Review

The effects of hypertension on the prognosis of coronavirus disease 2019: a systematic review and meta-analysis on the interactions with age and antihypertensive treatment

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Background: Hypertension and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) have been reported to be associated with the prognosis of COVID-19, but the findings remain controversial. Here, we conducted a systematic review to summarize the current evidence.

Methods: We retrieved all the studies by MEDLINE via PubMed, CENTRAL, and Embase using the MeSH terms until 30 April 2021. A fixed or random effect model was applied to calculate pooled adjusted odds ratio (AOR) with 95% confidence interval (CI). Interactive analysis was performed to identify the interaction effect of hypertension and age on in-hospital mortality.

Results: In total, 86 articles with 18 775 387 COVID-19 patients from 18 countries were included in this study. The pooled analysis showed that the COVID-19 patients with hypertension had increased risks of in-hospital mortality and other adverse outcomes, compared with those without hypertension, with an AOR (95% CI) of 1.36 (1.28–1.45) and 1.32 (1.24–1.41), respectively. The results were mostly repeated in countries with more than three independent studies. Furthermore, the effect of hypertension on in-hospital mortality is more evident in younger and older COVID-19 patients than in 60–69-year-old patients. ACEI/ARBs did not significantly affect the mortality and adverse outcomes of COVID-19 patients, compared with those receiving other antihypertensive treatments.

Conclusion: Hypertension is significantly associated with an increased risk of in-hospital mortality and adverse outcomes in COVID-19. The effect of hypertension on in-hospital mortality among consecutive age groups followed a U-shaped curve. ACEI/ARB treatments do not increase in-hospital mortality and other poor outcomes of COVID-19 patients with hypertension.

Keywords: adverse outcomes, angiotensin-converting enzymes/angiotensin–renin blocker treatment, coronavirus disease 2019, hypertension, mortality

Abbreviations: ACEI, angiotensin-converting enzymes; ARB, angiotensin–renin blockers; COVID-19, coronavirus disease 2019; RAAS, renin–angiotensin–aldosterone system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

BACKGROUND

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection resulted in public health crisis worldwide. Globally, as of 1747 h. CET, 29 April 2022, there have been 510 270 667 confirmed COVID-19 cases, including 6 233 526 deaths, reported to WHO [1]. The overall crude fatality rate was approximately 1.22%. A number of studies have shown that ageing, immune and inflammation, and underlying comorbidities are the most common factors associated with the mortality and severity of COVID-19 [2–4]. Hypertension is a common health issue in adults, especially in elderly populations. However, the findings from the published studies about the effect of hypertension on the prognosis of COVID-19 remain controversial. Some studies showed COVID-19 patients with hypertension had a higher risk of developing severe COVID-19 or mortality, compared with those without hypertension [5–7]. Conversely, hypertension did not have a significant effect on the prognosis of COVID-19 in another group of researches [8–10]. Furthermore, as SARS-CoV-2 infected patients of all ages were at risk of dying from COVID-19, few studies illustrated the effect of

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comorbidities on the mortality in different age groups. Thus, an interactive effect of hypertension and age on the mortality of COVID-19 remains to be determined. In addition, evidence regarding the effect of antihypertensive treatments on clinical outcomes is still limited in real world, especially for angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). ACEIs and ARBs are the two types of renin–angiotensin–aldosterone system (RAAS) inhibitors widely used for the treatment of hypertension. Previous researches showed that ACEI/ARBs could increase the expression of angiotensin-converting enzyme 2 (ACE2), which is required for SARS-CoV-2 entry and propagation [11,12]. Hence, it has been speculated that COVID-19 patients receiving RAAS inhibitors had an increased risk of adverse clinical outcome [13,14], although this hypothesis was not supported by some other studies [15,16]. To clarify the effects of hypertension and age as well as the use of ACEI/ARB treatment on the outcomes of COVID-19, we conducted a systematic review and meta-analysis to provide more reliable and comprehensive evidence.

METHODS

Protocol registration

We previously registered the protocol for this systematic review on PROSPERO (https://www.crd.york.ac.uk/PROSPERO, ID: CRD42021274578).

Search strategy

A systematic literature searching was performed using MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and Embase using the medical subject heading (MeSH) terms. The relevant literature published before 30 April 2021 was all retrieved. There were no restrictions on study design, publication type, or language. Non-English studies were translated into English after the inclusion. The searching terms were as follows: Corona Virus Disease-2019, 2019 novel coronavirus, SARS-CoV-2, COVID-19, 2019-nCoV, antihypertensive treatment, hypertension with COVID-19, ACEI, ARB, and RAAS.

Selection criteria

The inclusion criteria for the articles were as follows: studies that included COVID-19 patients with or without hypertension/antihypertensive treatment; endpoints of the studies related to in-hospital mortality and/or other adverse outcomes relevant to COVID-19, such as ICU admission. The exclusion criteria were as follows: patients younger than 18 years old; the studies with sample size of smaller than 20; the studies not published as the full reports or lack of necessary information for data extraction.

Definition of exposure and endpoints

Hypertension and the use of ACEI/ARB therapy were defined as those COVID-19 patients diagnosed as or noted with ‘hypertension’, ‘Arterial hypertension’, ‘High blood pressure’, ‘Antihypertensive medication’, ‘RAAS inhibitors’, ‘ACEI(s)’, ‘ARB(s)’ from the electronic medical record system. Non-RAAS inhibitors were defined as antihypertensive treatment with beta-blockers, calcium channel blockers, or diuretics. The primary endpoint was all-cause mortality within 28 days or longer after hospital admission, labeled as ‘dead’, ‘died’, ‘death’, ‘not survivor’, or ‘deceased’, while the survival was defined as those patients with an outcome labeled as ‘alive’, ‘survivor’, ‘discharged’, ‘recovered’. The secondary endpoints were the adverse outcomes related to COVID-19: ICU admission, invasive mechanical intubation requirement, and severe COVID-19. The severity of COVID-19 disease was evaluated according to WHO’s interim guidelines [17].

Study selection

Our systematic searching followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA, http://www.prisma-statement.org) purposely for recommendations. All the potential related records have been exported into the Endnote Library for further screening and management by order of author names and years. We also reviewed the reference lists of the studies and established cross citation searching in Google Scholar. We also searched the conference proceedings to acquire the relevant articles for the meta-analysis. If the duration and sources of study population recruited overlapped more than 30% in two or more articles written by the same authors, we only included the most recent study or the study with the largest sample size. The studies were also recruited when they shared different outcomes, although the participants of these studies were from the same source. Three reviewers (A.U.K., Y.L., and Y.F.) independently established study selection, including screening of titles and abstracts, and ultimately resolved disagreements. The complicated articles, which could not be identified by those reviewers were arbitrated by the third experienced reviewer (G.C. or P.L.).

Data extraction

Data were independently extracted by three authors (A.U.K., Y.L., and Y.F.), and then checked by the other co-authors. The concordance rate between the three authors was 95%. The extracted data were managed in a standardized data extraction form. The information as followed was extracted from all included publications: author, study design, sample collection time, country, sample size, other demographic characteristics, description of prognostic elements, outcomes, and their definitions. The effects of hypertension or ACEI/ARB treatment on the outcomes of COVID-19 patients were evaluated by odds ratio (OR) and 95% confidence interval (CI). Specifically, the adjusted OR (AOR) was preferred when the AOR and the crude OR were both presented in the studies, in order to minimize confounding effects.

Statistical analysis

The baseline information of the included studies was synthesized and presented in a tabular form. The items including the sample size, data collection time, demographic characteristics, and the risk of bias in each study were summarized. Categorical variables were presented as counts (%) and continuous variables were described using means. A fixed-effect model with the Mentel–Haenszel method was applied to estimate pooled OR (95% CI) if no evidence of significant heterogeneity existed; otherwise, a random-effect model with the DerSimonian–Laird method was applied. A P value of less than 0.05 was considered significant. The heterogeneity was assessed by I^2 statistics, I^2 less than 25 indicating low heterogeneity, $25 \leq I^2 < 75$ moderate heterogeneity, and I^2 at least 75 high heterogeneity. Generally, I^2 statistic of greater than 50% was considered significant heterogeneity. The subgroup analysis was conducted to figure out the source of heterogeneity according to the basic characteristics of patients or other features. The interactive analysis was performed to identify the interaction effect of hypertension and age on in-hospital mortality. Additionally, the sensitivity analysis was also performed using the leave-one-out method to track the source of heterogeneity and evaluate the statistical robustness. The publication bias of the included studies was evaluated qualitatively by funnel plot and quantitatively by the Egger's test. When the number of the studies was less than 10, the publication bias assessment was not applicable and discarded. These statistical analyses and plots were performed using Meta package from R software, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Quality assessment

We used the Cochrane's Collaboration Tool to assess the risk of bias in the included studies. Newcastle–Ottawa Scale (NOS) was recommended to evaluate cohort and case–control studies by Agency for Healthcare Research and Quality (AHRQ) [18,19]. A study could be awarded a maximum of nine stars in three sections. Quality assessment for the randomized trials was waived because of the absence of eligible randomized trials after study selection. The methodological quality of cross-sectional studies was assessed using an 11-item checklist, which was recommended by AHRQ [19]. The quality of the articles was judged as follows: low quality = 0–3; moderate quality = 4–6; high quality at least 7. Two reviewers (A.U.K. and and P.L.) independently assessed the risk of bias of each study twice.

RESULTS

Characteristics of studies and coronavirus disease 2019 participants

A total of 7087 potentially relevant articles were identified by our searching strategy. After excluding 6001 unqualified articles, 86 articles were involved in the subsequent analysis [2,4–7,9,10,14–16,20–95]. Of these, 23 studies contained multiple endpoints with two more kinds of comparisons (Fig. 1). A summary of baseline characteristics of the 86 studies was illustrated in Table 1. A total of 18 775 387 COVD-19 patients from 18 countries worldwide were enrolled in this study. Of these, the top three counties were China, the United States of America (USA), and Mexico. The duration of most population collection was from January 2020 to July 2020. The mean age of the total population was approximately 60 years. The proportion of hypertension in each included study varied from 7.9 to 100%. Of the 86 included studies, 24 targeted particular populations, such as the severe and elderly COVID-19 patients. All the included studies were observational, and there were no randomized clinical trials (RCTs). Of these, 60 were retrospective studies; 17 were prospective cohort studies; and nine were cross-sectional studies. For quality assessment, the risk of bias in the most studies was low or moderate.

The effect of hypertension on the mortality of coronavirus disease 2019 inpatients

Of 60 studies evaluating the impact of hypertension on the risk of mortality in COVID-19 patients, 50 exhibited AORs (95% CI). The crude ORs were reported in the rest 10 studies because of the nonsignificant results from the univariate or multivariate analysis. Our pooled analysis indicated that COVID-19 patients with hypertension had a higher risk of mortality, compared with those without hypertension (Random effects model, AOR: 1.36, 95% CI 1.28–1.45; $P < 0.001$), although the heterogeneity was statistically significant ($I^2 = 80\%$). Consequent subgroup analysis stratified by country, age, and demographic characteristics of the population was conducted to seek for the source of heterogeneity. Of these factors, country partly explained the heterogeneity (the counties with more than three studies were incorporated into this analysis). The subgroup effects were significant in China, Italy, Mexico, and the United Kingdom (UK) but marginally insignificant in USA [China: 1.68 (1.34–2.10), Italy: 1.85 (1.09–3.14), Mexico: 1.37 (1.25–1.50), UK: 1.26 (1.04–1.52) and USA: 1.07 (0.98–1.16)]. The heterogeneity was moderate in China, UK, and USA ($I^2 = 47\%$, $I^2 = 57\%$, $I^2 = 30\%$) but high in Italy ($I^2 = 73\%$) and Mexico ($I^2 = 92\%$) (Figs 2 and 3). Furthermore, the sensitivity analysis indicated that the association of hypertension with a higher mortality risk in COVID-19 was consistently evident, after removal of any single study (Figure S1, http://links.lww.com/HJH/C47).

Interactive effect of hypertension and age on the mortality of coronavirus disease 2019 inpatients

Regarding nonlinear association between age and hypertension on the mortality, mean age was transformed into age groups to identify the interactive effect. AOR appeared to have an ascent trend after an initial decline with age, divided by a 10-year interval (Fig. 4a). Specifically, the effect of hypertension on the mortality was higher in COVID-19 patients aged 49 or less and at least 70 years than that in those aged 50–69 years ($P < 0.001$). To further determine this interactive effect, age was divided into eight groups by 5-year interval. The effects of hypertension on in-hospital mortality among those age groups followed a similar U-shaped curve. A decreased trend was evident in COVID-19 patients younger than 60 years and then increased in patients older than 69 years (Fig. 4b).

Effect of hypertension on the adverse outcomes of coronavirus disease 2019 patients

In total, 25 eligible studies were included in this analysis. On the basis of fixed-effect model, hypertension had an adjusted OR of 1.32 (1.24–1.41) for the adverse outcomes in COVID-19 patients and the heterogeneity was generally

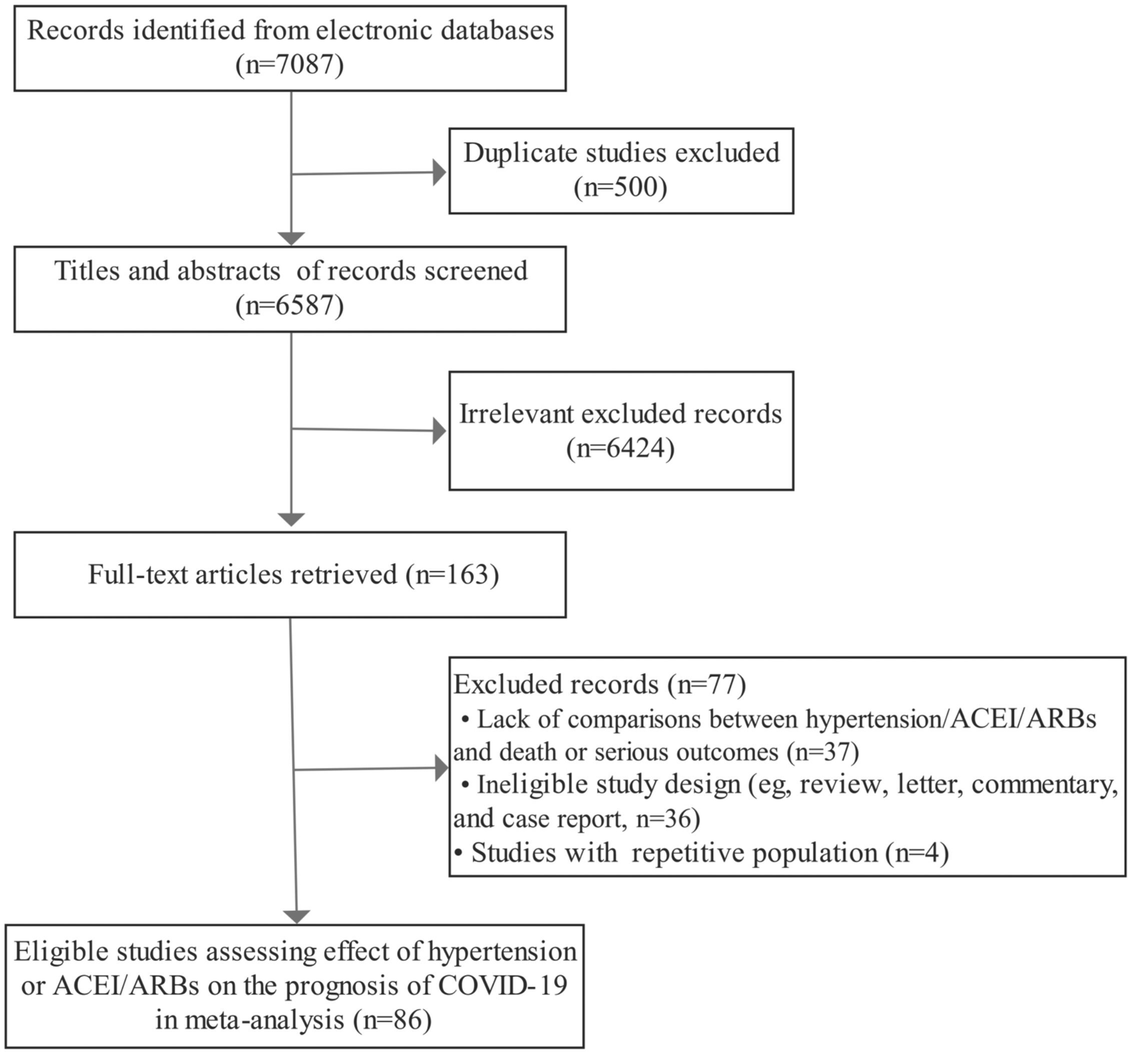

FIGURE 1 Flowchart of study selection.

acceptable ($I^2 = 48\%$, $\tau^2 = 0.0246$, $P < 0.01$). Subsequently, the analysis of subgroup stratified by the outcomes was performed. The subgroup effects for ICU admission ($n = 11$, AOR: 1.26, 95% CI 1.15–1.38, $I^2 = 13\%$) and invasive intubation requirement ($n = 7$, AOR: 1.27, 95% CI 1.15–1.39, $I^2 = 24\%$) were similar. However, the subgroup effect of hypertension on the severe COVID-19 ($n = 7$, AOR: 1.90, 95% CI 1.59–2.29, $I^2 = 39\%$) was higher than that of other two adverse outcomes. Generally, the effects of hypertension on ICU admission, mechanical intubation requirement, and severe COVID-19 were consistently significant (Fig. 5).

Effect of angiotensin-converting enzyme-inhibitors/angiotensin–renin blockers on the mortality of coronavirus disease 2019 inpatients

In total, 15 studies were included to investigate the relationship between ACEI/ARB medication and the mortality of COVID-19 patients with hypertension. The fixed-effect model showed that the use of ACEI/ARBs was not significantly associated with the risk of in-hospital mortality [0.97 (0.87–1.08)], compared with the hypertensive COVID-19 patients taking non-RAAS inhibitors. In addition, the moderate heterogeneity ($I^2 = 41\%$) indicated an acceptable systematic difference between those studies (Fig. 6).

Effect of angiotensin-converting enzyme-inhibitors/angiotensin–renin blockers on the adverse outcomes in coronavirus disease 2019 patients

In total, nine eligible studies were analyzed to evaluate the impact of antihypertensive RAAS inhibitors on the adverse outcomes. The random-effect model revealed that no significant association was detected between ACEI/ARB use and the adverse outcomes in hypertensive patients with COVID-19 (AOR: 0.93, 95% CI: 0.68–1.27; $P = 0.636$; $I^2 = 64\%$). Although the subgroup analysis stratified by the adverse outcome was not performed because of the limited studies, the robustness of our findings was demonstrated by the sensitivity analysis with leave-one-out method (Fig. 7, Figure S2, http://links.lww.com/HJH/C47).

Publication bias analysis

Funnel plots were symmetrical for the effects of hypertension and ACEI/ARB use on the mortality of COVID-19

TABLE 1. Characteristics of studies and coronavirus disease 2019 participants included in the meta-analysis

Study (First author, year [ref])	Study Design	Country	Sample collection time	Sample size	Age, years (mean)	Gender, male (n, %)	Hypertension (n, %)	Physical status of population	Risk of bias
AbadÚa, 2020 [20]	Prospective study	Spain	Within April 2020	83	82	35 (42.2)	63 (75.9)	General	3
Agarwal, 2021 [21]	Cross-sectional study	India	25 April to 12 July 2020	95	47	196 (69.8)	39 (13.8)	Severe	9
Albitar, 2020 [22]	Cross-sectional study	Worldwide data	On 21 April 2020	828	49	489 (59.1)	90 (10.9)	General	7
Altunok, 2020 [23]	Retrospective study	Turkey	15 March to 1 May 2020	722	57	371 (51.4)	251 (34.8)	General	7
An, 2020 [24]	Retrospective study	South Korea	23 January to 2 April 2020	10 237	44	4088 (39.9)	1864 (18.2)	General	7
Atkins, 2020 [4]	Prospective study	UK	16 March to 26 April 2020	269 070	73	311 (61.3)	302 (59.6)	General	6
Bae, 2020 [16]	Retrospective study	South Korea	20 January to 31 March 2020	864	_	444 (51.4)	846 (97.9)	With CVD	7
Barrett, 2020 [25]	Retrospective study	USA	9 March to 4 April 2020	1122	62	_	_	General	_
Besharat, 2020 [26]	Cross-sectional study	Iran	Within April 2020	62	67	44 (71.0)	5 (11.1)	General	9
Boulle, 2021 [27]	Retrospective study	South Africa	1 March to 9 June 2020	2978	40	1 455 144 (42.0)	563 908 (16.0)	General	7
Bousquet, 2020 [28]	Prospective study	French	March to April 2020	108	78	60 (55.5)	77 (71.0)	Elderly	4
Burrell, 2020 [29]	Prospective study	Australia	27 February to 30 June 2020	204	63	140 (69.0)	29 (24.0)	Severe	4
Caliskan, 2020 [30]	Retrospective study	Turkey	15 March and 10 May 2020	565	48	_	128 (22.7)	General	6
Cao, 2020 [31]	Retrospective study	China	5 January to 22 February 2020	101	56	67 (66.3)	38 (37.6)	Severe	6
Carrillo-Vega, 2020 [32]	Cross-sectional study	Mexico	Ended on 23 April 2020	10 544	46	6082 (57.7)	2272 (21.7)	General	7
Cetinkal, 2020 [33]	Retrospective study	_	10 March to 10 May 2020	349	69	176 (44.7)	349 (100.0)	General	6
Gao, 2020 [34]	Retrospective study	China	5 February to 15 March 2020	2877	_	1470 (51.1)	850 (29.5)	General	6
Chaudhri, 2020 [35]	Retrospective study	USA	7 March to 1 April 2020	300	_	166 (55.3)	133 (44.3)	General	6
Chilimuri, 2020 [2]	Retrospective study	USA	9 March to 9 April 2020	375	63	236 (63.0)	225 (60.0)	General	7
Cho, 2020 [36]	Retrospective study	South Korea	1 February to 15 May 2020	7327	47	2964 (40.5)	1559 (21.3)	General	8
Crouse, 2020 [37]	Retrospective study	USA	25 February to 22 June 2020	604	60	272 (45.0)	420 (69.5)	General	6
Cummings, 2020 [38]	Prospective study	USA	2 March to 1 April 2020	257	62	171 (67.0)	86 (33.0)	Severe	6
Dai, 2020 [39]	Retrospective study	China	29 January to 25 February 2020	492	_	226 (45.9)	141 (28.7)	General	5
de Souza, 2020 [40]	Cross-sectional study	Brazil	On 2 August 2020	9807	>60	4662 (47.5)	597 (6.1)	Elderly	6
Denova-Gutierrez, 2020 [41]	Cross-sectional study	Mexico	27 February to 10 April 2020	3844	45.4	2230 (58.0)	727 (18.9)	General	7
Dublin, 2021 [42]	Retrospective study	USA	Ended on February 2020	322 044	_	148 330 (46.1)	66 443 (20.6)	General	8
Felice, 2020 [43]	Retrospective study	Italy	9 March to 31 March 2020	133	_	86 (64.7)	133 (100.0)	General	6
Galloway, 2020 [44]	Retrospective study	UK	1 March to 17 April 2020	1157	71	666 (57.6)	611 (52.9)	General	6
Gottlieb, 2020 [45]	Retrospective study	USA	4 March to 21 June 2020	8673	41	4045 (46.6)	1917 (22.1)	General	7
Guisado-Vasco, 2020 [46]	Retrospective study	Spain	10 March to 15 April 2020	607	69	394 (65.0)	276 (46.9)	Severe	7
Gupta, 2020 [47]	Prospective study	USA	4 March to 4 April 2020	2215	60.5	1436 (64.8)	390 (18.3)	Severe	7
Hernandez-Galdamez, 2021 [48]	Cross-sectional study	Mexico	Ended on 27 June 2020	211 003	45.7	115 442 (54.7)	42 453 (20.1)	General	8
Hernandez-Vasquez, 2020 [49]	Cross-sectional study	Mexico	Ended on 18 May 2020	51 053	46	29 422 (57.6)	11 090 (21.7)	General	6
Hu, 2020 [50]	Retrospective study	China	January to March 2020	105	58	66 (62.9)	18 (17.1)	Severe	6
Hu, 2020 [51]	Retrospective study	China	24 January to 16 February 2020	213	44	102 (47.8)	30 (14.0)	General	7
Iaccarino, 2020 [52]	Cross-sectional study	Italy	9 March to 29 April 2020	2378	68.2	1489 (62.6)	1391 (58.5)	General	8
Imam, 2020 [53]	Retrospective study	USA	1 March to 1 April 2020	1305	61	702 (53.8)	734 (56.2)	General	7
Ioannou, 2020 [10]	Retrospective study	USA	28 February to 14 May 2020	10 131	63	9221 (91.0)	3837 (37.9)	General	8
Jiang, 2021 [54]	Retrospective study	China	30 January to 8 March 2020	281	60	143 (50.9)	137 (48.8)	Elderly and severe	6
Josef Smolen, 2020 [55]	Retrospective study	French	Ended on 18 May 2020	694	73	199 (32.2)	133 (21.6)	Rheumatic and inflammatory diseases	6
Kabarriti, 2020 [56]	Retrospective study	USA	14 March to 15 April 2020	5902	58	2768 (46.9)	_	General	7
Kammar-GarcÚa, 2020 [57]	Retrospective study	Mexico	1 January and 25 April 2020	13 842	46	5853 (42.3)	2969 (21.4)	General	6
Kim, 2020 [6]	Retrospective study	South Korea	18 February to 10 July 2020	2254	58	808 (35.8)	646 (28.7)	General	7
Klang, 2020 [58]	Retrospective study	USA	1 March to 9 May 2020	1320	75	772 (58.5)	1003 (76.0)	Elderly	7
Kocayigit, 2020 [59]	Cross-sectional study	Turkey	20 March to 10 April 2020	169	65.8	79 (46.7)	169 (100.0)	General	6

TABLE 1 (Continued)

Study (First author, year [ref])	Study Design	Country	Sample collection time	Sample size	Age, years (mean)	Gender, male (n, %)	Hypertension (n, %)	Physical status of population	Risk of bias
Kvale, 2021 [60]	Cross-sectional study	Norwegian	30 June to 4 December 2020	8809	60	4365 (49.5)	645 (7.3)	General	9
Lee, 2020 [61]	Retrospective study	South Korea	Ended on 15 May 2020	1609	_	699 (43.4)	_	General	7
Li, 2020 [62]	Retrospective study	China	26 January 2020 to 5 February 2020	548	60	279 (50.9)	166 (30.3)	General	7
Liu, 2020 [63]	Retrospective study	China	1 January to 4 March 2020	665	57	318 (47.8)	158 (23.8)	General	6
Lohia, 2020 [64]	Retrospective study	USA	10 March to 30 June 2020	1871	66	965 (51.6)	1485 (79.4)	Elderly	7
Lu, 2020 [65]	Retrospective study	China	19 January to 8 March 2020	20	69	394 (65.0)	276 (46.9)	Severe	7
Mancilla-Galindo, 2020 [7]	Retrospective study	Mexico	1 June to Jul 23, 2020	83 779	46	47 386 (56.6)	17 609 (21.0)	General	7
MartÚnez-del, 2020 [66]	Retrospective study	Spain	1 March to 30 April 2020	921	78	500 (54.3)	545 (59.2)	General	6
Martos-BenÚtez, 2020 [67]	Retrospective study	Mexico	1 January to 12 May 2020	65 535	44	22,362 (58.3)	_	General	7
Mehta, 2020 [68]	Retrospective study	USA	8 March 8 to 12 April 2020	18 472	49	7384 (40.0)	1235 (94.0)	General	7
Mithal, 2020 [69]	Cross-sectional study	India	9 July to 8 August 2020	401	_	276 (68.8)	164 (40.9)	General	7
Mora, 2020 [70]	Prospective study	Italy	12 March to 11 April 2020	431	65	263 (61.0)	221 (51.0)	Elderly	9
Muhammad, 2020 [71]	Retrospective study	USA	1 March to 30 May 2020	200	58.9	121 (60.5)	130 (65.0)	General	6
Olivas-MartÚnez, 2020 [72]	Prospective study	Mexico	26 February to 5 June 2020	800	51	488 (61.0)	240 (30.0)	Severe	5
Palaiodimos, 2020 [73]	Retrospective study	USA	9 March to 12 April 2020	200	64	98 (49.0)	152 (76.0)	General	5
Pantea Stoian, 2020 [15]	Retrospective study	Romania	26 February to 20 April 2020	432	67	282 (65.3)	162 (37.5)	General	7
Pena, 2020 [74]	Cross-sectional study	Mexico	February to 13 November 2020	323 671	_	12 118 (38.6)	25 587 (7.9)	General	9
Rossi, 2020 [75]	Prospective study	Italy	27 February to 2 April 2020	2653	_	1328 (50.1)	430 (18.1)	General	6
Rozaliyani, 2020 [76]	Retrospective study	Jakarta	2 March to 27 April 2020	4052	45	2169 (53.5)	390 (18.3)	General	7
Rubio-Rivas, 2021 [77]	Retrospective study	Spain	1 March to 31 July 2020	12 066	67	7052 (58.5)	6030 (50.0)	Elderly	7
Ruocco, 2020 [78]	Cross-sectional study	Italy	On or after 22 February 2020	864	65	537 (62.2)	420 (48.6)	General	7
Selçuk, 2020 [14]	Retrospective study	Turkey	_	113	_	59 (52.2)	113 (100.0)	General	6
Seo, 2020 [79]	Cross-sectional study	South Korea	On 15 May 2020	423	78	100 (47.0)	_	General	7
Shah, 2020 [80]	Retrospective study	USA	2 March to 6 May 2020	522	63	218 (41.8)	416 (79.7)	General	7
Simonnet, 2020 [81]	Retrospective study	French	27 February to 5 April 2020	124	60	90 (73)	60 (49)	Severe	6
Suleyman, 2020 [82]	Cross-sectional study	USA	9 March to 27 March 2020	463	57.5	204 (44.1)	295 (63.7)	General	7
Sun, 2020 [9]	Retrospective study	China	January to April 2020	3400	61	1649 (48.5)	1782 (52.4)	General	7
Thompson, 2020 [83]	Retrospective study	UK	12 March to 19 May 2020	470	71	255 (54.3)	218 (46.4)	General	6
Vicenzi, 2020 [84]	Retrospective study	Italy	_	69	61	50 (72.0)	31 (45.0)	Severe	6
Wang, 2020 [85]	Retrospective study	China	7 January to 11 February 2020	296	47	140 (47.3)	42 (14.2)	General	6
Wang, 2020 [86]	Retrospective study	China	1 January to 6 February 2020	339	69	173 (51.0)	138 (40.8)	General	5
Williamson, 2020 [5]	Retrospective study	UK	Ended on 6 May 2020	17 278 392	50	8 647 989 (50.1)	5 925 492 (34.3)	General	6
Wu, 2020 [87]	Retrospective study	China	25 December 2019 to 26 January 2020	201	51	128 (63.7)	39 (19.4)	General	6
Xie, 2020 [88]	Retrospective study	USA	30 March to 5 April 2020	287	61.5	124 (43.2)	230 (80.1)	General	8
Xu, 2020 [89]	Retrospective study	China	22 January to 1 April 2020	659	50	332 (50.4)	167 (26.1)	General	6
Yang, 2020 [90]	Retrospective study	China	1 January to 29 February 2020	226	70	113 (50.0)	137 (48.8)	Elderly	5
Zangrillo, 2020 [91]	Retrospective study	Italy	20 February to 2 April 2020	73	54	61 (83.6)	38 (52.9)	Severe	6
Qian, 2020 [92]	Retrospective study	China	December 2019 to February 2020	582	64	289 (50.3)	194 (33.0)	Severe	6
Zhang, 2021 [93]	Retrospective study	China	31 December 2019 to 20 February 2020	1128	64	608 (53.5)	1,128 (100.0)	General	7
Zhou, 2020 [94]	Retrospective study	China	29 December 2019 to 31 January 2020	191	56	119 (62.0)	58 (30.0)	General	6
Zhu, 2020 [95]	Cross-sectional study	China	23 January to 28 March 2020	136	50.2	51 (37.5)	33 (24.3)	General	6

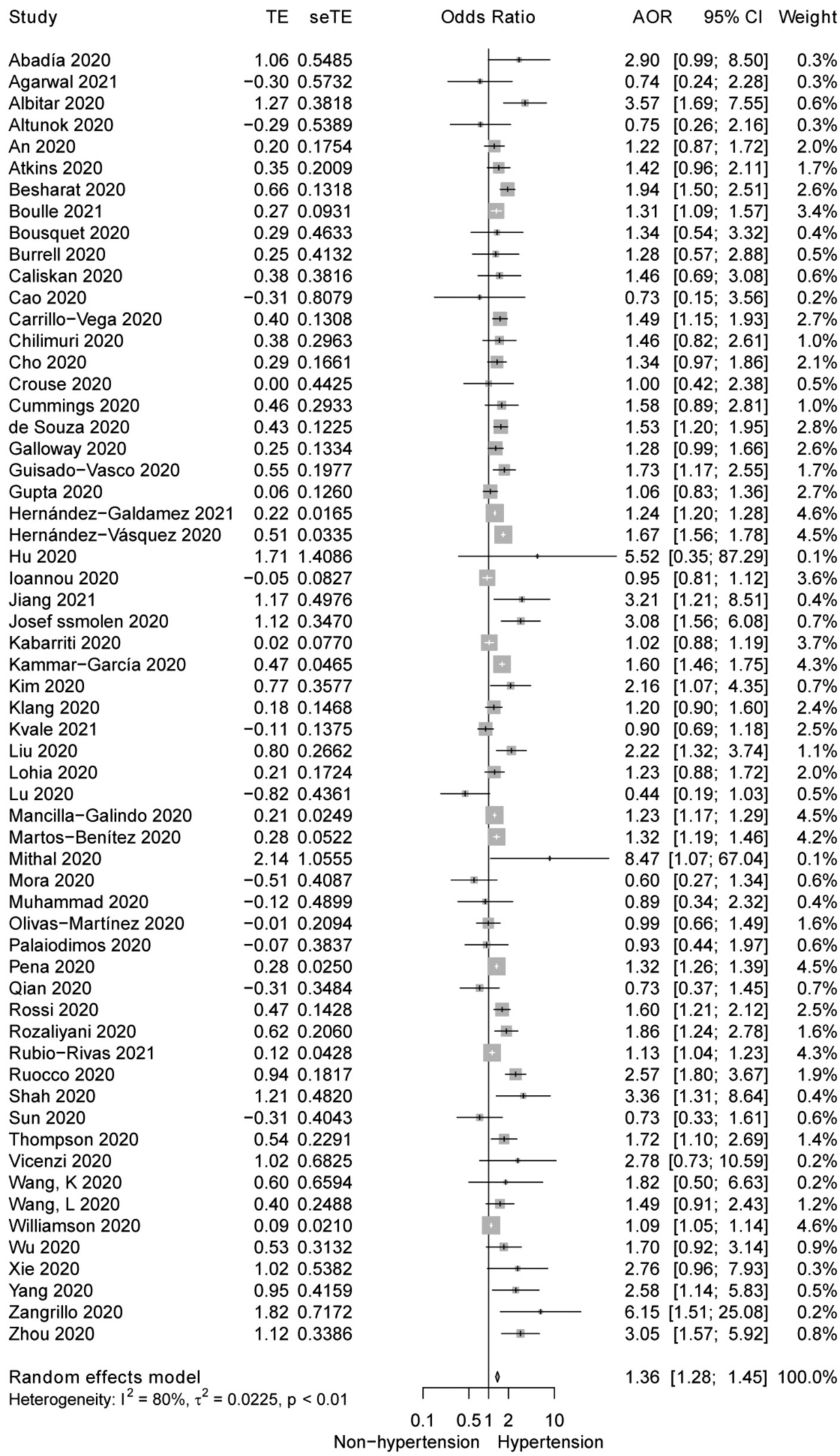

FIGURE 2 Forest plot for the effect of hypertension on in-hospital mortality of coronavirus disease 2019 patients. AOR, adjusted odds ratio; COVID-19, coronavirus disease 2019.

inpatients ($P=0.062$, $P=0.567$, respectively), but slightly asymmetrical for the impact of hypertension on the adverse outcomes ($P=0.028$). Overall, strong evidence of publication bias was not detected. Nevertheless, the assessment of the publication bias in the studies evaluating the effect of ACEI/ARB use on the adverse outcomes was waived as the number of studies was less than 10 (Figure S3, http://links.lww.com/HJH/C47).

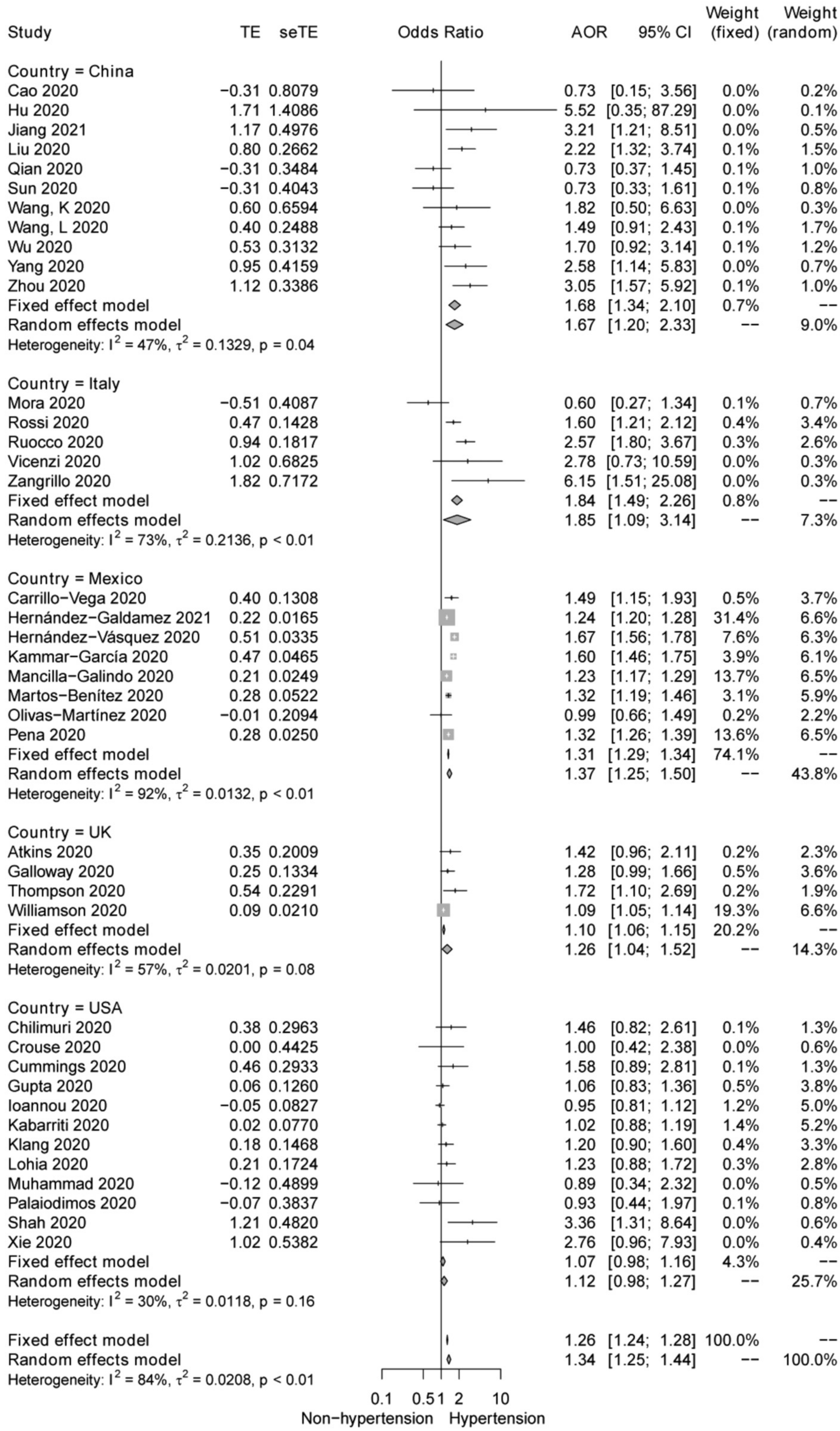

FIGURE 3 Forest plot of subgroup analysis by country for the effect of hypertension on in-hospital mortality of coronavirus disease 2019 patients. AOR, adjusted odds ratio; COVID-19, coronavirus disease 2019.

DISCUSSION

In this study, we investigated the effects of hypertension and the use of ACEI/ARB treatment on the clinical outcomes in COVID-19 inpatients. A significant association of the mortality with hypertension was found in those inpatients. However, the use of ACEI/ARBs was not associated with increased mortality risk or the severity in the hypertensive inpatients with COVID-19 compared with the treatment with non-RAAS inhibitors.

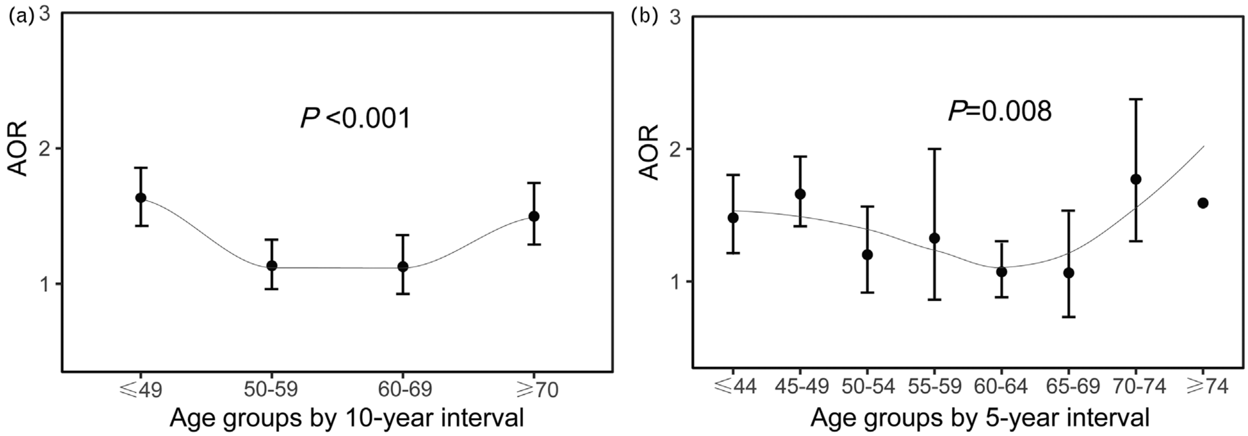

FIGURE 4 Interactive effect of hypertension and age on in-hospital mortality of coronavirus disease 2019 patients. Dark points represent AORs and line bars represent 95% CIs. 95% CI was discarded in the oldest age group (≥74 years), as only two studies were included. AOR, adjusted odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019.

In an earlier systematic review, the risk of getting serious clinical outcomes (including ICU admission, ARDS, and mechanical ventilation) in hypertensive patients with COVID-19 was 2.95 (2.21–3.94) times higher than those without hypertension, based on eight studies and the univariate analysis [96]. By contrast, another systematic review reported the association between hypertension and the mortality as well as mechanical ventilation was not statistically significant, based on 29 studies and age-adjusted model [OR, 95% CI 1 (0.94–1.06) and 1.01 (0.93–1.09), respectively) [97]. Our pooled results based on the multivariate analysis of 86 studies suggested that hypertension was an independent risk factor for the mortality and the adverse outcomes in COVID-19 inpatients, despite that nearly half of the studies presented insignificant results (Figs 2 and 5). Hence, it is reasonably considered that the inconsistent evidence is probably attributable to the quantity and the sample sizes of eligible studies, or the adjustment for potential confounders. More importantly, seeking out the source of heterogeneity among the diverse populations exhibited a greater value. In our study, the subgroup analysis stratified by country could account for part of the heterogeneity. Specifically, the influence of hypertension on the mortality risk was significantly different in domestic regions of Mexico and Italy. We also found interactive effects of hypertension and age on the mortality among COVID-19 inpatients, following a U-shaped curve (Fig. 4). The results indicated that antihypertension treatment needs to be emphasized in younger (<60 years) and older patients (>69 years). Although the prevalence of hypertension is relatively lower in younger patients but this regimen is crucial to prevent young patients from developing severe illness. This finding was supported by a large, prospective, and multicenter cohort study in the UK in which younger people with comorbidities were identified to have a much higher mortality rate than those who had complications, compared with those at the same age without complications [98].

This pooled analysis did not identify the significant effects of the ACEI/ARB treatment on in-hospital mortality and the adverse outcomes [AOR, 95% CI 0.97 (0.87–1.08) and 0.93 (0.68–1.27), respectively] (Figs 5 and 6). Our results are consistent with the findings of WHO's rapid review. There is low-certainty evidence that patients on long-term treatment with ACE inhibitors or ARBs are not at higher risk of poor outcomes from COVID-19 [99].

The underlying mechanisms by which hypertension worsens the prognosis of COVID-19 inpatients remain unknown. There are two widely recognized explanations: RAAS activation of hypertensive patients was assumed to be associated with severe COVID-19, which could trigger the inflammation response and vasoconstriction [100–103]; it has been well documented that the prevalence of hypertension increased in line with old age and comorbidities, which may distort this correlation [2–5]. For the latter point, our meta-analysis showed hypertension was an independent predictor of severe COVID-19 via adjusting for those confounders (Figs. 2 and 5). It is worth noting that younger people have relatively well developed immune system and fewer comorbidities, thus cytokine storm was presumed to play a prominent role in aggravating COVID-19 in younger patients. Thus, hypertension management should be emphasized to control inflammation and enhance host immunity.

The possible mechanisms by which ACEI/ARBs affect the prognosis of COVID-19 have been explained [104]. However, the hypothesis is still controversial, because of the complicated molecular mechanism and absence of high-certainty evidence in humans. At the early stage of COVID-19 outbreak, ACEI/ARB treatment was considered to aggravate lung injury, as some studies reported this treatment could promote the expression of ACE2 [11,105], which linked with SARS-CoV-2 entry and propagation [11,12]. However, most clinical studies presented that ACEI/ARB treatment was neutral and even beneficial to critical COVID-19 (Fig. 6). An RCT also showed no significant difference in the mean number of days alive and out of the hospital for those assigned to discontinue versus continue ACEI/ARB medications [106]. Specially, it was reported that ACEI treatment dampened COVID-19-related

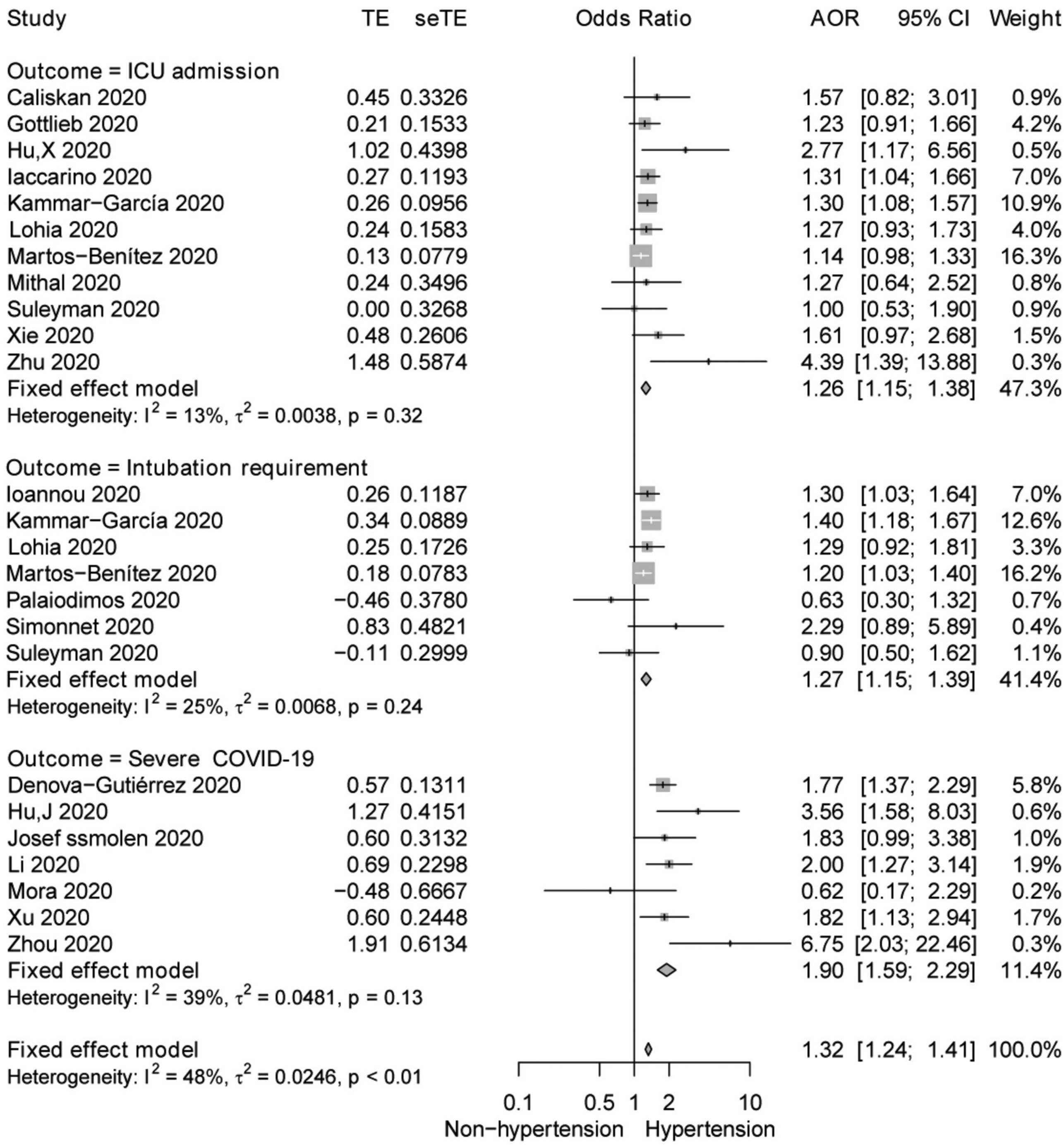

FIGURE 5 Forest plot for the effect of hypertension on ICU admission, mechanical intubation requirement, and severe disease in coronavirus disease 2019 patients. AOR, adjusted odds ratio; COVID-19, coronavirus disease 2019.

hyperinflammation and increased cell-intrinsic antiviral responses, whereas ARB treatment enhanced epithelial–immune cell interactions, based on the clinical data ($n = 144$) and single-cell sequencing data ($n = 48$) [107]. Therefore, it is reasonable to believe that ACEI/ARB treatment has positive or neutral effects on clinical outcomes in patients with COVID-19, although the negative impact exists theoretically.

To the best of our knowledge, this systematic review is the most comprehensive exploration and analysis of the existing literature on this topic to date. More importantly, it was the first systematic review illustrating the interactive effect of hypertension and age on the mortality of COVID-19 patients. However, our study also has limitations. First, no relevant RCTs were available, even though we tried our best to mitigate this by establishing broad searching terms and enrolling in the repositories and databases as many as possible. Second, the heterogeneity was not probed enough, although the subgroup and sensitivity analyses were performed.

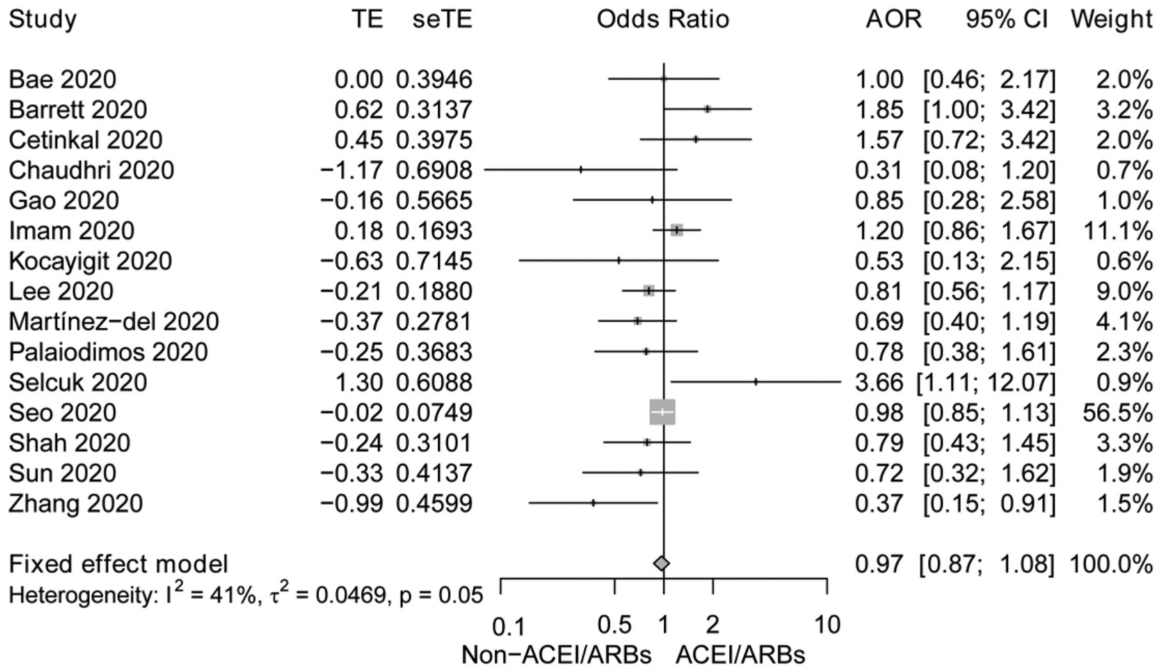

FIGURE 6 Forest plot for the effect of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker treatment on in-hospital mortality of coronavirus disease 2019 patients with hypertension. ACEI, angiotensin-converting enzyme inhibitor; AOR, adjusted odds ratio; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019.

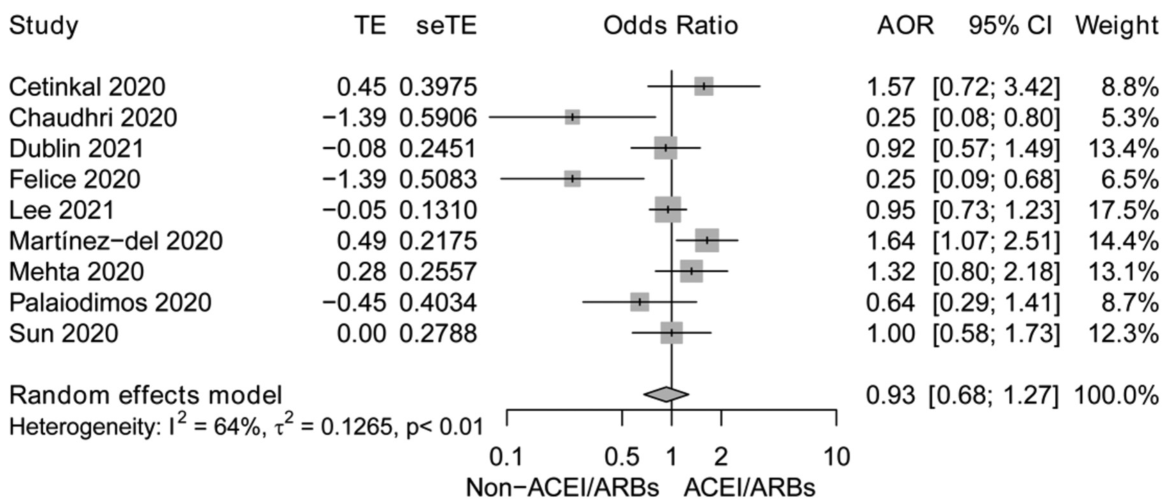

FIGURE 7 Forest plot for the effect of coronavirus disease 2019 treatment on ICU admission, mechanical intubation requirement, and severe disease in coronavirus disease 2019 patients with hypertension. ACEI, angiotensin-converting enzyme inhibitor; AOR, adjusted odds ratio; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019.

Further investigations, including RCTs, are highly recommended.

In conclusion, the pooled analysis of 86 articles included in our study showed that hypertension is independently associated with an increased risk of mortality and adverse outcomes for COVID-19 inpatients. Younger and older hypertensive patients have a higher mortality risk compared with those of the same age without hypertension. Hence, hypertension management should be emphasized in those patients. However, ACEI/ARB treatments do not increase the mortality and other poor outcomes of hypertensive COVID-19 patients. Thus, ACEI/ARBs are suggested to be applied to treat hypertension in patients with COVID-19.

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Authors' contributions: A.U.K., Y.L., Y.F., K.Y., and M.H.; study search, data extraction, and arrangement. A.U.K., P.L, Z.J., and D.J.: quality control, data analysis, and composition of figures and table. G.C.: conceptualization, supervision, funding acquisition. G.C., X.T., and P.L.: article writing.

Conflicts of interest

There are no conflicts of interest.

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