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

Chia Siang Kow1,2 · Dinesh Sangaran Ramachandram2 · Syed Shahzad Hasan3,4

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Abstract
We aimed to perform a systematic review and meta-analysis to determine the overall effect of the preadmission/prediagnosis 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/prediagnosis use of CCBs relative to the nonuse of CCBs at 95% confidence intervals (CIs). The meta-analysis revealed a significant reduction in the odds of all-cause mortality with the preadmission/prediagnosis use of CCBs relative to the nonuse of CCBs (pooled OR = 0.65; 95% CI 0.49–0.86) and a significant reduction in the odds of severe illness with preadmission/prediagnosis use of CCBs relative to the nonuse of CCBs (pooled OR = 0.61; 95% CI 0.44–0.84), and is associated with adequate evidence to reject the model hypothesis of ‘no significant difference’ at the current sample size. 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/prediagnosis use of comedication in patients with coronavirus disease 2019 (COVID-19) have been a means for researchers to establish their safety and to identify therapeutic agents that 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, which can lead to profound hypoxemia in patients with COVID-19 [1]. Nevertheless, some researchers have 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 developed as a response to 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/prediagnosis 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 the preadmission/prediagnosis use of CCBs and the nonuse 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 and 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/prediagnosis use and nonuse 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 noninvasive ventilation, mortality, and/or that death was defined as admission to the intensive care unit, the requirement of invasive or noninvasive ventilation or death. Meta-analysis of four studies [4, 6, 7, 9] with a total of 2618 patients with COVID-19 revealed a significant reduction in the odds of all-cause mortality with the preadmission/prediagnosis use of CCBs relative to the nonuse of CCBs; the estimated effect indicates mortality reduction (Fig. 1; pooled OR = 0.65; 95% confidence interval 0.49–0.86) and is associated with adequate evidence to reject the model hypothesis of ‘no significant difference’ at the current sample size. However, sensitivity analysis with IVhet model (performed due to presence of heterogeneity) revealed no significant mortality reduction with the preadmission/prediagnosis use of CCBs relative to the nonuse of CCBs (pooled OR = 0.75; 95% confidence interval 0.52–1.09). Visual inspection of the funnel plot (Supplementary Fig. S1) revealed some degree of publication bias, as we found asymmetry in the scatter of studies (with more studies with positive findings than studies with negative findings), but the triangular 95% confidence region included almost all studies, suggesting that only a small bias was present.

The definition of severe illness varied 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 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. Meta-analysis of four studies [4, 6, 7, 9] with a total of 8413 patients with COVID-19 revealed a significant reduction in the odds of severe illness with the preadmission/prediagnosis use of CCBs relative to the nonuse of CCBs; the estimated effect...
| Study                  | Country          | Design                          | Total number of patients | Age (mean [SD]/median [IQR]) | Proportion of patients with hypertension | Mortality | Severe illness* | Adjusted covariates | Adjusted estimates |
|-----------------------|------------------|---------------------------------|--------------------------|------------------------------|-----------------------------------------|-----------|-----------------|---------------------|--------------------|
|                       |                  |                                 |                          |                              |                                         | CCB users (n/N; %) | Non-CCB users (n/N; %) | CCB users (n/N; %) | Non-CCB users (n/N; %) |                     |
|                       |                  |                                 |                          |                              |                                         | Adjusted estimate (95% CI) | Adjusted estimate (95% CI) |                     |
| Oh et al. [3]         | South Korea      | Retrospective database review   | 7713                     | N/A                          | 24.5%                                   | N/A       | N/A             | —                   | —                  |
| 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 = 0.58 (0.38–0.89) | N/A       | N/A             | Hypertensive subgroup: OR = 0.78 (0.49–1.26) |
| Chouchana et al. [5]  | France           | Retrospective, multicenter      | 3686                     | All patients = 68.0 (25.9)   | 100%                                    | N/A       | N/A             | —                   | —                  |
| 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, 613, 6.4 | RR = 0.61 (0.25–1.47) |
| Yan 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) |
| Neuraz et al. [8]     | France           | Retrospective database review   | 3965                     | N/A                          | 100%                                    | N/A       | N/A             | HR = 0.82 (0.71–0.94) | -                  | -                  |
| 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) |
| 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) | -                  | -                  |
| Mendez et al. [1]     | United States    | Retrospective, multicenter      | 245                      | CCB users = 70.0 (15.0) Non-CCB users = 70.0 (14.0) | 100%                                   | -         | -               | -                   | -                  |

*The 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 study by Yan 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 defined as the use of invasive or noninvasive mechanical ventilation or death.

CCB: calcium channel blocker, CI: confidence interval, COVID-19: coronavirus disease 2019, OR: odds ratio, IQR: interquartile range, NOS: Newcastle–Ottawa Scale, RR: hazard ratio, CI: confidence interval, SD: standard deviation.
indicates a reduction in severe illness (Fig. 1; pooled OR = 0.61; 95% confidence interval 0.44–0.84) and is associated 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 the preadmission/prediagnosis use of CCBs against all-cause mortality and COVID-19-associated severe illness in patients with COVID-19 and concurrent hypertension relative to the nonuse of CCBs. Although the studies [3–10] included in our meta-analysis were of 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 the preferential prescription 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 were mostly retrospective in design, and thus, the generalizability of the findings may be limited. Furthermore, our analysis focused on the preadmission/prediagnosis use of CCBs; the effect of the 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 analysis.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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