Calcium channel blockers and the risk of all-cause mortality and severe illness in patients with COVID-19: a systematic review and meta-analysis

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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. During the early pandemic, there have been suggestions of replacing renin-angiotensin system inhibitors with calcium channel blockers in patients diagnosed with COVID-19 due to concerns that using the renin-angiotensin system inhibitors could portend a worse prognosis [1,2]. Nevertheless, such claims have been discredited by the systematic review and meta-analysis of randomized controlled trials reporting no difference in clinical outcomes between the use and non-use of renin-angiotensin system inhibitors in patients with COVID-19 [3]. However, recently, it has also 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 [4]. Therefore, due to the reported safety concerns, we aimed to perform a systematic review and meta-analysis to determine the effect of preadmission/pre-diagnosis use of CCBs on the clinical outcomes in patients with COVID-19.

Methods

Search strategy and selection criteria

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. 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 a diagnosis of COVID-19; (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.

Data collection

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.

Statistical analysis

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, China, Europe, and East 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 records. After deduplication and application of eligibility criteria, 39 relevant articles were shortlisted for inclusion through full-text examination (**Figure 1**). Of these, 16 studies were excluded since they either reported no adjusted association estimates, reported no clinical outcomes, or compared clinical outcomes between COVID-19 and non-COVID-19 patients. Eventually, 23 studies [4-26] were included in this systematic review and meta-analysis; 17 studies [5-21] reported adjusted association estimates for all-cause mortality, while 12 studies [4,7,9-12,15,22-26] reported adjusted association estimates for COVID-19 associated severe illness. The study characteristics are depicted in **Table 1**. Across the included studies investigating the effect of preadmission/pre-diagnosis use of CCBs in patients with COVID-19, all [4-9,11-26] but one [10] studies were retrospective in design, with ten multicentered studies, eight database reviews, and four single-centered studies; the remaining one study [10] is a prospective database review. The included studies were originated from the United States [4,7,9,13,23,24] (n=6), Europe (Italy [15,20,21] [n=3], France [8,14] [n=2], Denmark [10,12] [n=2], the

United Kingdom [6] [n=1], Spain [19] [n=1], Sweden [18] [n=1]), and East Asia (China [11,16,17,22,25,26] [n=6] and South Korea [5] [n=1]). The average age of patients across the included studies ranged from 43.0 to 84.4. Age and sex were the most commonly adjusted covariates (adjusted in all but two studies [25,26]), followed by the presence of various comorbidities (adjusted in 15 studies [4,6-16,19,23,26]). All the included studies [4-26] are deemed high quality with a Newcastle-Ottawa Scale ranging from 7 to 8 (**Table 1**).

Risk of mortality with calcium channel blockers

The meta-analysis of 11 studies with a total of 53,963 patients with COVID-19 revealed no significant difference in the odds of all-cause mortality with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs; the estimated effect, though, indicates mortality reduction (**Figure 2(A)**; pooled OR=0.82; 95% confidence interval 0.68-1.00, I^2=69%, p=0.01), but is with inadequate evidence to reject the model hypothesis of 'no significant difference' at the current sample size. Similarly, the meta-analysis of 6 studies (all originated from Europe) with a total of 65,649 patients with COVID-19 observed a non-significant reduction in the hazard of all-cause mortality (**Figure 2(B)**; pooled HR=0.91; 95% confidence interval 0.74-1.12, I^2=82%, p=0.01). The findings from the sensitivity analysis using the IVhet model are consistent with the main findings, where no significant difference in the odds (pooled OR=0.77; 95% confidence interval 0.55-1.07) and hazard (pooled HR=1.00; 95% confidence interval 0.76-1.32) of all-cause mortality with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs was observed. Subgroup analysis of studies originated from the United States (pooled OR = 0.96; 95% confidence interval 0.57-1.61) and Europe (pooled OR=0.99; 95% confidence interval 0.80-1.23) reported no significant difference in the odds of all-cause mortality; conversely, subgroup analysis of studies originated from East Asia (pooled OR=0.50; 95% confidence interval 0.37-0.68) reported a significant reduction in the odds of all-cause mortality.

Risk of severe illness with calcium channel blockers

The definition of severe illness varies across studies; in the studies by Choksi et al. [7], Christiansen et al. [10], Fosbøl et al. [12], and Peng et al. [16], it was defined as admission to the intensive care unit; in the studies by Yan F et al. [11] and Yan H et al. [22], it was defined according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia by the Chinese National Health Commission; in the studies by Reynolds et al. [23] and Xiong et al. [26], it was defined as admission to the intensive care unit, the use of invasive or noninvasive mechanical ventilation, or death; in the study by Mendez et al. [4], it was defined as the use of invasive or noninvasive mechanical ventilation or death; in the study by Bauer et al. [24], it was defined as hospitalization or death; and in the study by Liu et al. [25], it was defined as admission to the intensive care unit.

The meta-analysis of 10 studies with a total of 46,091 patients with COVID-19 revealed no significant difference in the odds of severe illness with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs; the estimated effect, though, indicates a reduction in severe illness (**Figure 3**; pooled OR=0.83; 95% confidence interval 0.61-1.15, I^2=68%, p=0.01), but is with inadequate evidence to reject the model hypothesis of 'no significant difference' at the current sample size. Sensitivity analysis using the IVhet model also reported no significant difference in the odds (pooled OR=1.00; 95% confidence interval 0.65-1.56) of severe illness with preadmission/pre-diagnosis use of CCBs relative to non-use of CCBs. In contrast, subgroup analysis of studies originated from the United States (pooled OR=1.11; 95% confidence interval reported no significant difference in the odds of severe illness. Conversely, subgroup analysis of studies that originated from East Asia (pooled OR=0.51; 95% confidence interval 0.33-0.78) reported a significant reduction in the odds of severe illness.

Discussion

Overall, from the real-world studies, we observed no significant effect with preadmission/pre-diagnosis use of CCBs on all-cause mortality and COVID-19 associated severe illness in patients with COVID-19,

relative to non-use of CCBs; therefore, there may not be safety concerns with the use of CCBs in patients with COVID-19 as raised by some researchers [4]. Our findings lend support to the guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic, issued by the European Society of Cardiology [27], which recommended continuing the use of CCBs in patients with hypertension based on the 2018 guidelines for the management of arterial hypertension issued by the ESC/European Society of Hypertension (ESH) [28]. In fact, it is important to disprove the doubts raised about the safety of CCBs, since in available clinical guidelines, CCBs, especially the dihydropyridine CCBs, is one of the recommended first-line antihypertensive drugs to treat primary hypertension, and thus their widespread use all around the world.

However, the findings of a significant reduction in the odds of mortality and the odds of severe illness in the subgroup analysis of East Asian studies should be investigated further since they indicate that the East Asian patients may be more sensitive toward the protective effects offered by CCBs in patients with COVID-19. It has been hypothesized 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 to SARS-CoV-2 infection, thus facilitating oxygen delivery and survival of host cells. Previously, East Asian studies [29,30] reported that genetic polymorphisms of the calcium channel α1C and α1D subunit genes, CACNA1C, are associated with the antihypertensive effects of CCBs; the single-nucleotide polymorphisms (SNPs) in CACNA1D and CACNA1D confer sensitivity to the antihypertensive effects of CCBs. Thus, the preferential protective effects of CCBs may be due to these SNPs, though the prevalence of these SNPs between the East Asian and Caucasian populations has not been reported thus far.

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, as well as the performance of sensitivity analyses and subgroup analyses.

Conclusion

In conclusion, we found no safety concerns with the use of CCBs in patients with COVID-19, but the potential protective effects offered by CCBs in East Asian patients with COVID-19 merit large-scale investigations.

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Reference

1. Kow CS, Zaidi STR, Hasan SS. Cardiovascular disease and use of renin-angiotensin system inhibitors in COVID-19. Am J Cardiovasc Drugs. 2020;20(3):217-221.
2. Hasan SS, Kow CS, Hadi MA, Zaidi STR, Merchant HA. Mortality and disease severity among COVID-19 patients receiving renin-angiotensin system inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2020;20(6):571-590.
3. Kow CS, Ming LC, Hasan SS. Renin-angiotensin system inhibitor use and the risk of mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials [published online ahead of print, 2021 May 20]. Hypertens Res. 2021;1-4.
4. 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.
5. 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.
6. Rezel-Potts E, Douiri A, Chowienczyk PJ, Gulliford MC. Antihypertensive medications and COVID-19 diagnosis and mortality: population-based case-control analysis in the United Kingdom [published online ahead of print, 2021 Apr 27]. Br J Clin Pharmacol. 2021;10.1111/bcp.14873.
7. 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.
8. 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.
9. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19 [published correction appears in JAMA Netw Open. 2021 Jan 4;4(1):e2036103]. JAMA Netw Open. 2020;3(12):e2029058.

10. 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.
11. 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.
12. Fosbøl EL, Butt JH, Østergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 Diagnosis and mortality. JAMA. 2020;324(2):168-177.
13. Jackson BR, Gold JAW, Natarajan P, et al. Predictors at admission of mechanical ventilation and death in an observational cohort of adults hospitalized with COVID-19 [published online ahead of print, 2020 Sep 24]. Clin Infect Dis. 2020;ciaa1459.
14. 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.
15. Trifirò G, Massari M, Da Cas R, et al. Renin-Angiotensin-Aldosterone system inhibitors and risk of death in patients hospitalised with COVID-19: a retrospective Italian cohort study of 43,000 patients. Drug Saf. 2020;43(12):1297-1308.
16. 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.
17. 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.
18. Xu H, Garcia-Ptacek S, Annetorp M, et al. Acute kidney injury and mortality risk in older adults with COVID-19. J Nephrol. 2021;34(2):295-304.
19. Águila-Gordo D, Martínez-Del Rio J, Mazoteras-Muñoz V, Negreira-Caamaño M, Nieto-Sandoval Martín de la Sierra P, Piqueras-Flores J. Mortalidad y factores pronósticos asociados en pacientes ancianos y muy ancianos hospitalizados con infección respiratoria COVID-19 [Mortality and associated prognostic factors in elderly and very elderly hospitalized patients with respiratory disease COVID-19] [published online ahead of print, 2020 Nov 11]. Rev Esp Geriatr Gerontol. 2020;S0211-139X(20)30174-8.
20. Mirani M, Favacchio G, Carrone F, et al. Impact of Comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: a case series from an academic hospital in Lombardy, Italy. Diabetes Care. 2020;43(12):3042-3049.
21. Polverino F, Stern DA, Ruocco G, et al. Comorbidities, cardiovascular therapies, and COVID-19 mortality: a nationwide, Italian observational study (ItaliCO) [published correction appears in Front Cardiovasc Med. 2020 Dec 09;7:631602]. Front Cardiovasc Med. 2020;7:585866.
22. Yan H, Valdes AM, Vijay A, et al. Role of drugs used for chronic disease management on susceptibility and severity of COVID-19: a large case-control study. Clin Pharmacol Ther. 2020;108(6):1185-1194.
23. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone system inhibitors and risk of Covid-19. N Engl J Med. 2020;382(25):2441-2448.
24. Bauer AZ, Gore R, Sama SR, et al. Hypertension, medications, and risk of severe COVID-19: a Massachusetts community-based observational study. J Clin Hypertens (Greenwich). 2021;23(1):21-27.
25. Liu Z, Bai X, Han X, et al. The association of diabetes and the prognosis of COVID-19 patients: A retrospective study. Diabetes Res Clin Pract. 2020;169:108386.

26. Xiong TY, Huang FY, Liu Q, et al. Hypertension is a risk factor for adverse outcomes in patients with coronavirus disease 2019: a cohort study. Ann Med. 2020;52(7):361-366.
27. Fulchand S. Covid-19 and cardiovascular disease. BMJ. 2020;369:m1997. Published 2020 May 20.
28. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension [published correction appears in J Hypertens. 2019 Jan;37(1):226]. J Hypertens. 2018;36(10):1953-2041.
29. Kamide K, Yang J, Matayoshi T, et al. Genetic polymorphisms of L-type calcium channel alpha1C and alpha1D subunit genes are associated with sensitivity to the antihypertensive effects of L-type dihydropyridine calcium-channel blockers. Circ J. 2009;73(4):732-740.
30. Kamide K, Asayama K, Katsuya T, et al. Genome-wide response to antihypertensive medication using home blood pressure measurements: a pilot study nested within the HOMED-BP study. Pharmacogenomics. 2013;14(14):1709-1721.

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of process of study selection

Table 1: Characteristics of included studies

Study	Country	Design	Total number of patients	Age (mean [SD]/median [IQR])	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. [5]	South Korea	Retrospective database review	7,713	N/A	N/A	N/A	OR=0.60 (0.39-0.92)	-	-	-	Age, sex, income level, presence of underlying disability, place of residence, use of other cardiovascular drugs	7/9
Rezel - Potts et al. [6]	United kIngdom	Retrospective database review	16,866	N/A	149/1763; 8.5	772/15103 ; 5.1	HR=0.87 (0.72-1.04)	-	-	-	Age, sex, blood pressure, ethnicity, smoking status, frailty level, body mass index, comorbidities, rate of consultation of general practice, month of diagnosis, use of other antihypertensives	8/9
Choksi et al. [7]	United States	Retrospective , single-center	841	All patients=57.9 (20.0)	N/A	N/A	OR=0.77 (0.45-1.33)	N/A	N/A	OR=0.72 (0.49-1.05)	Age, sex, race/ethnicity, comorbidities, COVID-19 treatment	8/9
Chouchana et al. [8]	France	Retrospective , multicenter	3,686	All patients=68.0 (25.9)	N/A	N/A	OR=0.83 (0.70-0.99)	-	-	-	Age, sex, comorbidities	8/9
Rosenthal et al. [9]	United States	Retrospective database review	35,302	All patients=63.6 (17.7)	N/A	N/A	OR=0.73 (0.68-0.79)	11/32; 34.4	38/225; 16.9	OR=2.54 (1.10-5.86)	Age, sex, race, ethnicity, payer type, type of admission, admission point of origin, geographic region, size, rural/urban status, teaching status, comorbidities, complications, medications and supplements used during index hospitalization	8/9
Christiansen et al. [10]	Denmark	Prospective database review	1,350	CCB users=68.0 (57.0-80.0) Non-CCB users=69.0 (58.0-80.0)	40/285; 13.9	131/1065; 12.3	RR=1.12 (0.76-1.64)	15/283; 5.4	66/1058; 6.3	RR=0.85 (0.46-1.56)	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. [11]	China	Retrospective , multicenter	655	All patients=64.6 (11.8)	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

Fosbøl et al. [12]	Denmark	Retrospective database review	1,091	CCB users=73.6 (61.8-81.2) Non-CCB users=72.8 (61.0-81.0)	36/196; 18.4	161/895; 18.0	HR=0.94 (0.65-1.37)	37/196; 18.9	201/895; 22.5	HR=0.88 (0.61-1.27)	Age, sex, highest obtained education, income level, comorbidities, use of other medications	8/9
Jackson et al. [13]	United States	Retrospective, multicenter	297	All patients=60.0 (45.0-69.0)	24/87; 27.6	27/210; 12.9	OR=1.91 (1.03-3.55)	-	-	-	Age, sex, ethnicity, residency in nursing homes, insurance status, substance use, comorbidities, number of antihypertensives, use of other antihypertensives	8/9
Neuraz et al. [14]	France	Retrospective database review	3,965	N/A	N/A	N/A	HR=0.82 (0.71-0.94)	-	-	-	Age, sex, comorbidities	8/9
Trifirò et al. [15]	Italy	Retrospective database review	42,926	All patients=69.0 (57.0-79.0)	822/2178; 37.7	10383/40748; 25.5	HR=1.11 (1.03-1.21)	-	-	-	Age, sex, Charlson Comorbidity Index, number of drugs dispensed, comorbidities, hospital location	7/9
Peng et al. [16]	China	Retrospective, multicenter	718	CCB users=65.0 (57.0-71.0) Non-CCB users=65.0 (57.0-72.0)	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. [17]	China	Retrospective, multicenter	217	All patients=58.0 (45.0-69.0)	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
Xu et al. [18]	Sweden	Retrospective, multicenter	316	All patients=82.2 (8.5)	N/A	N/A	OR= 1.36 (0.61-3.02)	-	-	-	Age, sex, admission sources, admitting hospital, vital signs, lab values, baseline estimated glomerular filtration rate, use of other medications	8/9
Águila-Gordo et al. [19]	Spain	Retrospective, single-center	416	All patients=84.4 (5.7)	62/178; 34.8	136/238; 57.1	HR=0.27 (0.12-0.62)	-	-	-	Age, sex, comorbidities, laboratory parameters, use of other antihypertensives, COVID-19 treatment	7/9
Mirani et al. [20]	Italy	Retrospective, single-center	385	All patients=66.0 (54.0-76.0)	N/A	N/A	HR=1.30 (0.80-2.00)	-	-	-	Age, sex	8/9
Polverino et al. [21]	Italy	Retrospective, multicenter	2,868	All patients=43.0 (32.0-53.5)	143/380; 37.6	646/2488; 26.0	OR= 1.13 (0.84-1.53)	-	-	-	Age, sex, number of comorbidities, smoking status	7/9

Mendez et al. [4]	United States	Retrospective, multicenter	245	CCB users=70.0 (15.0) Non-CCB users=70.0 (14.0)	-	-	-	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
Yan H et al. [22]	China	Retrospective, multicenter	134	All patients=49.2 (14.2)	-	-	-	33/86; 38.4	24/48; 50.0	OR=0.62 (0.30-1.27)	Age, sex, body mass index	7/9
Reynolds et al. [23]	United States	Retrospective database review	5,894	N/A	-	-	-	263/992; 26.5	739/4902; 15.1	OR=1.24 (1.02-1.50)	Age, sex, race, ethnicity, smoking status, body mass index, comorbidities	7/9
Bauer et al. [24]	United States	Retrospective database review	661	All patients=66.1 (18.2)	-	-	-	N/A	N/A	OR=1.02 (0.70-1.48)	Age, sex, body mass index, race, ethnicity, systolic blood pressure	8/9
Liu et al. [25]	China	Retrospective, single-center	64	All patients=66.0 (59.0-71.0)	-	-	-	N/A	N/A	OR=0.09 (0.01-0.72)	A1c at admission	7/9
Xiong et al. [26]	China	Retrospective, multicenter	472	All patients=43.0 (32.0-53.5)	-	-	-	N/A	N/A	OR=1.18 (0.29-4.78)	Age, laboratory parameters, comorbidities, use of other antihypertensives	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

[a]The definition of severe illness varies across studies; in the studies by Choksi et al., Christiansen et al., Fosbøl 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; in the studies by Reynolds et al. and Xiong et al., it was defined as admission to the intensive care unit, the use of invasive or noninvasive mechanical ventilation, or death; in the study by Mendez et al., it was denied as the use of invasive or noninvasive mechanical ventilation or death; in the study by Bauer et al., it was defined as hospitalization or death; and in the study by Liu et al., it was defined as admission to the intensive care unit.

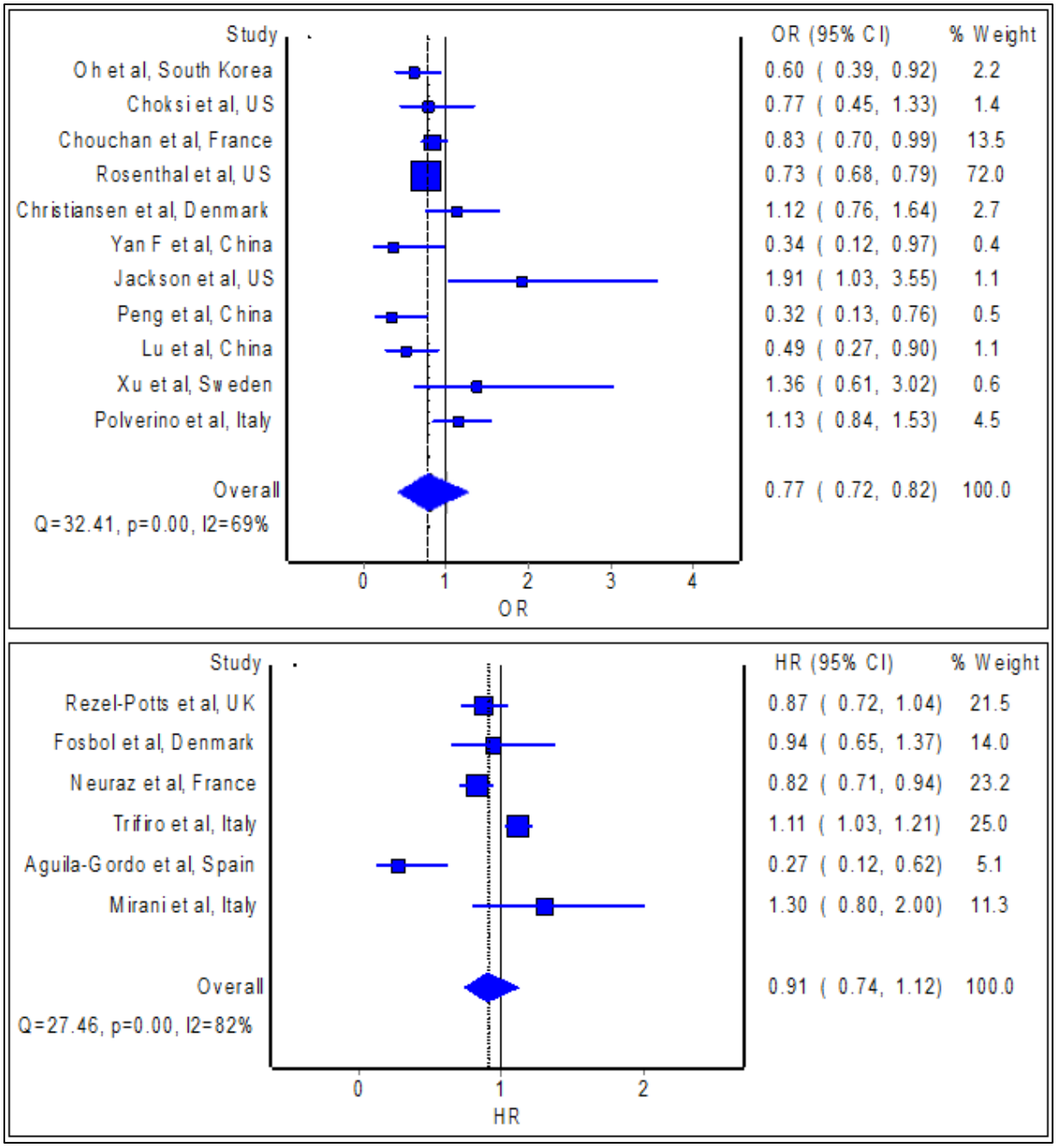

Figure 2: Pooled odds ratio (OR) of mortality (A) and pooled hazard ratio of mortality (B) between CCB users and non-CCB users with COVID-19

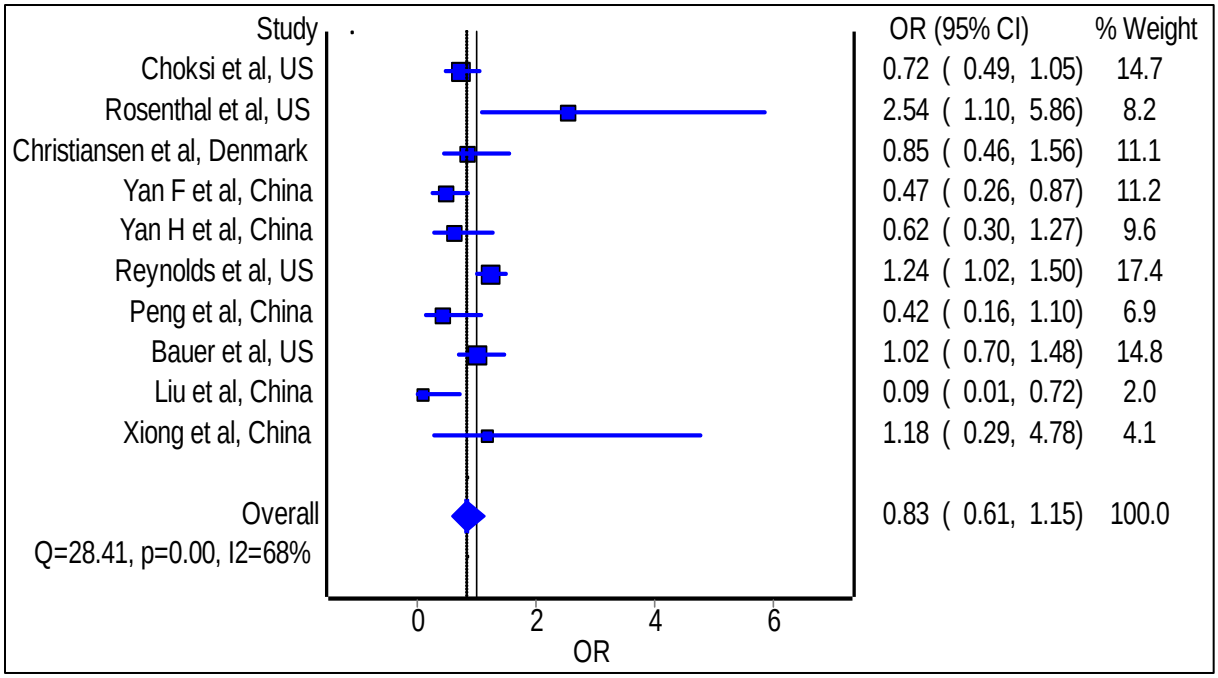

Figure 3: Pooled odds ratio (OR) of severe illness (C) between CCB users and non-CCB users with COVID-19