Clinical outcomes of hypertensive patients with COVID-19 receiving calcium channel blockers: a systematic review and meta-analysis

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Abstract

We aimed to perform a systematic review and meta-analysis to determine the overall effect of preadmission/pre-diagnosis use of calcium channel blockers (CCBs) on the clinical outcomes in hypertensive patients with COVID-19. A systematic literature search with no language restriction was conducted in electronic databases in July 2021 to identify eligible studies. A random-effects model was used to estimate the pooled summary measure for outcomes of interest with the preadmission/pre-diagnosis use of CCBs relative to non-use CCBs, at 95% confidence intervals (CIs). The meta-analysis revealed a significant reduction in the odds of all-cause mortality with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs (pooled OR=0.65; 95% CI 0.49-0.86) and a significant reduction in the odds of severe illness, with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs (pooled OR=0.61; 95% CI 0.44-0.84). The potential protective effects offered by CCBs in hypertensive patients with COVID-19 merit large-scale prospective investigations.

Keywords: CCB; antihypertensive; mortality; severity

Introduction

Investigations of the effect of the preadmission/pre-diagnosis use of co-medications in patients with coronavirus disease 2019 (COVID-19) have been a means for the researchers to establish their safety and to identify therapeutic agents which could be repurposed for the treatment of COVID-19. However, recently, it has been hypothesized that using calcium channel blockers (CCBs) could disrupt hypoxic pulmonary vasoconstriction and thus worsen ventilation/perfusion mismatch that can lead to profound hypoxemia in patients with COVID-19 [1]. In addition, some also commented that the vasodilatory effects of CCBs in the pulmonary and systemic vasculature could mitigate the effects of inflammation, hypercoagulation, edema, and local vasoconstriction as a response SARS-CoV-2 infection, thus facilitating oxygen delivery and survival of host cells [2]. Therefore, we aimed to perform a systematic review and meta-analysis to determine the overall effect of preadmission/pre-diagnosis use of CCBs on the clinical outcomes in patients with COVID-19.

Methods

This study was conducted and reported according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two investigators (CSK and SSH) independently conducted a systematic literature search in multiple electronic databases, including PubMed, Google Scholar, Scopus, EMBASE, and Web of Science, in July 2021. The search strategy was designed to identify all publications comparing clinical outcomes between preadmission/pre-diagnosis use of CCBs and non-use of CCBs in patients with COVID-19 and concurrent hypertension. We applied various combinations of Boolean operators by using the following keywords for our search: [(SARS-Cov-2 OR 2019-nCOv OR COVID-19 OR coronavirus) AND (calcium channel OR calcium antagonist OR amlodipine OR dihydropyridine)]. In addition, the references from narrative reviews or other systematic reviews were cross-checked to identify additional missing publications during the initial search. Studies were eligible for inclusion in our systematic review and meta-analysis if they (1) were observational studies (of any design, for example, case-control, cohort, case series); (2) included human patients with COVID-19 and hypertension; (3) compared clinical outcomes between preadmission/pre-diagnosis use and non-use of CCBs; and (4) reported adjusted association estimates. We excluded preprints and editorials, commentaries, and narrative reviews that reported no original data.

The outcomes of interest were all-cause mortality and COVID-19 associated severe illness, for example, admission to the intensive care unit, the requirement of invasive or non-invasive ventilation, mortality,

and/or as defined by the authors. All relevant information from the eligible studies was extracted and recorded in a pre-determined data collection table. The following information was extracted from each study: first author's surname, year of publication, the country where the study was performed, sample size (the number of patients with COVID-19 being analyzed), mean/median age of patients, number and proportion of patients with all-cause mortality, number and proportion of patients with severe illness, adjusted effect estimates, and covariates adjusted in the study. Newcastle-Ottawa Scale was used for critical appraisal of the quality of included observational studies. Two investigators (CSK and SSH) independently evaluated the quality of studies, and a Newcastle-Ottawa Scale of at least 7 indicating high quality. Consensus discussions between the two investigators were carried out to resolve disagreements on the inclusion of studies, extraction of study characteristics, and quality appraisal.

A random-effects model was used to estimate the pooled hazard ratio (HR) and pooled odds ratio (OR) for outcomes of interest between preadmission/pre-diagnosis use and non-use of CCBs, at 95% confidence intervals. We examined the heterogeneity across studies using the I^2 statistics and the χ^2 test, with 50% and $p < 0.10$ respectively, which were considered as an indication of the presence of heterogeneity. With heterogeneity, sensitivity analysis was conducted to investigate the robustness of the results by using an alternative meta-analytic model, namely the inverse variance heterogeneity (IVhet) model. Subgroup analyses were conducted based on the geographical region (United States, Europe, and Asia) of the included studies. All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Results

Our literature search yielded 547 abstracts. After deduplication and application of eligibility criteria, 39 relevant articles were shortlisted for inclusion through full-text examination. Of these, 30 studies were excluded since they either reported no adjusted association estimates, reported no clinical outcomes, included mixed hypertensive and non-hypertensive patients without subgroup analysis on hypertensive patients, and compared clinical outcomes between COVID-19 and non-COVID-19 patients. Eventually, nine studies [1,3-10] were included in this systematic review and meta-analysis; 8 studies [3-10] reported adjusted association estimates for all-cause mortality, while five studies [1,4,6,7,9] reported adjusted association estimates for COVID-19 associated severe illness. The study characteristics are depicted in **Table 1**. The meta-analysis of 7 studies [3-7,9,10] with a total of 8,413 patients with COVID-19 revealed a significant reduction in the odds of all-cause mortality with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs; the estimated effect indicates mortality reduction (**Figure 1**; pooled OR = 0.65;

95% confidence interval 0.49 to 0.86) and is with adequate evidence to reject the model hypothesis of 'no significant difference', at the current sample size.

The definition of severe illness varies across studies; in the studies by Choksi et al. [4], Christiansen et al. [6], and Peng et al. [9], it was defined as admission to the intensive care unit; in the studies by Yan F et al. [7], it was defined according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia by the Chinese National Health Commission. In the study by Mendez et al. [1], it was defined as the use of invasive or noninvasive mechanical ventilation or death. The meta-analysis of 4 studies [4,6,7,9] with a total of 2,618 patients with COVID-19 revealed a significant reduction in the odds of severe illness with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs; the estimated effect indicates a reduction in severe illness (**Figure 1**; pooled OR=0.61; 95% confidence interval 0.44 to 0.84) and is with adequate evidence to reject the model hypothesis of 'no significant difference', at the current sample size.

Discussion

Overall, the real-world studies observed a significant protective effect with preadmission/pre-diagnosis use of CCBs against all-cause mortality and COVID-19 associated severe illness in patients with COVID-19 and concurrent hypertension relative to non-use of CCBs. Although, however, the studies [3-10] included in our meta-analysis are of the retrospective design, the potential protective effects offered by CCBs in hypertensive patients with COVID-19 merit large-scale prospective investigations. Indeed, patients with hypertension are at high risk of a worse prognosis when they acquire COVID-19; the establishment of protective effects with CCBs could lead to preferential prescribing of these widely available agents for patients with a diagnosis of hypertension during the COVID-19 pandemic and potential deaths due to COVID-19 could be averted.

It should be noted that the studies included in our meta-analysis are mostly of the retrospective design, and thus generalizability of the findings may be limited. Furthermore, our analysis focused on the preadmission/pre-diagnosis use of CCBs; the effect of de novo introduction of CCBs in patients with COVID-19 cannot be ascertained. In addition to these limitations, our systematic review and meta-analysis have some strengths that should be acknowledged, including the number of studies and patients included and the performance of sensitivity analyses and subgroup analyses.

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Reference

1. Mendez SR, Frank RC, Stevenson EK, Chung M, Silverman MG. Dihydropyridine Calcium Channel Blockers and the Risk of Severe COVID-19. Chest. 2021;160(1):89-93.
2. Crespi B, Alcock J. Conflicts over calcium and the treatment of COVID-19. Evol Med Public Health. 2020;9(1):149-156.
3. Oh TK, Cho HW, Suh JW, Song IA. Incidence and Mortality Associated with Cardiovascular Medication among Hypertensive COVID-19 Patients in South Korea. Yonsei Med J. 2021;62(7):577-583.
4. Choksi TT, Zhang H, Chen T, Malhotra N. Outcomes of Hospitalized COVID-19 Patients Receiving Renin Angiotensin System Blockers and Calcium Channel Blockers. Am J Nephrol. 2021;52(3):250-260.
5. Chouchana L, Beeker N, Garcelon N, et al. Association of Antihypertensive Agents with the Risk of In-Hospital Death in Patients with Covid-19 [published online ahead of print, 2021 Feb 17] [published correction appears in Cardiovasc Drugs Ther. 2021 Mar 4;:]. Cardiovasc Drugs Ther. 2021;1-6.
6. Christiansen CF, Pottegård A, Heide-Jørgensen U, et al. SARS-CoV-2 infection and adverse outcomes in users of ACE inhibitors and angiotensin-receptor blockers: a nationwide case-control and cohort analysis. Thorax. 2021;76(4):370-379.
7. Yan F, Huang F, Xu J, et al. Antihypertensive drugs are associated with reduced fatal outcomes and improved clinical characteristics in elderly COVID-19 patients. Cell Discov. 2020;6(1):77.
8. Neuraz A, Lerner I, Digan W, et al. Natural Language Processing for Rapid Response to Emergent Diseases: Case Study of Calcium Channel Blockers and Hypertension in the COVID-19 Pandemic. J Med Internet Res. 2020;22(8):e20773.
9. Peng C, Wang H, Guo YF, et al. Calcium channel blockers improve prognosis of patients with coronavirus disease 2019 and hypertension. Chin Med J (Engl). 2021;134(13):1602-1609.
10. Lu QB, Jiang WL, Zhang X, et al. Comorbidities for fatal outcome among the COVID-19 patients: A hospital-based case-control study. J Infect. 2021;82(1):159-198.

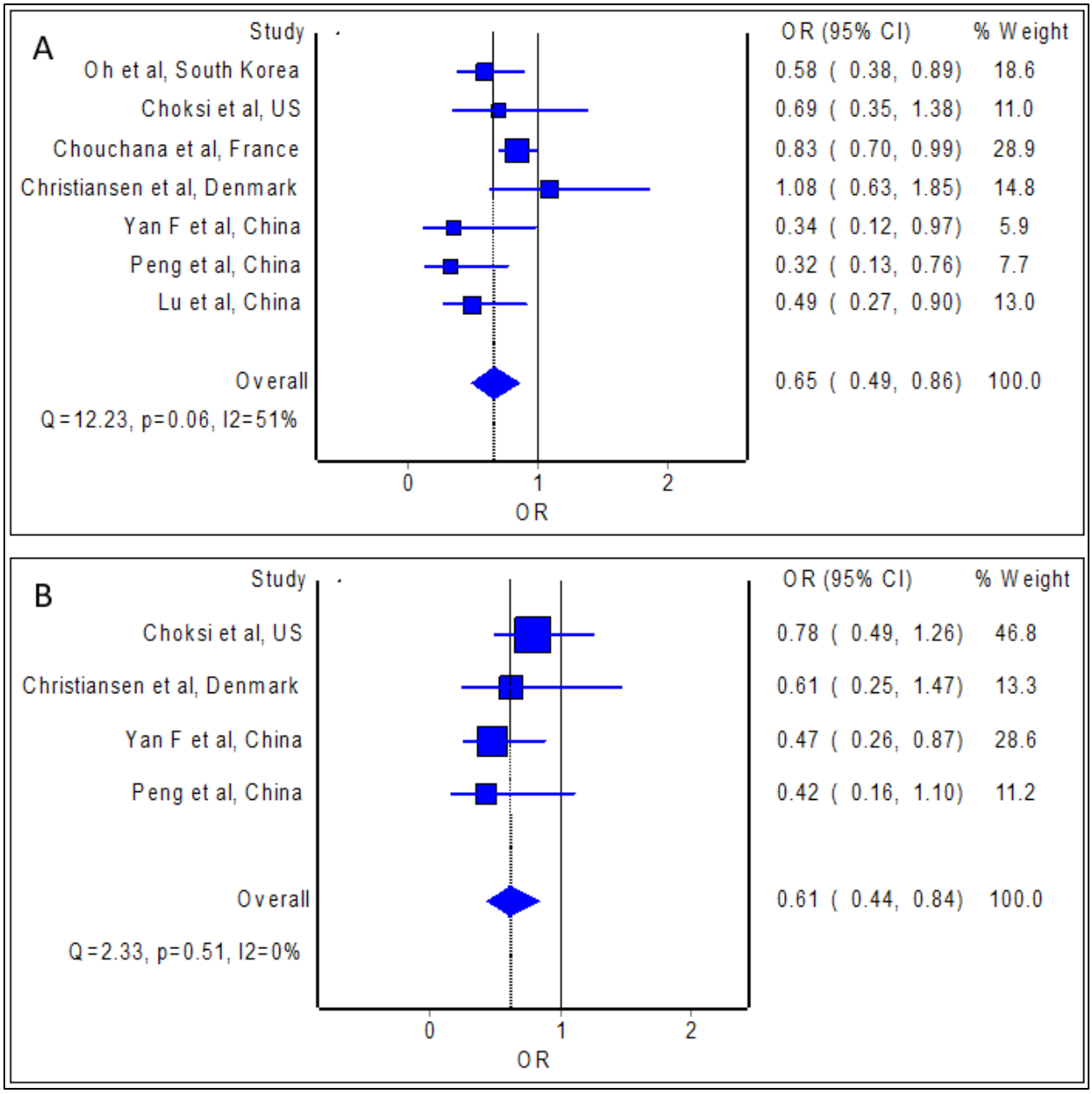

Figure 1: Pooled odds ratio (OR) of mortality (A) and pooled odds ratio (OR) of severe illness (B) between CCB users and non-CCB users with COVID-19 and concurrent hypertension

Table 1: Characteristics of included studies

Study	Country	Design	Total number of patients	Age (mean [SD]/median [IQR])	Proportion of patients with hypertension	Mortality			Severe illness[a]			Adjusted covariates	NOS
						CCB users (n/N; %)	Non-CCB users (n/N; %)	Adjusted estimate (95% CI)	CCB users (n/N; %)	Non-CCB users (n/N; %)	Adjusted estimate (95% CI)		
Oh et al. [3]	South Korea	Retrospective database review	7,713	N/A	24.5%	N/A	N/A	Hypertensive subgroup: OR=0.58 (0.38-0.89)	-	-	-	Age, sex, income level, presence of underlying disability, place of residence, use of other cardiovascular drugs	7/9
Choksi et al. [4]	United States	Retrospective, single-center	841	All patients=57.9 (20.0)	53.9%	N/A	N/A	Hypertensive subgroup: OR=0.69 (0.35-1.38)	N/A	N/A	Hypertensive subgroup: OR=0.78 (0.49-1.26)	Age, sex, race/ethnicity, comorbidities, COVID-19 treatment	8/9
Chouchana et al. [5]	France	Retrospective, multicenter	3,686	All patients=68.0 (25.9)	100%	N/A	N/A	OR=0.83 (0.70-0.99)	-	-	-	Age, sex, comorbidities	8/9
Christiansen et al. [6]	Denmark	Prospective database review	795	CCB users=68.0 (57.0-80.0) Non-CCB users=69.0 (58.0-80.0)	100%	17/179; 9.5	55/616; 8.9	RR=1.08 (0.63-1.85)	7/179; 3.9	39/613; 6.4	RR=0.61 (0.25-1.47)	Age, sex, ethnicity, status as healthcare professional, use of other medications, comorbidities, markers of smoking, marital status, place of residence	7/9
Yan F et al. [7]	China	Retrospective, multicenter	655	All patients=64.6 (11.8)	100%	21/441; 4.8	15/214; 7.0	OR=0.34 (0.12-0.97)	106/441; 24.0	63/214; 29.4	OR=0.47 (0.26-0.87)	Age, sex, baseline blood pressure, comorbidities	8/9
Neuraz et al. [8]	France	Retrospective database review	3,965	N/A	100%	N/A	N/A	HR=0.82 (0.71-0.94)	-	-	-	Age, sex, comorbidities	8/9
Peng et al. [9]	China	Retrospective, multicenter	718	CCB users=65.0 (57.0-71.0) Non-CCB users=65.0 (57.0-72.0)	100%	7/359; 1.9	21/359; 5.9	RR=0.32 (0.13-0.76)	6/359; 1.7	14/359; 3.9	RR=0.42 (0.16-1.10)	Age, sex, temperature, respiratory rate, pulse rate, comorbidities, COVID-19 treatment, use of other antihypertensives	8/9

Lu et al. [10]	China	Retrospective, multicenter	217	All patients=58.0 (45.0-69.0)	100%	41/133; 30.8	41/84; 48.8	OR=0.49 (0.27-0.90)	-	-	-	Age, sex, delay from symptom onset to hospital admission	7/9
Mendez et al. [1]	United States	Retrospective, multicenter	245	CCB users=70.0 (15.0) Non-CCB users=70.0 (14.0)	100%	-	-	-	40/70; 57.1	71/175; 40.6	HR=1.80 (1.20-2.80)	Age, sex, race/ethnicity, body mass index, comorbidities, Charlson Comorbidity Index, use of other cardiovascular medications	8/9

CCB Calcium channel blocker; CI confidence interval; COVID-19 coronavirus disease 2019; COVID-19 coronavirus disease 2019; HR hazard ratio; IQR interquartile range; NOS Newcastle-Ottawa Scale; OR odds ratio; RR risk ratio; SD standard deviation

aThe definition of severe illness varies across studies; in the studies by Choksi et al., Christiansen et al., and Peng et al., it was defined as admission to the intensive care unit; in the studies by Yan F et al. and Yan H et al., it was defined according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia by the Chinese National Health Commission; and in the study by Mendez et al., it was denied as the use of invasive or noninvasive mechanical ventilation or death.