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**(COVID-19): a pooled analysis**

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# **Hypertension and its severity or mortality in Coronavirus Disease 2019**

## **(COVID-19): a pooled analysis**

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## **What's New?**

Hypertension has been widely reported to increase severity and mortality of patients with the novel coronavirus-2019 disease (COVID-19). However, early COVID-19 studies have reported mixed findings with respect to hypertension. We aimed to assess the relationship between COVID-19 and hypertension in a pooled analysis of early COVID-19 reports. We found that hypertension is associated with ~2.5-fold increased risk of both increased severity and mortality. In a meta-regression, we observed that this effect is mainly attributed to those over the age of 60. While more data is needed, we encourage increased public health precautions be applied to patients with hypertension. Hypertension should be considered as a clinical predictor of COVID-19 severity in older patients.

## **Abstract**

**Introduction:** As the coronavirus disease 2019 (COVID-19) outbreak, identification of clinical predictors of severe or fatal disease are necessary to enable risk stratification and optimize allocation of limited resources. Hypertension has been widely reported to be associated with increase disease severity, however, other studies have reported different findings.

**Objectives:** To evaluate the association of hypertension and severe and fatal COVID-19.

**Patients and methods:** Scopus, Medline, and Web of Science was performed to identify studies reporting the rate of hypertension in COVID-19 patients with severe or non-severe disease or among survivors and non-survivors. The obtained data was pooled into a meta-analysis to calculate odds ratio (OR) with 95% confidence intervals (95%CI).

**Results:** Hypertension was associated with a nearly 2.5-fold significantly increased risk of severe COVID-19 disease (OR: 2.49 [95%CI: 1.98-3.12]  $I^2=24\%$ ), as well as with a similarly significant higher risk of mortality (OR: 2.42 [95%CI: 1.51-3.90]  $I^2=0\%$ ). In meta-regression, a significant correlation was observed with an increase in mean age of patients with severe COVID-19 associated with increased log odds of hypertension and severity ( $p=0.03$ ).

**Conclusions:** The results of this pooled analysis of the current scientific literature would suggest that hypertension may be associated with an up to 2.5-fold higher risk of severe and fatal COVID-19, especially among older individuals.

## **Introduction**

The coronavirus disease 2019 (COVID-19) outbreak, has spread across the world, affecting over 500,000 people and causing over 25,000 deaths to-date.<sup>1</sup> This infection is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),<sup>2</sup> and is responsible for human-to-human transmission of disease, entering the cells through its predicated receptor angiotensin converting enzyme 2 (ACE2).<sup>3</sup> The function of this enzyme is to catalyze the conversion of angiotensin II to angiotensin 1-7, a peptide which opposes the pro-inflammatory, pro-oxidative, vasoconstrictive and fibrotic properties of angiotensin II.<sup>4</sup>

Due to the interplay between SARS-CoV-2 and ACE2, it has been suggested that hypertension may be involved in the pathogenesis of COVID-19, by either playing a direct role as a pre-existing clinical predictor of disease severity, or by contributing to deterioration late in disease course, characterized by acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS) and/or multiple organ failure (MOF).<sup>5</sup> Considering the virtually unstoppable current trajectory of SARS-CoV-2,<sup>6</sup> together with the high prevalence of hypertension (an estimated 26% of worldwide population),<sup>7</sup> it is now predictable that the combination of these two conditions will soon pose overwhelming clinical, societal and economic burdens to humanity.<sup>8</sup> However, while widely reported in the media that hypertension increases the risk of severe COVID-19, some early reports found no association between hypertension and disease severity.<sup>9,10</sup> Therefore, this article is aimed to investigate the possible existence of a clinical interplay between hypertension and COVID-19, investigating whether hypertensive patients infected by SARS-CoV-2 may be at particularly enhanced risk of worst clinical outcomes, and if so, the strength of such associations.

## **Methods**

### ***Search Strategy and Study Selection***

A systemic search was carried out in Scopus, Medline (through PubMed interface) and Web of Science, based on the free keywords “hypertension” OR “coronavirus disease 2019” OR “COVID-19” OR “SARS-CoV-2” in all fields, up to present date (i.e., March 26, 2020). We used no language restrictions. Additionally, the references of all included studies were hand-searched for detecting other possibly eligible studies. The articles detected through these search criteria were then carefully assessed by title, abstract and full text, when available. This study was performed in compliance with the declaration of Helsinki and local legislation, without need for ethics committee approval. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Supplement 1).

Each study was evaluated by two reviewers for inclusion. Disagreements were solved through a consensus process with all authors. All studies reporting data on prevalence of hypertension in adult (i.e., aged 18 years or older) laboratory-confirmed COVID-19 patients, with or without severe disease, or COVID-19 non-survivors and survivors, were eligible for inclusion in a pooled analysis. A clinically validated definition of “severe disease” (i.e., patients experiencing severe respiratory distress, needing mechanical ventilation, vital life support or intensive care unit admission) was required. Due to the limited literature on COVID-19, no exclusion criteria were applied.

### ***Data Collection***

Data was collected independently by two reviewers from the included studies. Articles in Chinese were translated by a medical professional fluent in both Chinese and English, prior to

data collection. Data was collected and entered into a spreadsheet. Variables included the authors, sample size, age, definition of severity, outcome, and rate of hypertension. No methodological risk of bias or publication bias assessment was performed as the expected data set was limited.

### ***Statistical Analysis***

Pooled analysis was performed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) of hypertension in COVID-19 patients with or without severe disease, or in survivors versus non-survivors. Pooled analysis was performed using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia), using an inverse variance model. Heterogeneity was evaluated using the  $\text{Chi}_2$  test and the  $I^2$  statistic. For the  $\text{Chi}_2$  test, significant heterogeneity amongst studies was indicated with a Cochran's Q p-value of  $<0.10$ . The  $I^2$  statistic results were interpreted as 25%, 50% and 75% representing low, moderate, and high heterogeneity, respectively. A leave-one-out sensitivity analysis was employed to probe the source of heterogeneity. Moreover, to evaluate the impact of mean age among severe patients on the association of hypertension with severity of COVID-19, a random effects meta-regression using log OR was applied.

## **Results**

### ***Search Results and Study Characteristics***

The flow of studies through the analysis is presented in Figure 1. Overall, following duplicate removal, 86 articles were initially identified based on our electronic and reference search, which after screening by title, abstract, and full text, 77 were excluded as not related to

COVID-19 (n=30), were review articles (n=12), did not provide relevant data (n=22), were editorials (n=8), or did not provide extractable data on hypertension (n=5). Four studies were identified from the reference search. Thus, 13 studies,<sup>9-21</sup> with a total of 2893 COVID-19 patients, were finally included in our analysis. Eleven studies compared the rate of hypertension in severe vs. non-severe cases of confirmed COVID-19 with a sample of 2552 patients, 748 (29.3%) of whom were classified as having developed severe disease.<sup>9-19</sup> Only 2 studies compared the prevalence of hypertension in non-survivors vs. survivors, in a total of 341 COVID-19 patients, 122 (35.8%) of whom were non-survivors.<sup>20,21</sup> The essential characteristics of included studies are shown presented in Table 1.

### ***Meta-Analysis***

The results of our pooled analysis are presented in Figure 2. Hypertension was found to be associated with a nearly 2.5-fold significantly enhanced risk of severe COVID-19 disease (OR: 2.49 [95%CI: 1.98-3.12]  $I^2=24%$ , Cochran's Q,  $p=0.21$ ), as well as with a similarly significant higher risk of dying (OR: 2.42 [95%CI: 1.51-3.90]  $I^2=0%$ , Cochran's Q,  $p=0.33$ ). Minimal heterogeneity was observed in the analyses. No significant differences were observed in the leave-one-out sensitivity analysis for severity (data not shown). In a meta-regression, a significant correlation was observed between mean age of patients with severe COVID-19 and log odds of hypertension and COVID-19 severity (correlation coefficient: 0.04,  $p=0.03$ ) (Figure 3).

## Discussion

As the COVID-19 pandemic continues, there is an increasing risk of overwhelming healthcare infrastructures and jeopardizing patient care even in the most developed countries. As such, identification of reliable demographic, clinical and laboratory indicators are needed to distinguish which COVID-19 patients are at enhanced risk, thus needing more aggressive management through hospitalization or intensive care, from those who could be safely managed as outpatients. Some laboratory parameters which may predict worse progression have already been identified, including leukocytosis, lymphopenia, thrombocytopenia, along with increased values of D-dimer, procalcitonin, cardiac biomarkers, pro-inflammatory cytokines and ferritin.<sup>22</sup> Notably, some clinical predictors of worse COVID-19 prognosis have also been reported in early studies, such as older age, male sex, as well as the presence of pre-existing cardiovascular diseases, diabetes, respiratory disorders, cancer and dementia.<sup>21,23</sup> These findings are supported by observations in other respiratory and systemic illnesses, as the presence of one or more such comorbidities is now universally recognized as unfavourable prognostic factor in patients with many other pneumonias<sup>24</sup>, ARDS<sup>25</sup> and SIRS.<sup>26</sup> However, the strength of those comorbidities for increased risk of severe COVID-19 has not been established.

In this study, we observed that hypertension carries a nearly 2.5-fold higher risk of developing severe disease or dying from SARS-CoV-2 infection (Figure 1). Although this association seems weaker than that earlier reported for other co-morbidities, such as chronic obstructive pulmonary disease (COPD; over 5-fold higher risk)<sup>27</sup> or chronic kidney disease (CKD; over 3-fold higher risk),<sup>28</sup> it still carries important clinical implications.

As previously discussed, SARS-CoV-2 enters the cells by binding ACE2. Some interesting studies have previously shown that administration of some antihypertensive drugs

such as ACE inhibitors (ACEis)<sup>29</sup> and angiotensin receptor blockers (ARBs)<sup>30</sup> may be associated with enhanced ACE2 expression at the cell surface, thus ultimately supplying SARS-CoV-2 with a larger number of “anchors” for infecting cells. While this is still the matter of contentious debate, it cannot be excluded that some hypertensive patients undergoing renin-angiotensin-aldosterone system (RAAS) inhibition, especially those taking ACEis, may be more susceptible to SARS-CoV-2 infection, which would ultimately translate into a higher risk of developing local (i.e., ARDS) or systemic (i.e., SIRS/MOF) adverse COVID-19 consequences.<sup>31</sup> On the other hand, others have argued that hypertensives may experience a decreased ACE2 expression, which when bound by SARS-CoV-2 attenuates residual ACE2, leading to elevated angiotensin II levels driving development of ARDS.<sup>32</sup> Moreover, evidence convincingly attest that both pulmonary and systemic hypertension is a risk factor for unfavourable progression in patients with pneumonia,<sup>33</sup> ARDS<sup>34,35</sup> and MOF.<sup>36</sup> It is therefore plausible that coexistence of hypertension and SARS-CoV-2 infection would interplay to synergistically increase the risk of unfavourable prognosis compared to normotensive COVID-19 patients.

The management of hypertensive patients is another important implication of our findings. The postulated higher vulnerability to severe COVID-19 would require specific precautions for these patients, such as reinforcing the restrictive measure for avoiding contagion (i.e., strict maintenance of spatial distance of at least 1 m, social isolation, wearing of more powerful personal protection equipment such as gloves, goggles, FFP2 (N95) or FFP3 masks), as well as constant monitoring of blood pressure, to prevent especially broad variations which are associated with higher risk of developing targeted (i.e., lung) or multiple organ failure.<sup>36</sup>

A limitation of the current analysed literature is the lack of age-adjusted data with respect to hypertension and disease severity. In our meta-regression by mean age of severe patients,

significant odds of COVID-19 severity associated with hypertension was only seen in those over age 60. It is possible that the observed risk may be attributed to the higher overall severity and mortality in older patients, within whom the prevalence of hypertension increases in parallel with advancing age. We hypothesize that in older individuals, hypertension contributes to a compounding effect with other co-morbidities on mortality. As such, in the coming weeks, we urgently need age-adjusted analyses for clinical predictors of severe and fatal COVID-19. Lastly, it is possible in the included studies that patients presenting without a history of hypertension, but presenting at admission with elevated blood pressure (potentially due to COVID-19), may be considered to have a history of hypertension, biasing results among individual studies.

In conclusion, we still lack the definitive clues for establishing which comes first between the chicken (i.e., hypertension) or the egg (i.e., severe COVID-19), or even if these two conditions interplay in their pathophysiology. However, the results of this pooled analysis of the current scientific literature would suggest that hypertension may be associated with a up to 2.5-fold higher risk of severe and fatal COVID-19, especially among older individuals.

**Conflicts of Interest:** None

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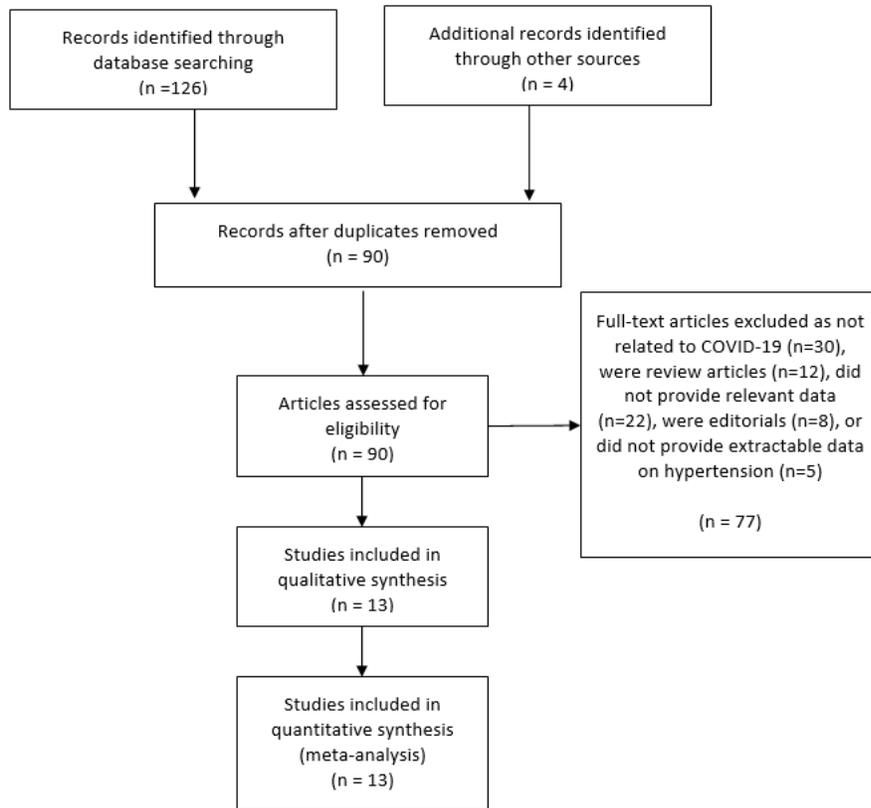
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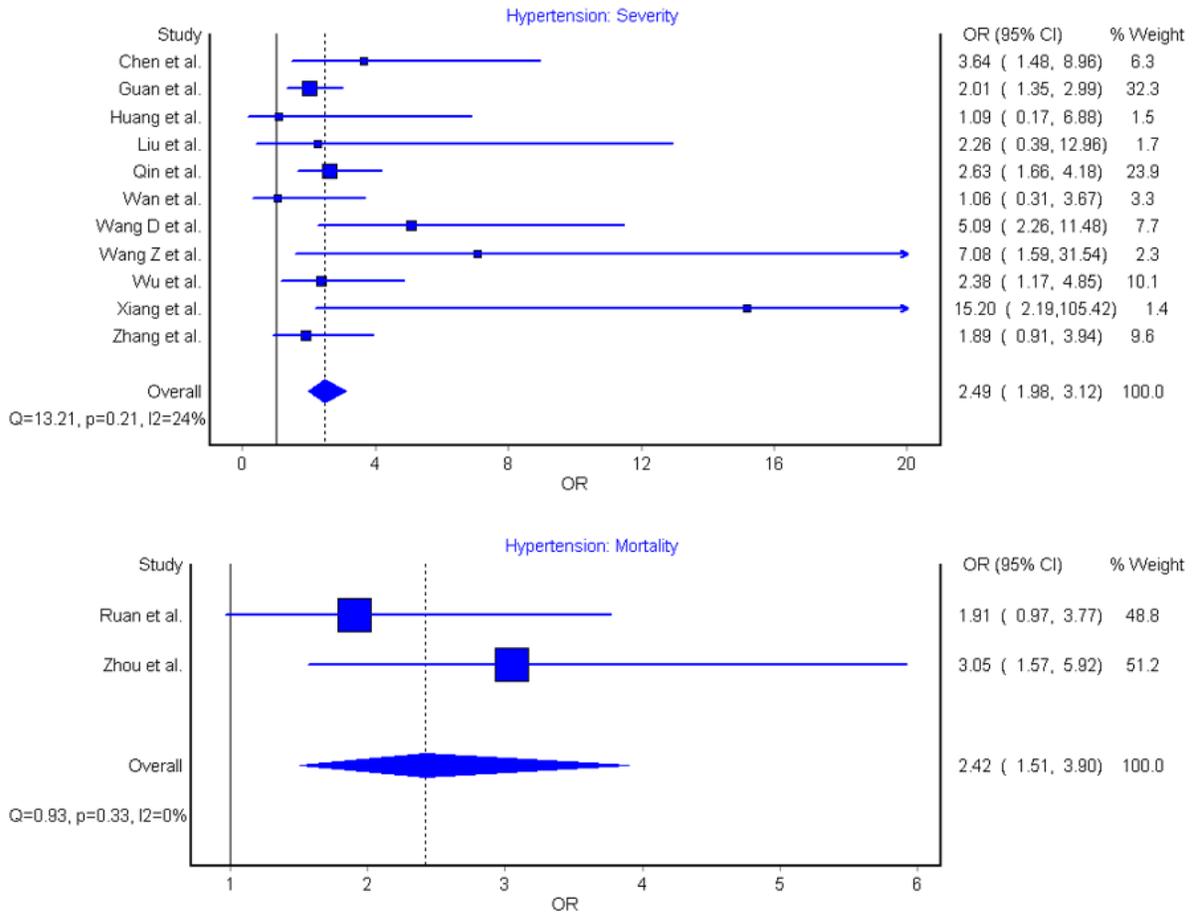
**Table 1. Characteristics of Included Studies.**

Study	Setting	Sample Size	Outcomes	Severe patients			Non-severe patients		
				n (%)	Age (yrs) *	HTN (%)	n (%)	Age (yrs) *	HTN (%)
Chen C et al. 2020	China	150	Respiratory Distress/Insufficiency	24 (16%)	68.5 (13.6)	14 (58.3%)	126 (84%)	51.1 (15.6)	35 (27.8%)
Guan W et al. 2020	China	1099	Admission to ICU, MV, Death	173 (15.7%)	52 (40–65)	41 (23.7%)	926 (84.3%)	45 (34–57)	124 (13.4%)
Huang C et al. 2020	China	41	ICU Care	13 (31.7%)	49 (41–61)	2 (15.4%)	28 (68.3%)	49 (41–58)	4 (14.3%)
Liu W et al. 2020	China	78	Admission to ICU, MV, Death	11 (14.1%)	66 (51–70)	2 (18.2%)	67 (85.9%)	37 (32–41)	6 (9.0%)
Ruan Q et al. 2020	China	150	Death	68 (45.3%)	67 (15–81)	29 (42.6%)	82 (54.6%)	50 (44–81)	23 (28.0%)
Qin C et al. 2020	China	452	Respiratory Distress/Insufficiency	286 (63.3%)	61 (51–69)	105 (36.7%)	166 (36.7%)	53 (41.25–62)	30 (18.1%)
Wan S et al.	China	135	Respiratory Distress/Insufficiency	40 (29.6%)	56 (52–73)	4 (10.0%)	95 (70.4%)	44 (33–49)	9 (9.5%)
Wang D et al. 2020	China	138	Clinical Variables, MV, Death	36 (26.1%)	66 (57–78)	21 (58.3%)	102 (73.9%)	51 (37–62)	22 (21.6%)
Wang Z et al. 2020	China	69	SpO <sub>2</sub> <90%	14 (20.3%)	70.5 (62–77)	5 (35.7%)	55 (79.7%)	37 (32–51)	4 (7.3%)
Wu C et al. 2020	China	201	ARDS	84 (41.8%)	58.5 (50–69)	23 (27.4%)	117 (58.2%)	48 (40–54)	16 (13.7%)
Xiang T et al. 2020	China	49	Respiratory Distress/Insufficiency	9 (18.4%)	53 (14)	4 (44.4%)	40 (81.6%)	40.6 (14.3)	2 (5.0%)
Zhang J et al. 2020	China	140	Respiratory Distress/Insufficiency	58 (41.4%)	64 (25–87)	22 (37.9%)	82 (58.6%)	52 (26–78)	20 (24.4%)
Zhou F et al. 2020	China	140	Death	54 (28.3%)	69 (63–76)	26 (48.1%)	137 (71.7%)	52 (45–58)	32 (23.4%)

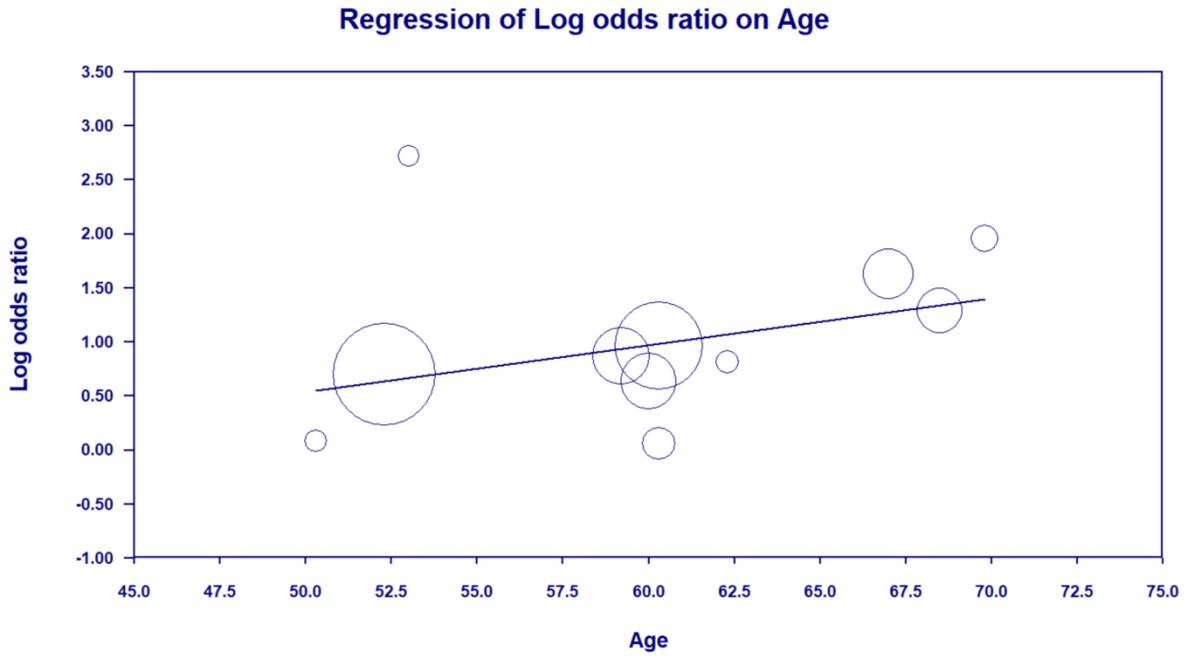
\*Age data presented as median (IQR) or mean (SD). MV – Mechanical Ventilation, ICU – Intensive Care Unit, NR – Not reported



**Figure 1.** Study flow chart.



**Figure 2.** Forest plots demonstrating the association of hypertension with COVID-19 severity and mortality.



**Figure 3.** Meta-regression of mean age of patients with severe COVID-19 and log odds ratio for association of hypertension with severe form of COVID-19.