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## Letter to the Editor

**The association of hypertension with the severity and mortality of COVID-19 patients: Evidence based on adjusted effect estimates**


To the Editor,

Previous studies have shown that common comorbidities were significantly associated with the increased risk of adverse outcomes in patients with coronavirus disease 2019 (COVID-19)<sup>1</sup>. As we know, hypertension was the most common comorbidities among COVID-19 patients<sup>2</sup>. Recently, a paper in the Journal of Infection by Zheng et al.<sup>3</sup> has reported that the proportion of hypertension was significantly higher in critical/mortal patients compared to the non-critical patients (odds ratio (OR)=2.72, 95% confidence interval (CI) [1.60–4.64],  $P=0.0002$ ). However, the findings were based on unadjusted effect estimates. It was worth mentioning that the data based on unadjusted effect estimates indicated hypertension was an important risk factor for the adverse outcomes of COVID-19 patients, but the pooled effects based on adjusted effect estimates were significantly reduced or even disappeared in several studies<sup>4–8</sup>. For instance, in the study of Wang et al., univariate analysis showed that hypertension was a risk factor for death in patients with COVID-19 (OR=5.000, 95% CI [1.748–14.301]), while multivariate analysis showed that hypertension was not significantly associated with the risk of mortality (OR=1.099, 95% CI [0.264–4.580])<sup>7</sup>. Similarly, univariate analysis in Cummings et al. indicated that hypertension was significantly associated with patients' death (hazard ratio (HR)=2.24, 95% CI [1.40–3.59]), but this association disappeared in the multivariate analysis (HR=1.58, 95% CI [0.89–2.81])<sup>5</sup>. The same findings were also observed in Wang et al.'s study<sup>8</sup>. This meant that the association of hypertension with the adverse outcomes of COVID-19 patients might be affected by various factors such as age, gender and other comorbidities. Therefore, it is urgently required to clarify the association between hypertension and the adverse outcomes of COVID-19 patients by a systematically quantitative meta-analysis on the basis of the published studies reporting the adjusted effect estimates.

Therefore, we systematically searched the electronic databases, including Web of Science, Chinese National Knowledge Infrastructure (CNKI) and PubMed to identify all observational studies published between January 1, 2020 and June 15, 2020 that compared outcomes in hospitalized COVID-19 patients with and without hypertension. These search engines used the following two sets of keywords to capture available literature: "Coronavirus 2019, 2019-nCoV, SARS-CoV-2, COVID-19" and "Hypertension". Only articles that reported adjusted effect estimates of hypertension and adverse outcomes (severity including severe and critical, and mortality) in patients with COVID-19 were qualified. All calculations were implemented with Stata 11.2 software. The pooled OR and pooled HR with their corresponding 95% CI were used to evaluate the risk

of adverse outcomes in patients with COVID-19 and hypertension. The degree of heterogeneity between studies was tested using  $I^2$  statistics. The  $I^2$  values were 25%, 50%, and 75%, indicating low, medium, and high heterogeneity, respectively<sup>9</sup>. If there was no evidence of between-studies heterogeneity ( $I^2 \leq 50\%$ ), a fixed-effects model was used to calculate the combined effects. Otherwise, a random-effects model was selected<sup>10</sup>. The sensitivity analysis was used to evaluate the robustness of the results. Both Begg's test and Egger's test were used to evaluate publication bias.

Overall, 521 documents were initially identified according to our search criteria, and the final analysis included 19 studies of 15,302 patients<sup>4–8,11–24</sup>. As shown in Table 1, the median age of COVID-19 patients ranged from 43.9 to 71 years, of which 38.2% had hypertension. The sample size ranged from 63 to 2877. Seventeen studies were retrospective and two prospective.

Totally, our meta-analysis showed that hypertension was significantly associated with the increased risk of adverse outcomes in COVID-19 patients on the basis of 19 studies with 15,302 cases (OR=1.44, 95% CI [1.24–1.66];  $I^2=41.4\%$ , random-effects model) (Fig. 1A). Of the 19 studies, 12 reported adjusted OR and 7 reported adjusted HR. Therefore, we conducted a subgroup analysis based on the adjusted OR and adjusted HR. We also found a significant correlation between hypertension and adverse outcomes on the basis of both 12 OR-adjusted studies with 8173 cases (OR=1.37, 95% CI [1.08–1.72];  $I^2=51.9\%$ ) and 7 HR-adjusted studies with 7129 cases (HR=1.55, 95% CI [1.35–1.78];  $I^2=0.0\%$ ) (Fig. 1A). As shown by the sensitivity analysis, none of the studies had a significant impact on the overall results, which proves the robustness of our results (Fig. 1B). No publication bias was detected in Begg's test ( $P=0.889$ ) or Egger's test ( $P=0.432$ ).

Previous studies have suggested that hypertension was a risk factor for adverse outcomes of COVID-19 patients, but the studies did not consider the effects of confounding factors on the findings<sup>2,25–28</sup>. Presently, our results showed that hypertension was significantly associated with the increased risk of adverse outcomes in COVID-19 patients on the basis of the adjusted effect estimates, which suggests that hypertension is an independent risk factor for predicting the severity and mortality of COVID-19 patients. Thus, COVID-19 patients with hypertension deserve more clinical attention. It should be acknowledged that some limitations existed in our study. Firstly, the judgment criteria of adverse results in the included studies were not uniform. Secondly, all the included studies reported the adjusted effect estimates, but the confounding factors adjusted in each study were not entirely consistent. Thirdly, the stage of hypertension and whether it is controlled or poorly controlled are also unknown. The included studies did not adequately report data on chronic hypertension medications and therefore these could not be analyzed.

In summary, our meta-analysis demonstrated for the first time that hypertension was an independent risk factor for predicting

**Table 1**  
Characteristics of the included studies.

Author	Location	Case	Age (years)	Male (%)	Study design	HTN	Adjusted effect estimate(95%CI)	Confounders
Chen C <sup>[12]</sup>	China	150	59(16)	84(56)	R	49(32.6)	OR 2.586 (0.609–10.980)	Age, gender, NT-proBNP, cTnl, hs-CRP, creatinine, CHD
Wang D <sup>[7]</sup>	China	107	51(31–65)	57(53.3)	R	26(24.3)	OR 1.099 (0.264–4.580)	Age, gender, CVD, creatinine concentration
Sun H <sup>[21]</sup>	China	244	NR	137(54.5)	R	138(56.6)	OR 0.82 (0.24–2.75)	Age, gender, vital signs, previous respiratory diseases, laboratory values
Shi S <sup>[20]</sup>	China	671	63(50–72)	322(48)	R	199(29.7)	HR 1.07 (0.46–2.53)	Age, gender, diabetes, CHD, chronic renal disease, chronic heart failure, atrial fibrillation, CVD, COPD, procalcitonin, CRP
Yan X <sup>[23]</sup>	China	1004	NR	493(49.1)	R	235(23.4)	OR 2.606 (0.988–6.870)	NLR, hs-CRP, NT-proBNP, BUN, respiratory failure, digestive system disease, CVD
Wang G <sup>[8]</sup>	China	209	NR	105(50.2)	R	27(12.9)	OR 0.357 (0.078–1.639)	Age, gender, creatine kinase, lymphocyte, AST, CRP
Cummings MJ <sup>[5]</sup>	America	257	62(51–72)	171(67)	P	162(63)	HR 1.58 (0.89–2.81)	Age, gender, symptom duration before hospital presentation, chronic cardiac disease, COPD or interstitial lung disease, diabetes, interleukin-6, d-dimer
Phipps MM <sup>[6]</sup>	America	2273	65(52–76)	1297(57)	R	1375(60)	OR 1.15 (0.85–1.56)	Age, peak ALT, BMI >35, diabetes, intubation, renal replacement therapy
Galloway JB <sup>[14]</sup>	UK	1157	71(57–82)	666(57.6)	R	611(52.9)	HR 1.53 (1.24–1.90)	Age, gender
Huang S <sup>[16]</sup>	China	310	62(40–70)	174(56.1)	R	113(36.5)	OR 1.562 (0.929–2.625)	Age, gender
Escalera-Antezana JP <sup>[13]</sup>	Bolivia	107	43.9(17.6)	55(51.4)	R	10(9.35)	OR 3.284 (1.276–6.291)	Age
Gao C <sup>[15]</sup>	China	2877	NR	1479(51.1)	R	850(29.5)	HR 2.06 (1.10–3.83)	Age, gender, medical history of diabetes, insulin-treated diabetes, myocardial infarction, underwent PCI/CABG, renal failure, stroke, heart failure, COPD
Zhao M <sup>[24]</sup>	China	1000	61(46–70)	466(46.6)	R	282(28.2)	HR 1.974 (1.297–3.003)	Age
Sabri A <sup>[19]</sup>	Iran	63	54.1(15.5)	NR	R	15(23.8)	OR 1.42 (1.13–1.71)	History of heart disease, pericardial effusion, blood oxygen saturation
Lim JH <sup>[18]</sup>	Korea	160	NR	86(53.8)	R	77(48.1)	HR 1.34 (0.71–2.52)	Acute kidney injury network, age, gender, diabetes
Chen F <sup>[4]</sup>	China	660	55(34–68)	295(44.7)	R	230(34.8)	OR 0.920 (0.420–2.016)	Age, cerebral infarction, SOFA, CRP, LDH
Targher G <sup>[22]</sup>	China	310	47	149(48.1)	R	NR	OR 2.68 (1.20–5.98)	Age, gender
Lala A <sup>[17]</sup>	America	2736	66.40(15.8)	1630(59.6)	R	1065(38.9)	OR 0.99 (0.79–1.23)	Age, gender, troponin strata, race, ethnicity, coronary artery disease, diabetes, heart failure, atrial fibrillation, chronic kidney disease
Cen Y <sup>[11]</sup>	China	1007	61 (49–68)	493(49.0)	P	270(26.8)	HR 1.442 (1.109–1.876)	Age, gender, smoking, diabetes, chronic obstructive lung disease, coronary artery disease, duration of anti-viral therapy

All values are n (%), mean (SD) or median (IQR); NR, not reported; HTN, hypertension; P, prospective; R, retrospective; HR, hazard ratio; OR, odds ratio; NT-proBNP, amino-terminal pro-brain natriuretic peptide; cTnl, cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; CHD, Coronary heart disease; CVD, cardiovascular or cerebrovascular disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; SOFA, Sequential Organ Failure Assessment; PCI/CABG, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); LDH, lactate dehydrogenase.

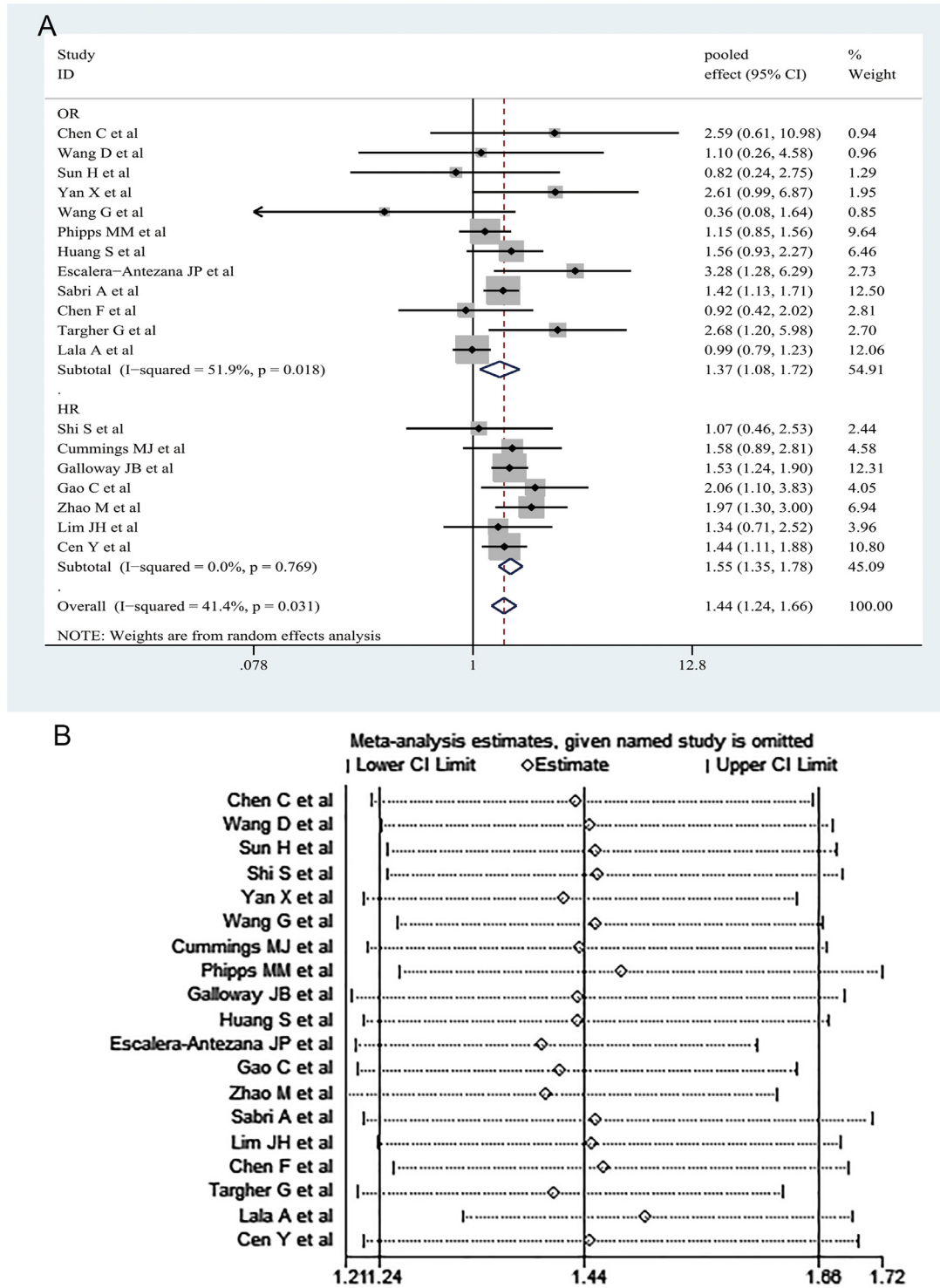


Fig. 1. The pooled effects and their 95% confidence interval (CI) of the relationship between hypertension and adverse outcomes in patients with COVID-19 (A). Sensitivity analysis of the relationship between hypertension and adverse outcomes in patients with COVID-19 (B).

the adverse outcomes of patients with COVID-19. Further well-designed studies with larger sample sizes are required to verify the findings of our present study.

**Declaration of Competing Interest**

All authors report that they have no potential conflicts of interest.

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