopolysaccharide.

Declarations

Consent for Publication

Not applicable.

Author Contributions

All the authors contributed substantially to the work presented in this article. Dr. TWS, XFD, YQC and YHZ conceived the study. HYL and LFL contributed to the data interpretation. XFD YQC and YHZ contributed to the study protocol and wrote the article. DW, QCK and LXW settled the controversy. QCK, LXW, and TWS revised the article. All authors approved the final version submitted for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of Data and Materials

All data generated or analysed during this study are included in this published article [and its

supplementary information files].

Ethical Approval and Consent to Participate

Not applicable.

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Figures

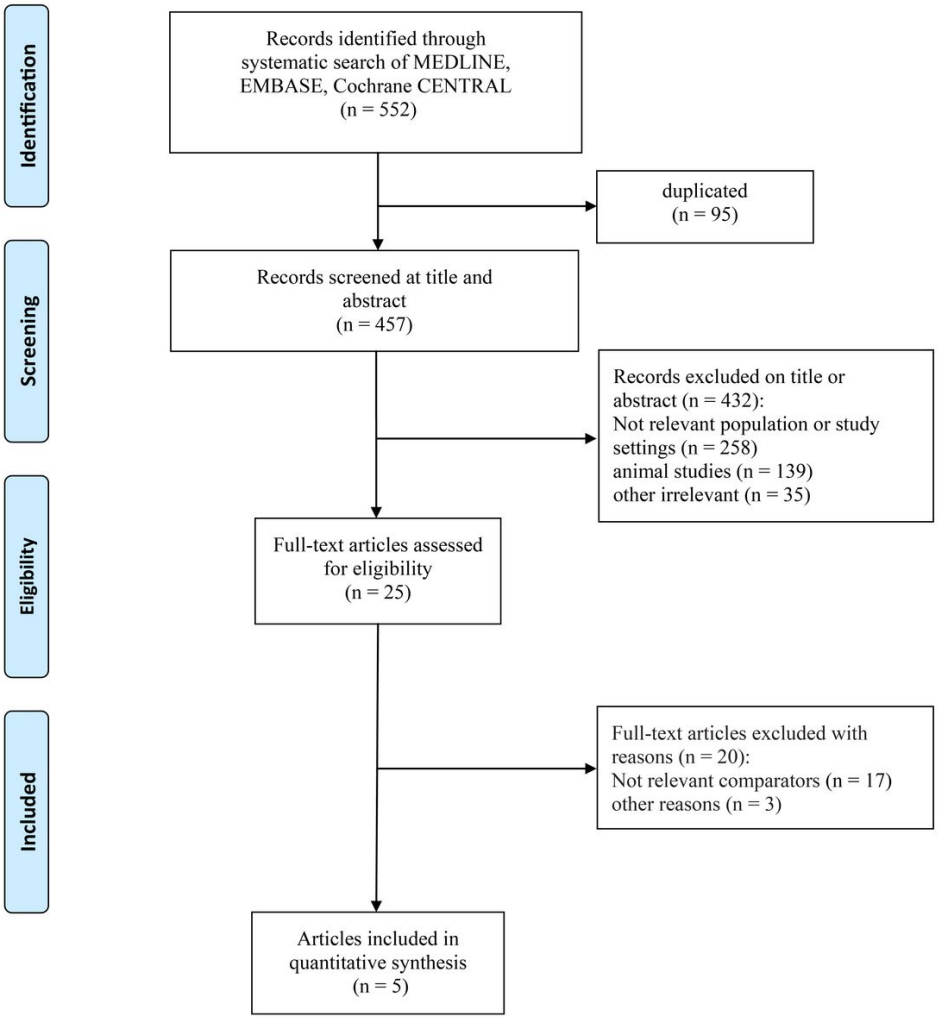

Figure 1

Flow chart of literature screening.

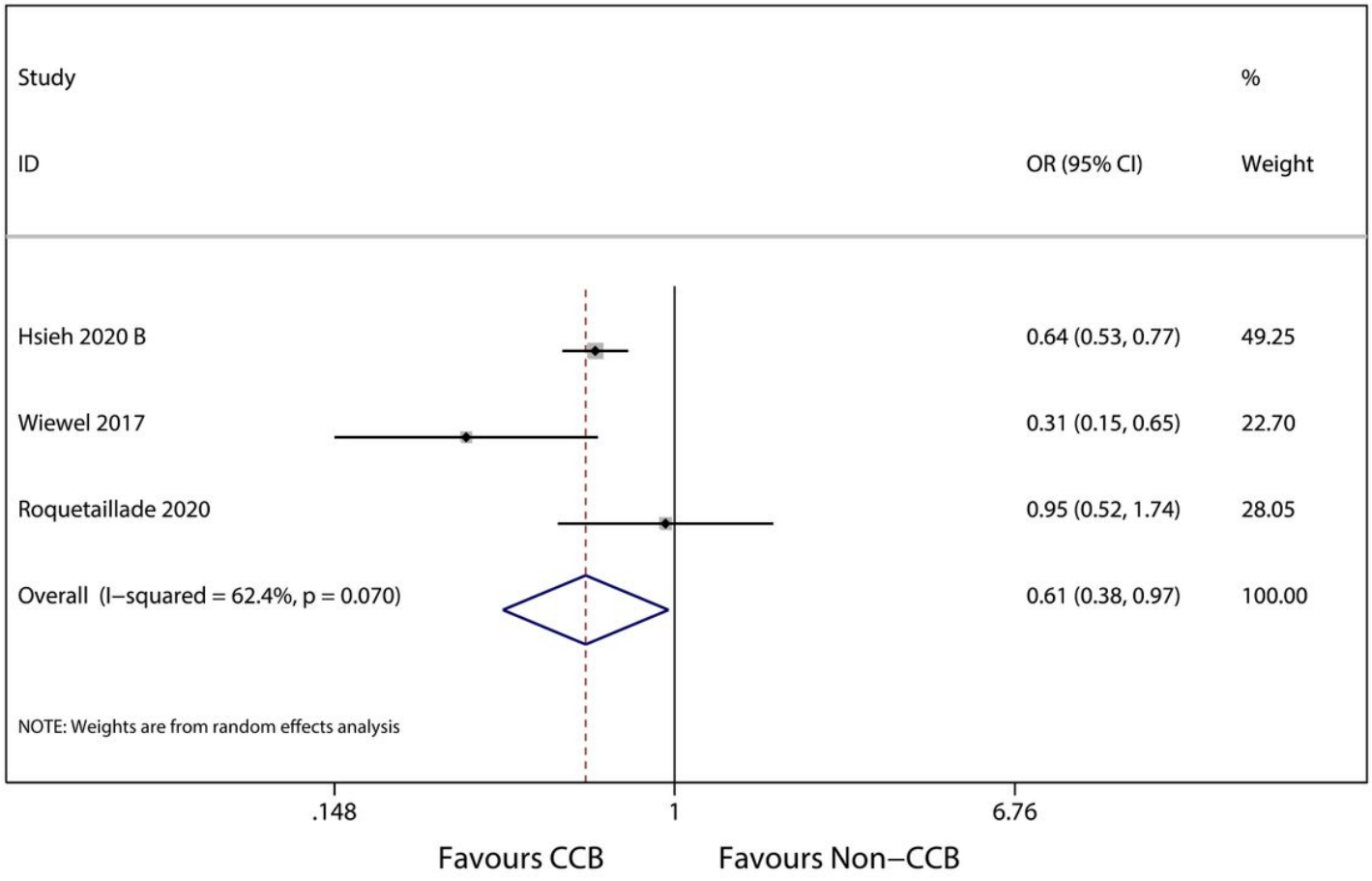

Figure 2

Meta-analysis of overall pooled ORs with 95% CIs across studies for primary outcomes in patients with septic shock. Forest plot showing the significance of the relationship between preadmission use of CCBs and 30-day mortality in patients with septic shock according to the random-effects model. OR = odds ratio, CCB = calcium channel blocker.

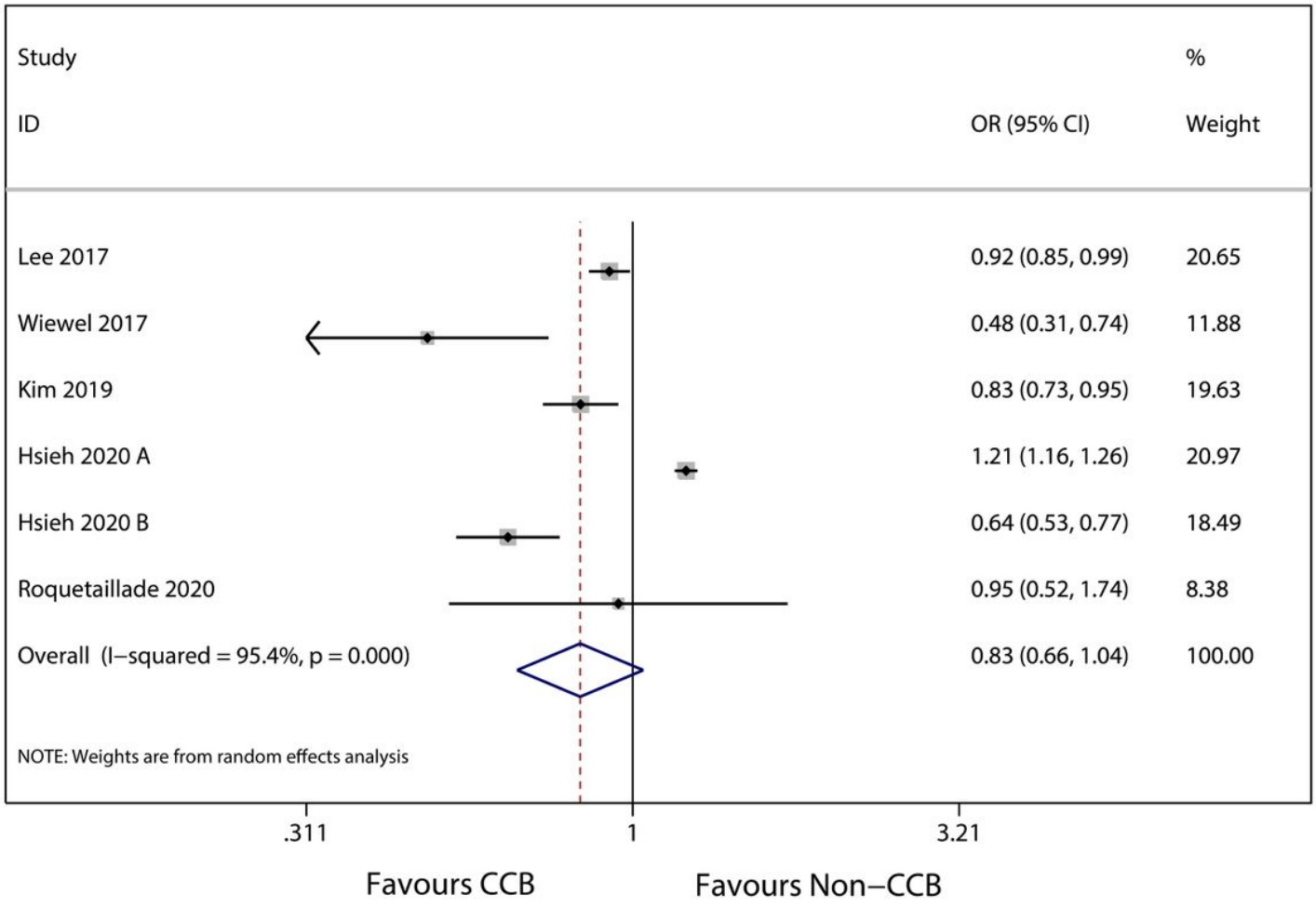

Figure 3

Meta-analysis of overall pooled ORs with 95% CIs across studies for primary outcomes in patients with sepsis. Forest plot showing the significance of the relationship between preadmission use of CCBs and 30-day mortality in patients with sepsis according to the random-effects model. OR = odds ratio, CCB = calcium channel blocker.

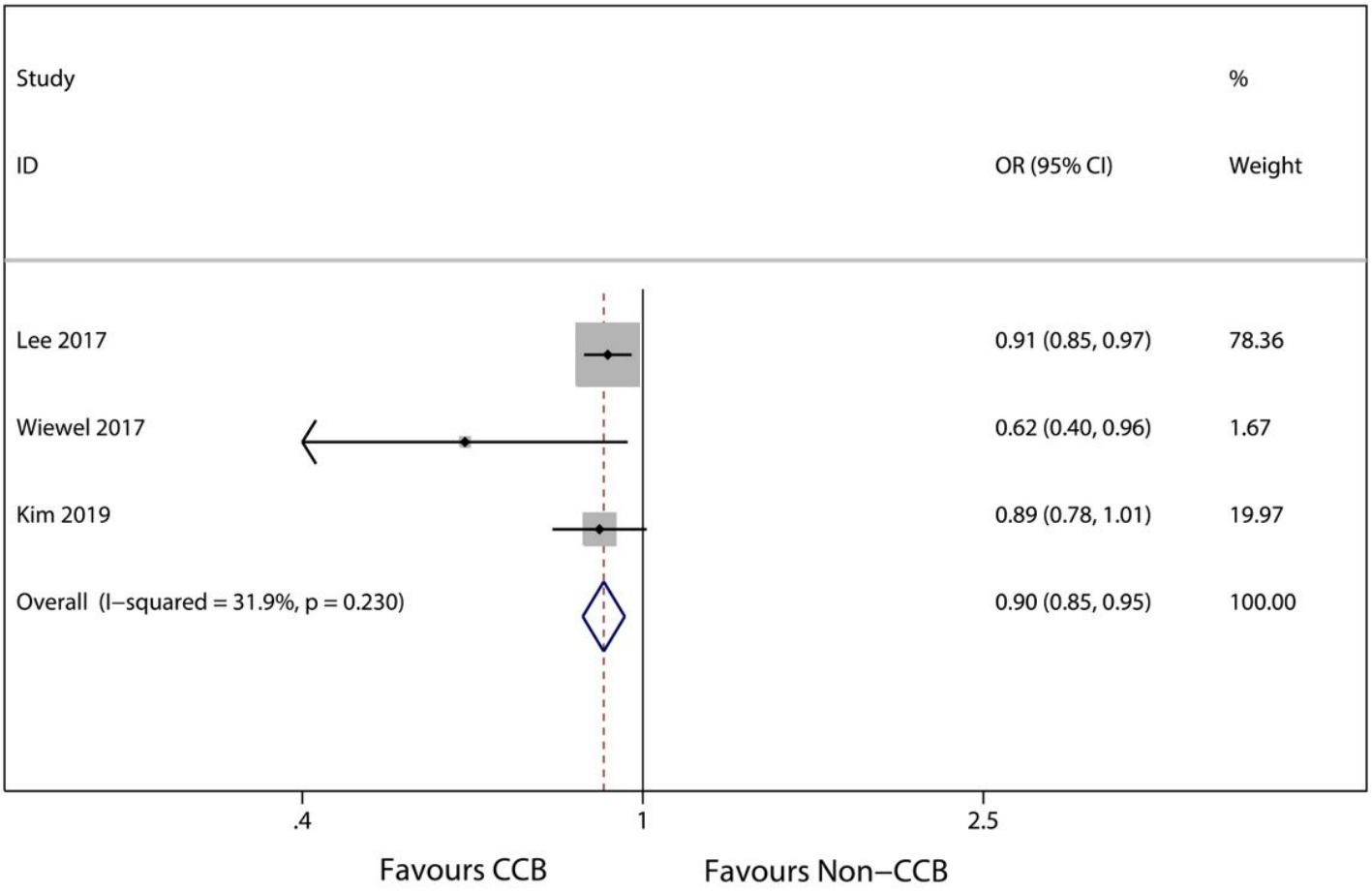

Figure 4

Meta-analysis of overall pooled ORs with 95% CIs across studies for primary outcomes in patients with sepsis. Forest plot showing the significance of the relationship between preadmission use of CCBs and 90-day mortality in patients with sepsis according to the fixed-effects model. OR = odds ratio, CCB = calcium channel blocker.

Supplementary Files

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- SupplementalTable2.docx
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