

Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression

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Abstract

Objective: To investigate the association between hypertension and outcome in patients with Coronavirus Disease 2019 (COVID-19) pneumonia.

Methods: We performed a systematic literature search from several databases on studies that assess hypertension and outcome in COVID-19. Composite of poor outcome, comprising of mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) care and disease progression were the outcomes of interest.

Results: A total of 6560 patients were pooled from 30 studies. Hypertension was associated with increased composite poor outcome (risk ratio (RR) 2.11 (95% confidence interval (CI) 1.85, 2.40), $p < 0.001$; I^2 , 44%) and its sub-group, including mortality (RR 2.21 (1.74, 2.81), $p < 0.001$; I^2 , 66%), severe COVID-19 (RR 2.04 (1.69, 2.47), $p < 0.001$; I^2 31%), ARDS (RR 1.64 (1.11, 2.43), $p = 0.01$; I^2 0%, $p = 0.35$), ICU care (RR 2.11 (1.34, 3.33), $p = 0.001$; I^2 18%, $p = 0.30$), and disease progression (RR 3.01 (1.51, 5.99), $p = 0.002$; I^2 0%, $p = 0.55$). Meta-regression analysis showed that gender ($p = 0.013$) was a covariate that affects the association. The association was stronger in studies with a percentage of males $< 55\%$ compared to $\geq 55\%$ (RR 2.32 v. RR 1.79).

Conclusion: Hypertension was associated with increased composite poor outcome, including mortality, severe COVID-19, ARDS, need for ICU care and disease progression in patients with COVID-19.

Keywords

Hypertension, coronavirus, COVID-19, severity, mortality

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Introduction

Coronavirus disease 2019 (COVID-19) has spread across the globe, and has been officially confirmed by the World Health Organization (WHO) as a public health emergency.¹ COVID-19 has infected more than 1.4 million people and killed more than 80,000 people globally, with the total number of cases and deaths increasing every day. Most COVID-19 patients present with mild or no symptoms, but a few portions of patients may develop severe pneumonia with progression to lethal complications, including acute respiratory distress syndrome (ARDS), multi-organ failure and death. Determining risk factors to anticipate the severity of COVID-19 are essential for efficient resource allocation², especially during this pandemic season.

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Hypertension is one of the most prevalent chronic diseases, affecting approximately 31.1% of adults (1.39 billion) worldwide in the year 2010.³ It is postulated that hypertensive patients have increased angiotensin-converting enzyme 2 (ACE2) expression due to associated genetic polymorphism and use of angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARB), which even though still controversial, may increase susceptibility and severity of COVID-19.⁴ This study was aimed at investigating the association between hypertension and poor outcome in patients with COVID-19 pneumonia by performing a systematic review and meta-analysis.

Materials and methods

Eligibility criteria

We included all research studies enrolling adult COVID-19 patients with information on hypertension and the specific outcome of interests – mortality, severe COVID-19, ARDS, intensive care unit (ICU) care and disease progression. We excluded: review articles, non-research letters, communications, and commentaries; studies with samples < 20; case reports and small case series; non-English language articles; research in paediatric populations (17 years of age and younger).

Search strategy and study selection

A comprehensive systematic literature search was performed using PubMed, SCOPUS, EuropePMC, and Google Scholar electronic databases using the search terms: (a) ‘COVID-19’ OR ‘SARS-CoV-2’ AND ‘hypertension’; (b) ‘COVID-19’ OR ‘SARS-CoV-2’ AND ‘Characteristics’. Records curated from the initial search were then screened for duplicates which were then removed. Two independent authors (IH and MAL) screened the title and abstracts for potential articles. The full-texts of remaining articles were evaluated by applying the inclusion and exclusion criteria. The systematic literature search was finalized on 7 April 2020. The study was carried out in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Data extraction

A standardized forms containing first author, year, study design, age, gender, cardiovascular diseases, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), need for ICU care and severe COVID-19 were used for data extraction. Two authors (MAL and RP) performed the data extraction independently.

The outcome of interest for this meta-analysis was the composite poor outcome which comprised of mortality, severe COVID-19, ARDS, need for ICU care and disease progression. Severe COVID-19 was defined according to

the report of the WHO–China Joint Mission on COVID-19,⁵ while ARDS was defined as per WHO interim guidance on severe acute respiratory infection (SARI) of COVID-19.⁶

Statistical analysis

To perform meta-analysis, we used Review Manager 5.3 (Cochrane Collaboration) and Stata version 16 softwares. To calculate dichotomous variables, we used Mantel–Haenszel formula to generate pooled effect estimate in form of risk ratios (RRs) along with its 95% confidence intervals (CIs). Random-effects model was used regardless of heterogeneity, to account for interstudy variability. All *p*-values in this study were two-tailed, and statistical significance was set at ≤ 0.05 . To assess the influence of covariates, restricted-maximum likelihood random effects meta-regression was performed for age, gender, cardiovascular disease, diabetes and COPD. Each individual components of composite poor outcome was then sub-analysed. Sensitivity analysis by leave-one-out method was used to single out cause of heterogeneity and test for statistical robustness. To evaluate the small-study effects, a regression-based Harbord’s test for binary outcome was performed. Funnel-plot analysis was performed to assess the risk of publication bias qualitatively.

Results

Study selection and characteristics

There were 848 records after initial database searching, of which 435 records remained after the removal of duplicates. After screening the title/abstract, 389 records were excluded. The 46 residual articles were then evaluated for eligibility by assessing its full-text article. 16 full-text articles were excluded because of: (a) no hypertension variable ($n = 7$); (b) specific groups (i.e. myocarditis, cardiac injury) ($n = 5$); (c) groups not divided based on outcome ($n = 4$). Thereby, 30 studies with a total of 6560 patients were included in the final qualitative and quantitative synthesis (Figure 1, Table 1).^{7–35}

Hypertension and outcome

This meta-analysis showed that hypertension was associated with increased composite poor outcome (RR 2.11 (1.85, 2.40), $p < 0.001$; I^2 44%, $p = 0.006$) (Figure 2). Sub-group analysis showed that hypertension was associated with increased mortality (RR 2.21 (1.74, 2.81), $p < 0.001$; I^2 66%, $p = 0.001$), severe COVID-19 (RR 2.04 (1.69, 2.47), $p < 0.001$; I^2 31%, $p = 0.14$), ARDS (RR 1.64 (1.11, 2.43), $p = 0.01$; I^2 0%, $p = 0.35$), ICU care (RR 2.11 (1.34, 3.33), $p = 0.001$; I^2 : 18%, $p = 0.30$) and disease progression (RR 3.01 (1.51, 5.99), $p = 0.002$; I^2 0%, $p = 0.55$).

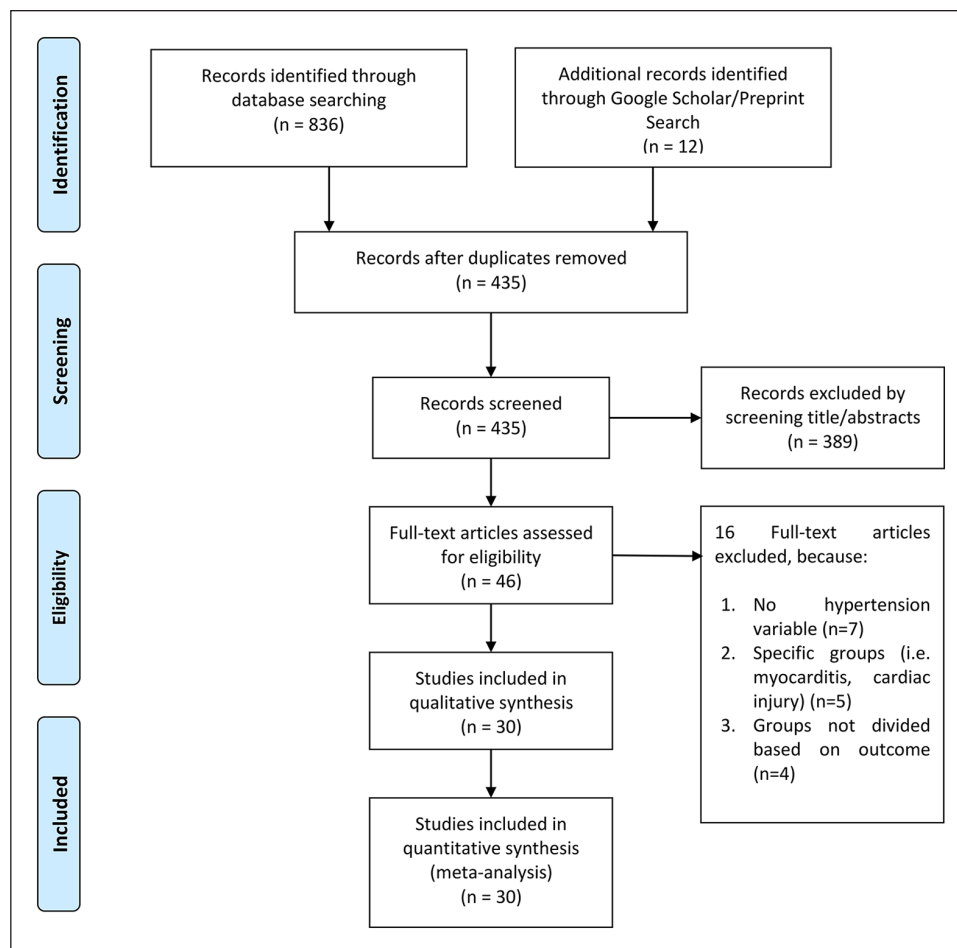


Figure 1. PRISMA flowchart.

Sensitivity analysis indicate robustness of the effect estimate, removal of Luo XM et al. study reduces heterogeneity while maintaining the association with increased composite poor outcome (RR 2.02 (1.80, 2.27), $p < 0.001$; I^2 : 27%, $p = 0.10$) and mortality (RR 2.03 (1.65, 2.49), $p < 0.001$; I^2 42%, $p = 0.08$).

Meta-regression

Meta-regression analysis showed that the association between hypertension and increased composite poor outcome was influenced by gender ($p = 0.013$) (Figure 3(a)), but not by age ($p = 0.233$) (Figure 3(b)), cardiovascular diseases ($p = 0.464$), diabetes ($p = 0.882$) and COPD ($p=0.094$).

Sub-group analysis

Sub-group analysis for studies with a percentage of males $\geq 55\%$ (RR 1.79 (1.58, 2.02), $p < 0.001$; I^2 0%, $p = 0.49$) has lower RR for composite poor outcome compared to

$< 55\%$ (RR 2.32 (1.93, 2.79), $p < 0.001$; I^2 47%, $p = 0.01$) (Figure 3(c)).

Sub-group analysis for studies with median age ≥ 55 years old (RR 2.17 (1.78, 2.64), $p < 0.001$; I^2 68%, $p < 0.001$) has only a slightly higher RR for composite poor outcome compared to < 55 years old (RR 2.02 (1.68, 2.43), $p < 0.001$; I^2 0%, $p = 0.77$).

Publication bias

Funnel-plot analysis showed a qualitatively symmetrical funnel plot for the association between hypertension and increased composite poor outcome (Figure 4(a)). Regression-based Harbord's test showed no indication of small-study effects for hypertension and increased composite poor outcome ($p = 0.219$) (Figure 4(b)).

Discussion

Based on our meta-analysis, hypertension was shown to be associated with increased composite poor outcome that consists of mortality, severe COVID-19, ARDS, need for

Table 1. Characteristics of the included studies.

Authors	Study design	Samples	Male (%)	Mean overall age (median) (years)	Hypertension (%)	Cardiovascular Comorbidity (%)	Diabetes (%)	Respiratory Comorbidity (%)	Outcome
Alkbari A 2020 ³⁶	Observational Retrospective	440 (13 vs 427)	56.4 (61.5 vs 56.2)	48	7.9 (15.3 vs 7.7)	5.7 (15.3 vs 5.4) [CAD]	7.5 (30.8 vs 6.8)	N/A	Mortality
Bai T 2020 ¹⁵	Observational Retrospective	127 (36 vs 91)	63 (77.8 vs 57.1)	55 (67 vs 50)	28.3 (41.7 vs 23.1)	2.4 (5.6 vs 1.1) [CVD]	11.8 (13.9 vs 11.0)	N/A	Mortality
Cao J 2020 ²⁷	Observational Retrospective	102 (17 vs 85)	52 (76.5 vs 47.1)	54 (72 vs 53)	27.5 (64.7 vs 20)	4.9 (17.6 vs 2.4) [CAD]	10.8 (35.3 vs 5.9)	9.8 (23.5 vs 7.1) [COPD]	Mortality
Chen 2020 ³¹	Observational Retrospective	123 (31 vs 92)	49 (71 vs 42)	56 (72 vs 53)	33.3 (48.4 vs 38.3)	12.2 (25.8 vs 7.6) [CAD]	11.4 (19.4 vs 8.7)	4.9 (9.7 vs 3.3) [COPD]	Mortality
Chen T 2020 ¹⁸	Observational Retrospective	274 (113 vs 161)	62 (73 vs 55)	62 (68.0 vs 51.0)	34 (48 vs 24)	8 (14 vs 4) [CVD]	17 (21 vs 14)	7 (10 vs 4) [CLD]	Mortality
Fu L 2020 ³⁰	Observational Retrospective	200 (34 vs 166)	49.5 (16.2 vs 67.7)	<49 (5.9 vs 28.3), 50-59 (23.5 vs 27.1), 60-69 (20.6 vs 31.3), >70 (5 vs 13.2)	50.5 (21.8 vs 12.1)	N/A	N/A	4 (50.0 vs 15.6) [CLD]	Mortality
Grasselli 2020 ²⁶	Observational Retrospective	1591	82	63	49	21	17	4 [COPD]	Mortality
Li K 2020 ¹⁴	Observational Retrospective	102 (15 vs 87)	58 (73 vs 55)	57 (69 vs 55)	30 (47 vs 28)	4 (13 vs 2) [CAD]	15 (13 vs 15)	2 (7 vs 1) [COPD]	Mortality
Luo X 2020 ¹¹	Observational Retrospective	403 (100 vs 303)	47.9 (57 vs 44.9)	56 (71 vs 49)	28 (60 vs 17.5)	8.9 (16 vs 6.6) [CAD]	14.1 (25 vs 10.6)	6.9 (17 vs 3.6) [COPD]	Mortality
Yuan M 2020 ⁷	Observational Retrospective	27 (10 vs 17)	45 (47 vs 40)	60 (68 vs 55)	19 (50 vs 0)	11 (30 vs 0) [CAD]	22 (60 vs 0)	N/A	Mortality
Zhou 2020 ³¹	Observational Retrospective	191 (54 vs 137)	62 (70 vs 59)	56 (69.0 vs 52.0)	30.4 (48 vs 23)	8 (24 vs 1) [CAD]	19 (31 vs 14)	3 (7 vs 1) [COPD]	Mortality
Guan 2020 ³³	Observational Retrospective	1099 (173 vs 926)	58.1 (57.8 vs 38.2)	47 (52.0 vs 45.0)	15.0 (23.7 vs 13.4)	2.5 (5.8 vs 1.8) [CAD]	7.4 (16.2 vs 5.7)	1.1 (3.5 vs 0.6) [COPD]	Severe COVID-19
Hu L 2020 ²²	Observational Retrospective	323 (172 vs 151)	51.4 (52.9 vs 49.7)	61 (65 vs 56)	32.5 (38.3 vs 25.8)	12.7 (19.2 vs 5.3) [CVD]	14.6 (19.2 vs 9.3)	1.9 (3.5 vs 0) [COPD]	Severe COVID-19
Li Q 2020 ³⁷	Observational Retrospective	325 (26 vs 299)	51.4 (76.9 vs 49.2)	51 (65 vs 49)	24 (46.2 vs 22.1)	5.5 (19.2 vs 4.3) [CAD]	9.2 (19.2 vs 8.4)	1.2 (7.7 vs 0.6) [COPD]	Severe COVID-19
Liu J 2020 ²⁴	Prospective Cohort	61 (17 vs 44)	50.8 (58.8 vs 47.7)	40 (56 vs 41)	19.7 (35.3 vs 13.6)	1.6 (5.9 vs 0) [CVD]	8.2 (1.6 vs 4.5)	8.2 (1.6 vs 4.5) [COPD]	Severe COVID-19
Liu L 2020 ²⁹	Observational Retrospective	51 (7 vs 44)	62.7 (57.1 vs 63.7)	45 (52 vs 44)	7.8 (14.3 vs 6.8)	N/A	7.8 (57.1 vs 0)	N/A	Severe COVID-19
Ma KL 2020 ²²	Observational Retrospective	84 (20 vs 64)	57.1 (60 vs 56.3)	48 (58 vs 46.5)	14.3 (20.0 vs 12.5)	6 (10 vs 4.7) [CAD]	11.9 (35 vs 4.7)	6.0 (10.0 vs 4.7) [CLD]	Severe COVID-19

(Continued)

Table 1. (Continued)

Authors	Study design	Samples	Male (%)	Mean overall age (median) (years)	Hypertension (%)	Cardiovascular Comorbidity (%)	Diabetes (%)	Respiratory Comorbidity (%)	Outcome
Qin 2020 ¹⁷	Observational Retrospective	452 (286 vs 166)	52.0 (54.2 vs 48.2)	58 (61 vs 53)	29.5 (36.7 vs 18.1)	5.9 (8.4 vs 1.8) [CVD]	16.4 (18.5 vs 13.3)	2.6 (3.1 vs 1.8) [COPD]	Severe COVID-19
Wan 2020 ¹⁶	Observational Retrospective	135 (40 vs 135)	53.3 (52.5 vs 54.7)	47 (56 vs 44)	9.6 (10 vs 9.4)	5.2 (15 vs 1) [CVD]	8.9 (22.5 vs 3.1)	0.7 (2.5 vs 0) [CLD]	Severe COVID-19
Wang D 2020 ³⁸	Observational Retrospective	143 (71 vs 72)	51 (62 vs 40.3)	58 (65 vs 44)	25.2 (43.7 vs 6.9)	11.2 (16.9 vs 5.6) [CAD]	9.1 (12.7 vs 5.6)	7.0 (9.9 vs 4.2) [COPD]	Severe COVID-19
Wang Y 2020 ³⁹	Observational Retrospective	110 (38 vs 72)	43 (63.2 vs 33.3)	≤40 (53%), 41-60 (21%), >60 (36%) ≤40 (7.9 vs 69.4), 41-60 (21.0 vs 18.1), >60 (71.0 vs 12.5)	20.9 (39.5 vs 11.1)	N/A	13.7 (21.0 vs 9.7)	5.4 (10.5 vs 2.8) [COPD]	Severe COVID-19
Zhang G 2020 ³²	Observational Retrospective	221 (55 vs 166)	48.9 (63.6 vs 44.0)	55 (62 vs 51)	24.4 (47.3 vs 16.9)	10 (23.6 vs 5.4) [CAD]	10 (12.7 vs 9.0)	2.7 (7.3 vs 1.2) [COPD]	Severe COVID-19
Zhang J 2020 ²⁰	Observational Retrospective	140 (58 vs 82)	50.7 (56.9 vs 46.3)	<30 (1.7 vs 4.9), 30-49 (15.5 vs 34.1), 50-69 (48.3 vs 50), ≥70 (34.5 vs 11.0)	30 (37.9 vs 24.4)	5 (6.9 vs 3.7) [CAD]	12.1 (13.8 vs 11.0)	1.4 (3.4 vs 0) [COPD]	Severe COVID-19
Liu Y 2020 ⁴⁸	Observational Retrospective	109 (53 vs 56)	59 (52.8 vs 55.4)	55 (61 vs 49)	37 (21 vs 26)	6.4 (5.7 vs 7.1) [CAD]	11 (20.8 vs 1.8)	3.7 (3.8 vs 3.6) [COPD]	ARDS
Wu C 2020 ²⁵	Observational Retrospective	201 (84 vs 117)	63.7 (71.4 vs 58.1)	51 (58.5 vs 48)	19.4 (27.4 vs 13.7)	4 (6 vs 2.6) [CAD]	10.9 (19 vs 5.1)	2.5 [CLD]	ARDS
Cao 2020 ⁹	Observational Retrospective	198 (19 vs 176)	51 (89.5 vs 46.9)	50.1 (63.7 vs 48.6)	21.2 (31.6 vs 20.1)	6.0 (26.3 vs 3.9) [CVD]	7.6 (10.5 vs 7.3)	N/A	ICU Care
Huang 2020 ²¹	Observational Retrospective	41 (13 vs 28)	73 (85 vs 68)	49.0 (49.0 vs 49.0)	14.6 (15 vs 14)	14.6 (23 vs 11) [CVD]	19.5 (8 vs 25)	2.4 (8 vs 0) [COPD]	ICU Care
Wang D 2020 ¹⁹	Observational Retrospective	138 (36 vs 102)	54.3 (61.1 vs 52.0)	56 (66 vs 51)	31.2 (58.3 vs 21.6)	14.5 (25 vs 10.8) [CAD]	10.1 (22.2 vs 5.9)	2.9 (8.3 vs 1.0) [COPD]	ICU Care
Feng 2020 ¹³	Observational Retrospective	141 (15 vs 126)	51.1 (46.7 vs 51.6)	44 (58 vs 41)	14.9 (40.0 vs 11.9)	2.1 (6.7 vs 1.6) [CVD]	5.7 (13.3 vs 4.8)	2.8 (13.3 vs 1.6) [COPD]	Disease Progression
Liu W 2020 ²³	Observational Retrospective	78 (11 vs 67)	50 (63.6 vs 47.8)	38 (55 vs 37)	40 (18.2 vs 9.0)	N/A	25 (18.2 vs 4.5)	10 (9.1 vs 1.5) [COPD]	Disease Progression

CAD, coronary artery disease; COVID-19, coronavirus disease 2019; CLD, chronic lung/pulmonary disease; CVD, cardiovascular disease; ICU, intensive care unit.
vs = Group A vs Group B.

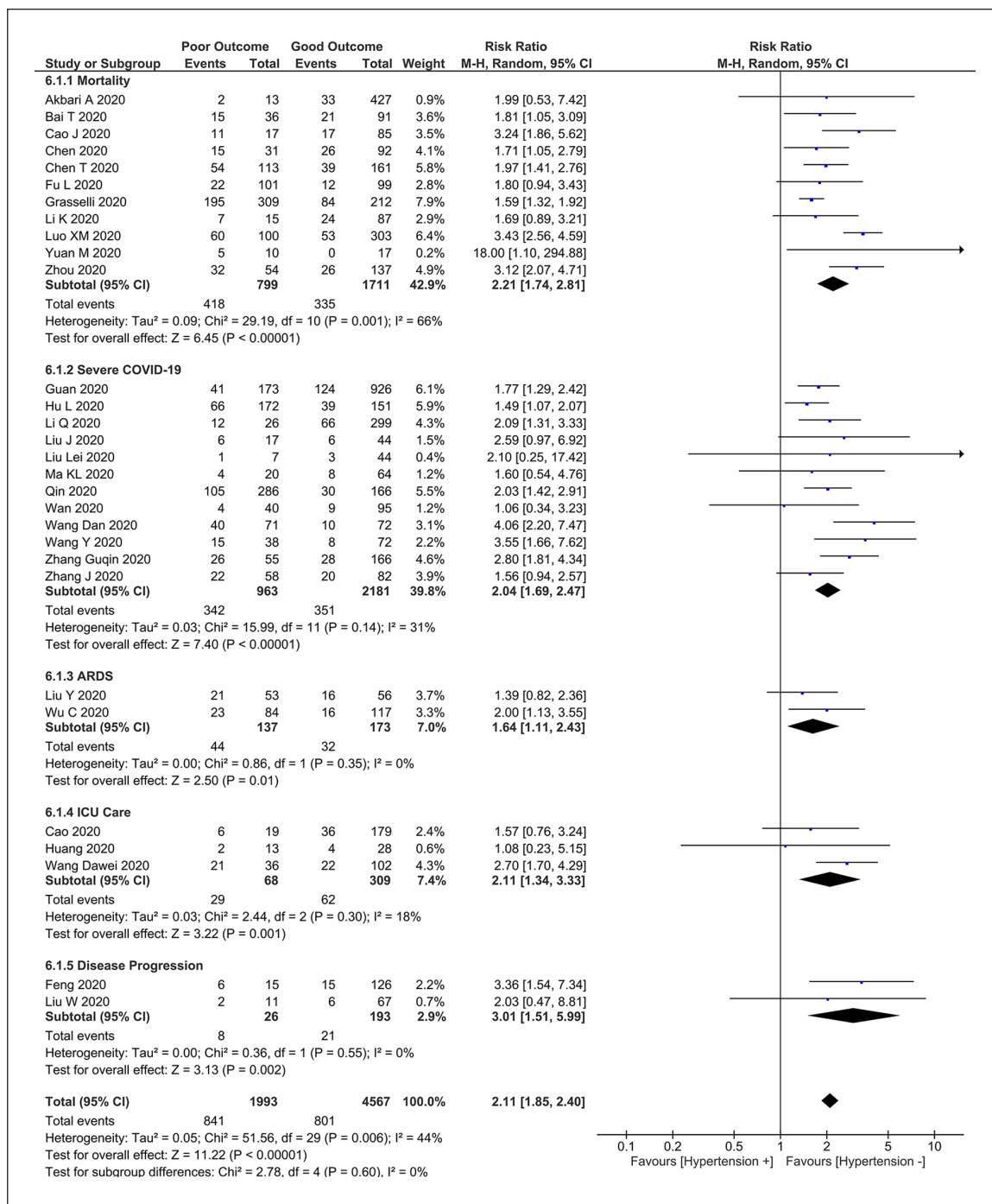


Figure 2. Hypertension and poor outcome. Forest plot shows that hypertension was associated with increased composite poor outcome and its sub-group which comprises of mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) care and disease progression in patients with COVID-19.

ICU care and disease progression in patients with COVID-19. This association was influenced by gender, but not age, cardiovascular disease, diabetes and COPD. The association between hypertension and increased poor outcome was stronger in studies with lower percentage of male patients.

It is still unclear whether hypertensive people are more likely to contract COVID-19 infection. However, individuals with hypertension tend to more severely affected by COVID-19, with ACE2 becomes a likely explanation.⁴⁰ ACE2, a type 1 integral membrane glycoprotein which is found in the epithelial cells of cardiac, kidney, lung and

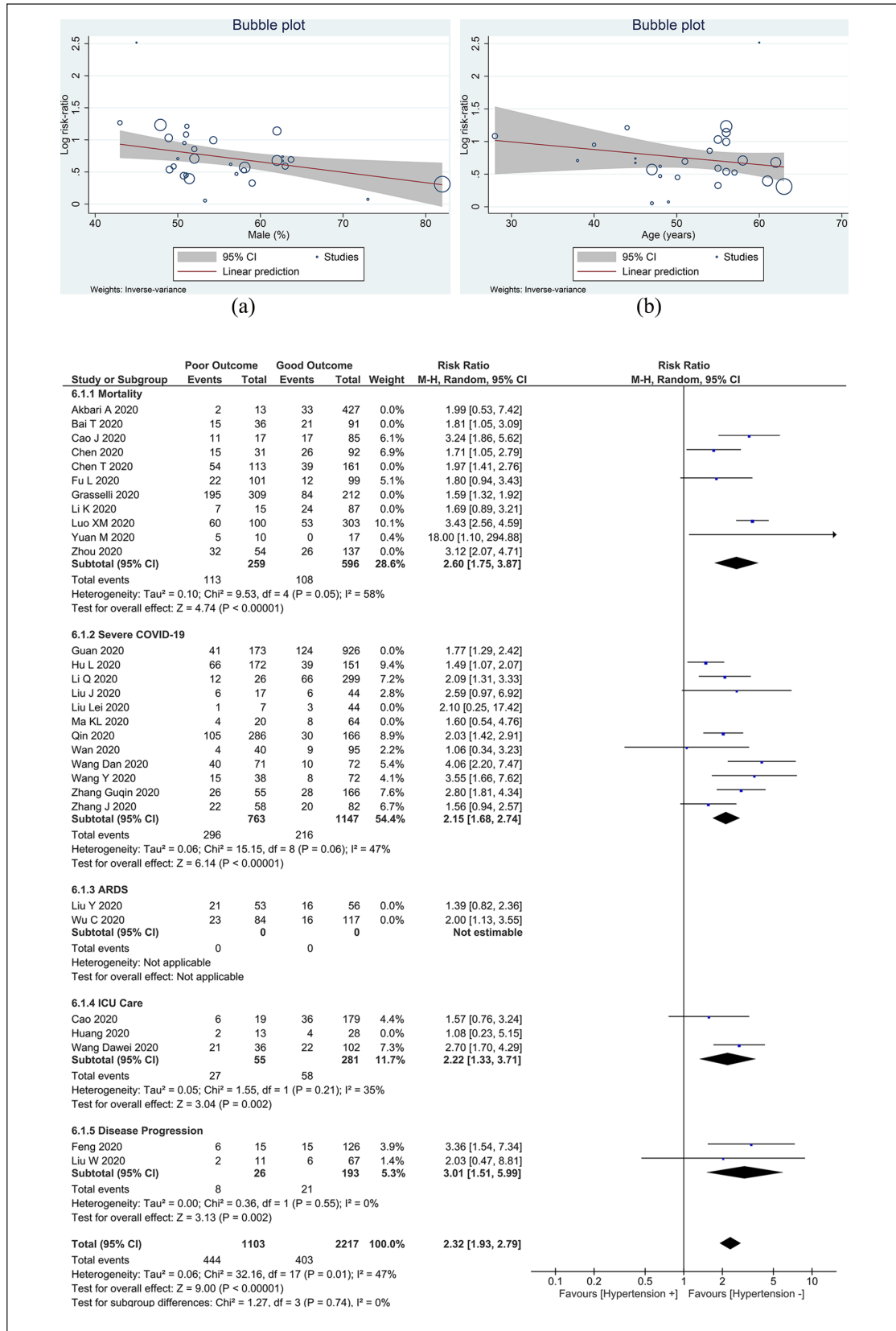


Figure 3. Meta-regression analysis showed that the association between hypertension and increased composite poor outcome was influenced by (a) gender, but not (b) age. (c) Sub-group analysis based on meta-regression results showed that studies of the association between hypertension and composite poor outcome was stronger in studies with a percentage of male <55%. ARDS: acute respiratory distress syndrome; ICU, intensive care unit.

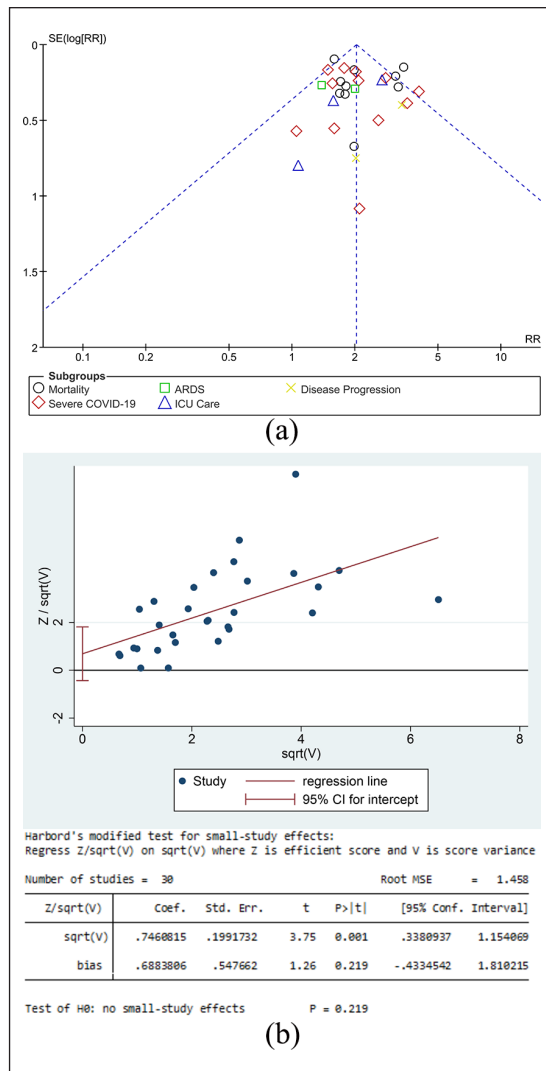


Figure 4. Publication bias analysis. (a) The funnel-plot analysis showed a qualitatively symmetrical funnel plot for the association between hypertension and increased composite poor outcome. (b) Regression-based Harbord's test showed no indication of small-study effects for hypertension and increased composite poor outcome.

intestinal tissue, converts angiotensin II to angiotensin 1–7.^{40,41} Thus, the presence of ACE2 neutralizes the inflammatory effects of angiotensin II, reduces the levels of proinflammatory cytokine interleukin-6, enhances the anti-inflammatory and antioxidant roles of angiotensin 1–7, increases the concentration of alveolar surfactant protein D and triggers vasodilation.^{42,43} It is likely that novel coronavirus responsible for COVID-19 worked through a similar pathway as the coronavirus that caused SARS-CoV, where they use ACE2 on the surfaces of epithelial cells as a receptor to attach and enter the host pneumocytes.^{40–42} Viral surface spike (S) protein of COVID-19 binds to ACE2 receptor following the spike protein activation by transmembrane protease serine 2 (TMPRSS2).^{44,45}

Activation of the renin-angiotensin system (RAS) in various tissues is associated with conditions such as hypertension. Regular use of medications, including ARB and ACEI upregulates ACE2 expression, therefore facilitating the entry of SARS-CoV-2 into pneumocytes which ultimately increases the severity and fatality of infection.^{40,42} Overexpression of ACE2, which is supposed to provide protection for the lungs, is downregulated after viral uptake as the enzyme gets diminished, resulting in reduced angiotensin-II degradation, increased aldosterone secretion and consequently loss of potassium via urine.⁴²

The interplay between hypertension, gender and RAS may be the explanation of our result regarding the association of hypertension and outcome in a lower percentage of male patients. In hypertensive females, there is greater activity of Angiotensin II type 2 receptor (AT2R) than angiotensin II type I (AT1R) which translates into attenuation of harmful response of AT1R activation.⁴⁶ More expression and activation of AT1R are seen in hypertensive males and hypothesized in causing vasoconstriction, pro-inflammatory response, increasing oxidative stress, leading to ARDS in severe COVID-19.^{47,48} This condition provides an explanation for the higher incidence of severe COVID-19 in males compared to females. Oestrogen is postulated in bringing the predisposition towards 'good' RAS in females.⁴⁹ Although we did not have data concerning the menopausal status of the women in the included studies, the majority of subjects included in the studies were in older age groups. This could explain why the association between hypertension and outcome was stronger in studies with a lower percentage of male patients. Nevertheless, this result has to be interpreted cautiously due to the known limitations of meta-regression, and is only a hypothesis-generating finding. An individual patient-level sub-group analysis (preferably with adjustment to various confounders) needs to be performed to confirm or deny this preliminary finding.

Currently, there is no scientific evidence showing that the termination of ACEI and ARB in patients with COVID-19 infection would be beneficial and the authorities in the field still recommend those patients to continue their regular anti-hypertensives. Theoretically, inhibiting the breakdown of angiotensin II (using ACEI) or blocking angiotensin AT1R (using ARB) could decrease inflammation systematically and specifically in the lung, heart and kidney, which ultimately reduces the potential complication of COVID-19, including ARDS, myocarditis and acute kidney injury.⁵⁰

Discontinuation of ACEI or ARB in COVID-19 patients with hypertension might potentially be harmful as they continue to offer cardiovascular and renal protection. In fact, the use of ARB has been studied for the treatment of COVID-19 and its complications. Studies have shown that COVID-19 downregulates ACE2 expression and hinders its organoprotective effect.⁵¹ It is hypothesized that

unregulated angiotensin-II activity leads to multiple organ injury.^{52,53} Furthermore, ACE2 has been shown to protect lungs from ARDS.⁵⁴ Hence, drugs that may increase ACE2 may offer protection rather than harm.

Although ACE2 is singled out as the port of entry for COVID-19, it plays a substantial anti-inflammatory role in renin–angiotensin–aldosterone system (RAS) signalling. The elderly with hypertension have lower ACE2 levels and higher RAS signalling, which develops to extremely low ACE2 levels and markedly elevated RAS signalling after COVID-19 infection, resulting in a likely reduced incidence of disease, but greater severity.⁵⁵ On the contrary, younger individuals without hypertension have higher ACE2 levels and lower RAS signalling, which turns to modestly low ACE2 levels and modestly enhanced RAS signalling after they are infected with COVID-19, resulting in a potentially increased incidence of disease, but lesser severity. This supports the suggestion of continuing treatment with RAS antagonists such as ACEI/ARB in order to prevent further lung injury due to COVID-19, including sepsis-associated lung injury.⁵⁵ The effect estimate for subgroup analysis for age ≥ 55 and < 55 years old differs slightly, in which ≥ 55 years old was associated with slightly higher risk. However, because meta-regression did not demonstrate significant differences across age groups, the significance remains uncertain, and direct comparison between the older and younger patients is needed.

Regardless of potential benefit or harm associated with ACEI/ARB, controlling blood pressure is important to prevent cardiovascular complications. Data on hypertensive medications were lacking in the included studies, hence, we are unable to provide meta-analysis or meta-regression for ACEI/ARB.

Implications for clinical practice

Hypertension was associated with increased poor outcome in patients with COVID-19 and the association was not affected by age, gender, presence of cardiovascular disease, diabetes or COPD. This designates that hypertension may act as one of the potential prognostic factors for COVID-19 severity that should be sought in the triage.

Limitations

The label hypertension is not universal; the included studies may have different definition of hypertension. The stage of hypertension and whether they are controlled or poorly controlled were also unknown. Data on chronic hypertensive medications were not adequately reported by the included studies, and so cannot be analysed. Such data may provide insight on the ACEI/ARB impact on prognosis. Additionally, the included studies were subject to potential confounders that may weaken or strengthen the effect estimate. The result of the meta-regression has to be

interpreted cautiously due to the known limitations of such analysis. Most of the articles included in the study were published at preprints servers, and as such are not yet peer reviewed. Majority of the studies originated from China, the patients perhaps overlapping across the reports. Most of the studies included were retrospective in design.

Conclusion

Hypertension was associated with increased mortality, severe COVID-19, ARDS, need for ICU care and disease progression in patients with COVID-19. The association was stronger in studies with a lower percentage of male patients.



Declaration of conflicting interests

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