Review Article

Hypertension and sex related differences in mortality of COVID-19 infection: A systematic review and Meta-analysis

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Abstract

Background: Hypertension is the leading cause of cardiovascular diseases and premature deaths. Hypertension plays a striking role in mortality and morbidity in case of Coronavirus Disease 2019 (COVID-19) infection; however, numerous studies have reported contradictory findings.

Objective: To assess the relationship of hypertensive disease and mortality of COVID-19 infection and to assess the sex and age differentials on the association.

Methods: We have conducted a systematic review of published literatures that identified the relationship between hypertension and mortality of COVID-19 infections. Nineteen articles were selected following structured inclusion and exclusion criteria for systematic review and analyses. A total of 21,684 hospital admitted COVID-19 patients were included in this review and meta-analysis from 19 studies. The studies covered the six months of the pandemic from December 2019 to May 2020.

Results: In the pooled analysis, the median age of patients was 58 years, and the proportion of male patients was 58.8%. In contrast, we estimated 33.26% of hypertensive and 19.16% of diabetes mellitus patients in the studies. Hypertension was found to be associated with COVID-19 mortality ("Risk ratio (RR) = 1.45, [95% confidence interval (CI): 1.35 - 1.55]; I2 = 77.1%, p - value < 0.001"). The association in the meta-regression was affected by sex (p - value = 0.050). The association was found to be stronger in the studies with males ≥ 55% and age ≥ 55 years ("RR = 1.65, [95% CI: 1.52 - 1.78]; I2 = 77.1%, p - value < 0.001") compared to male < 55% or age < 55 years ("RR = 1.11, [95% CI: 0.94 - 1.28]; I2 = 72.2%, p - value < 0.001").

Conclusion: Hypertension was significantly strong associated with COVID-19 mortality which may account for the contradiction in the many studies. The association between hypertension and mortality was affected by sex and there were significantly higher fatalities among older male patients.

Introduction

The Coronavirus Disease 2019 (COVID-19) outbreak initially emerged in the early in December 2019 in Wuhan city, Hubei province, China [1]. It was declared a pandemic on 12 March 2020 by the World Health Organization (WHO) [2]. To date, this disease has spread to all five continents and has caused a "Public Health Emergency of International Concern (PHEIC) since 30 January 2020" [3]. As of early August 2020, it has already infected more than 20 million people along with more than 0.7 million deaths. Among them, 99% of cases were mild, 72.50% cases which had an outcome and 5% of fatalities have occurred in 14.50 million known outcomes [4], with deaths rapidly emerging around the globe. Determining the

potential factors related to increased mortalityin COVID-19 patients is required for competent resource allocation during the pandemic period, especially in the low-middle income countries.

The burden of chronic diseases has rapidly emerged and causes 41 million deaths each year around the world, in which cardiovascular diseases account for 17.9 million deaths [5]. Hypertension is one of the most severe medical conditions which increases the risk of cardiovascular diseases. Highest prevalence of this condition was observed among COVID-19 patients, followed by other comorbidities [6]. Globally, 1.13 billion people have hypertension and low-middle income countries account for 75% of the total hypertensive patients [7]. Hypertension also causes cognitive impairment in two-thirds of elderly people [8,9]. In an influenza pandemic, older men were more likely to have a severe outcome [10]. Previous studies have shown that virally infected advanced age men with other co-morbidities suffered from weak immune function, however uncertain, may increase susceptibility and mortality of COVID-19 infection [11–13]. Hence hypertension is an important contributor to COVID-19 mortality in relation to age and, and is consistent in different countries worldwide. We aimed to explore the relationship between hypertension disease and mortality due to COVID-19 infection and to assess the sex and age influence on the relationship.

Materials and methods

Eligibility criteria

We enrolled all the studies which included COVID-19 infection with hypertension disease, mortality and survival. The original research articles with sample size > 50 hospital admitted patients published in English language were included.

Search strategy and study selection

We carried out a comprehensive systematic peer-reviewed literature search by using PubMed, SCOPUS, EuroePMC and Google Scholar databases with the terms: "COVID-19" OR "SARS-CoV-2" AND ("Comorbidities" OR "hypertension"). We removed the replicas of the extracted articles. Two authors (AI and PKG) screened for relevant information in the abstracts of the remaining literature. Based on the eligibility criteria, we examined the full text of selected articles. We completed the article extraction on 31 July 2020following the guideline of "Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)" [14] (Figure 1).

Quality assessment of the studies: Quality of the studies included for final review was also assessed in terms of study size, sample selection methods and measurement of study outcomes. The studies were considered poor in quality if they have small sample size, non-random individuals and study outcomes were not measured objectively, moderate quality and better quality studies are those who used large sample,
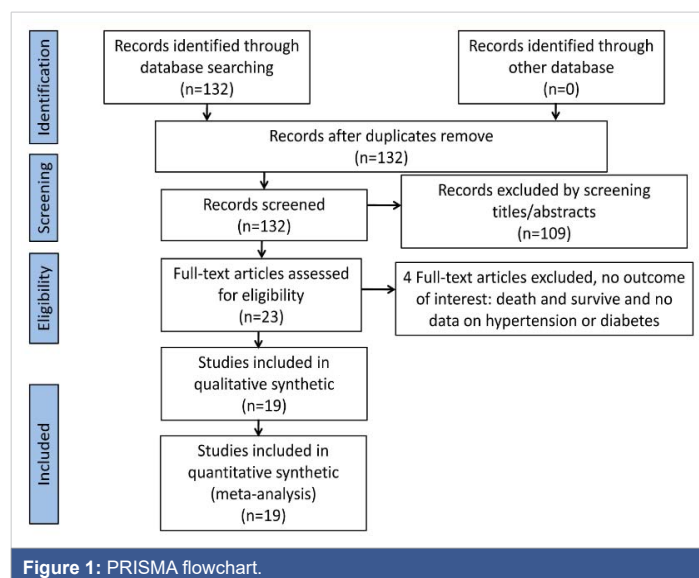

Figure 1: PRISMA flowchart.

used randomization in patients section, and study outcomes were measured objectively.

Data extraction

Two independent authors (AI and PKG) extracted the 19 studies. We used standardized forms that included author, year, study design, sample size, age, sex, hypertension, diabetes and death of COVID-19 patients. The outcome of interest was mortality due to COVID-19 infection.

Statistical analysis

We performed Mantel-Haenszel formula to estimate the effect in risk ratio (RRs) with 95% confidence interval (95% CI) and performed Random-effects model to account for inter-study variability. All p-values in this study were two-tailed and statistical significance was set at ≤ 0.05. Meta-regression was performed to examine the influence of covariates on the RR. We conducted further subgroup analysis to assess the more influential group in the magnitude of RR based on median age and average proportion of hypertension in the studies. To evaluate the small-study effects, we performed a regression-based Egger's test. We performed Funnel-plot analysis to identify the qualitative bias in the publication.

Results

Characteristics of the included studies

While we extracted an initial 132 studies, there were no duplicate records and we excluded 109 studies after screening the abstracts. The remaining 23 studies were eligible for full-text screening. We eliminated four studies because of no available data on sex, age, hypertension or diabetes. Finally, we included 19 articles for qualitative synthesis and meta-analysis (Figure 1) (Table 1).

The selected studies covered the six months of the pandemic from December 2019 to May 2020 and included 21,684 patients. In the pooled analysis, the median age of

Table 1: Characteristics in the included studies.

Study	Setting	Duration	Sample size	Study Design	Median/Mean age	Male (%)	Diabetes Mellitus (%)	Hypertension (%)
Lang W, et al. [33]	Renmin Hospital, Wuhan, China	1 Jan to 5 Mar 2020	339	Observational Retrospective	71	49.00	16.00	40.80
James, et al. [34]	King's college and Prince university hospital, London	1 Mar to 22 April 2020	1157	Observational Retrospective	71	57.60	35.30	52.90
Hu K, et al. [35]	Yangtze River Shipping General hospital, Wuhan, China	Jan to Mar 2020	105	Observational Retrospective	58	62.90	0.00	17.10
Chen L, et al. [36]	Union, Central, General and Jin-Yin-Tan Hospital, Wuhan, China	26 Jan to 4 April	1651	Observational Retrospective	59	50.00	14.00	31.0
Ali, et al. [37]	Fars, Iran	18 Feb to 19 Mar 2020	440	Observational Retrospective	46.5	56.40	7.50	7.95
Pablo, et al. [38]	Three hospital, London	25 Feb to 4 April 2020	614	Observational Retrospective	69	62.00	27.50	35.00
Riccardo, et al. [17]	Civil hospitals of Brescia, Lombardy, Italy	4 Mar to 25 Mar	99	Observational Retrospective	67	81.00	31.00	64.00
Chao G, et al. [39]	Zhongnan hospital, Wuhan, China	5 Feb to 15 Mar 2020	2877	Observational Retrospective	60	51.10	13.50	29.50
Zhou, et al. [18]	Jinyintan and Pulmonary hospital, Wuhan, China	Up to 31 Jan 2020	191	Observational Retrospective	56	62.00	19.00	30.00
Giacomo, et al. [40]	Lombardy, Italy	20 Feb to 30 May 2020	3988	Observational Retrospective	63	79.90	12.89	41.20
Chaomin, et al. [19]	Jinyintan hospital, Wuhan, China	25 Dec 2019 to 26 Jan 2020	201	Observational Retrospective	51	63.70	10.90	19.40
Mandeep, et al. [41]	Asia, Europe and North American hospital	20 Dec 2019 to 15 Mar 15 2020	8910	Observational Retrospective	52	59.90	14.28	26.30
Bai T, et al. [6]	Jinyintan hospital, Wuhan, China	26 Dec 2019 to 31Jan 2020	127	Observational Retrospective	55	63.00	11.80	28.30
Cao J, et al. [39]	Huoshenshan hospital, Wuhan, China	3 Jan to 1 Feb 2020	102	Observational Retrospective	54	52.00	10.80	27.50
Lu Z, et al. [42]	Seventh hospital, Wuhan, China	1 Jan to 15 Feb 2020	123	Observational Retrospective	63	49.60	11.40	33.30
Chen T, et al. [32]	Zhongnan hospital, Wuhan, China	1 Jan to 10 Feb 2020	55	Observational Retrospective	74	61.80	30.90	38.20
Lin Fu, et al. [20]	Union hospital of Huazhong Wuhan, China	1 Jan to 30 Jan 2020	200	Observational Retrospective	55	49.30	68.20	51.50
Kaiyan L, et al. [21]	Tongji hospital, Wuhan, China	as of Mar 20	102	Observational Retrospective	57	58.00	15.00	30.00
Xia L, et al. [43]	Eastern campus of Renmin hospital, Wuhan, China	as of Feb 25	403	Observational Retrospective	56	47.90	14.10	28.00

patients was 58 years, and the proportion of male patients was 58.8%. In contrast, we estimated 33.26% of hypertensive and 19.16% of diabetes mellitus patients in the studies.

Association between male and mortality of COVID-19 outcome

The meta-analysis showed that male patients had a higher mortality due to COVID-19 infection compared to that with female patients ("RR = 1.28, [95% CI: 1.20-1.36]; I^2 = 58.7%, p - value = 0.001") (Figure 2A). In the leave-one-out sensitivity analysis, we observed that elimination of the highest weight (Giacomo, et al.) study could not change the heterogeneity and the magnitude of association ("RR = 1.31, [95% CI: 1.21 - 1.42]; I^2 = 60.2%, p - value = 0.001") (Figure 3A). The association between being male and mortality was not affected by age (p - value = 0.199) in the meta-regression.

Association between hypertension and mortality of COVID-19 outcome

Hypertensive patients with COVID-19 infection were found to be at higher risk of mortality compared to non-hypertensive patients ("RR = 1.45, [95% CI: 1.35 - 1.55]; I^2 = 77.1%,

p – value < 0.001") (Figure 2B). In the leave-one-out sensitivity analysis, the elimination of highest weight (Giacomo, et al.) study slightly reduced the magnitude of the association ("RR = 1.27, [95% CI: 1.13 - 1.40]; I^2 = 72.9%, p - value < 0.001") (Figure 3B). The association between hypertension and mortality was affected by sex (p = 0.049), but not age (p = 0.301) and diabetes mellitus (p = 0.343) in the meta-regression analysis. The studies with male ≥ 55% and median age ≥ 55 years ("RR = 1.65, [95% CI: 1.52 - 1.78]; I^2 = 77.1%, p – value < 0.001") had significantly higher association compared to those of studies with male < 55% or median age < 55 years "(RR = 1.11, [95% CI: 0.94 - 1.28]; I^2 = 72.2%, p – value < 0.001") (Figure 4) in the subgroup analysis.

Publication bias

We found a qualitatively symmetrical association with mortality and other factors (male and hypertension) in the funnel-plot analysis (Figure 5). A further Regression-based Egger's test showed that there was no effect of a small study on the association with mortality and other factors (male: p - value = 0.138; hypertension: p –value = 0.290).
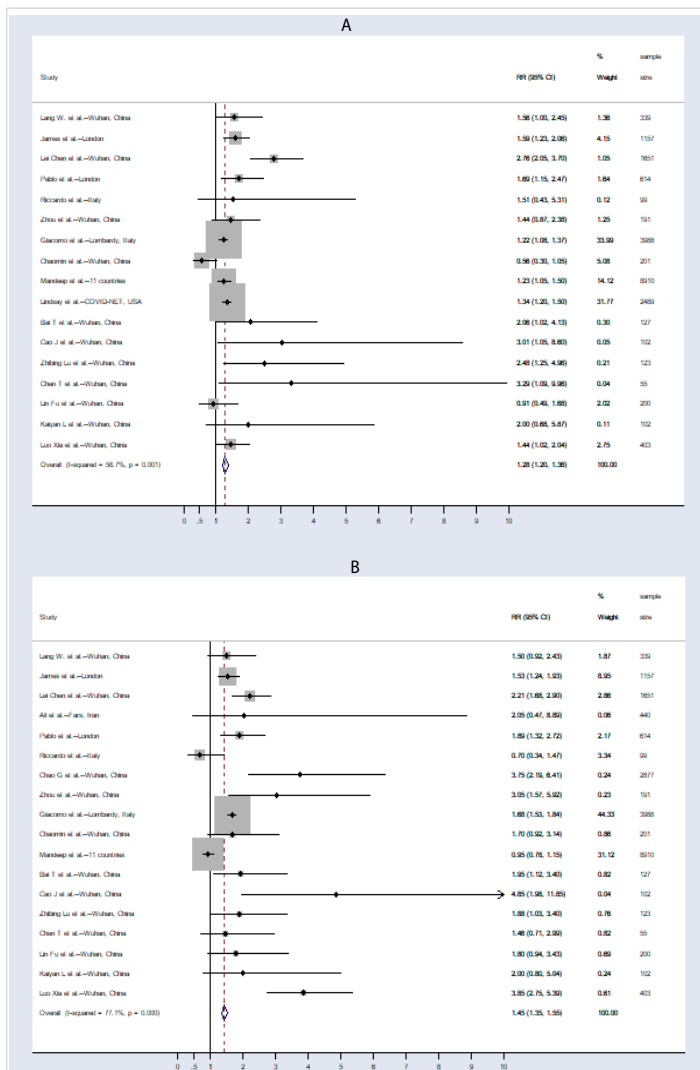
Figure 2: Forest plot for (A) male and mortality of COVID-19 disease; (B) hypertension and mortality of COVID-19 disease: plots show that male and hypertension were associated with mortality with COVID-19 outcome.
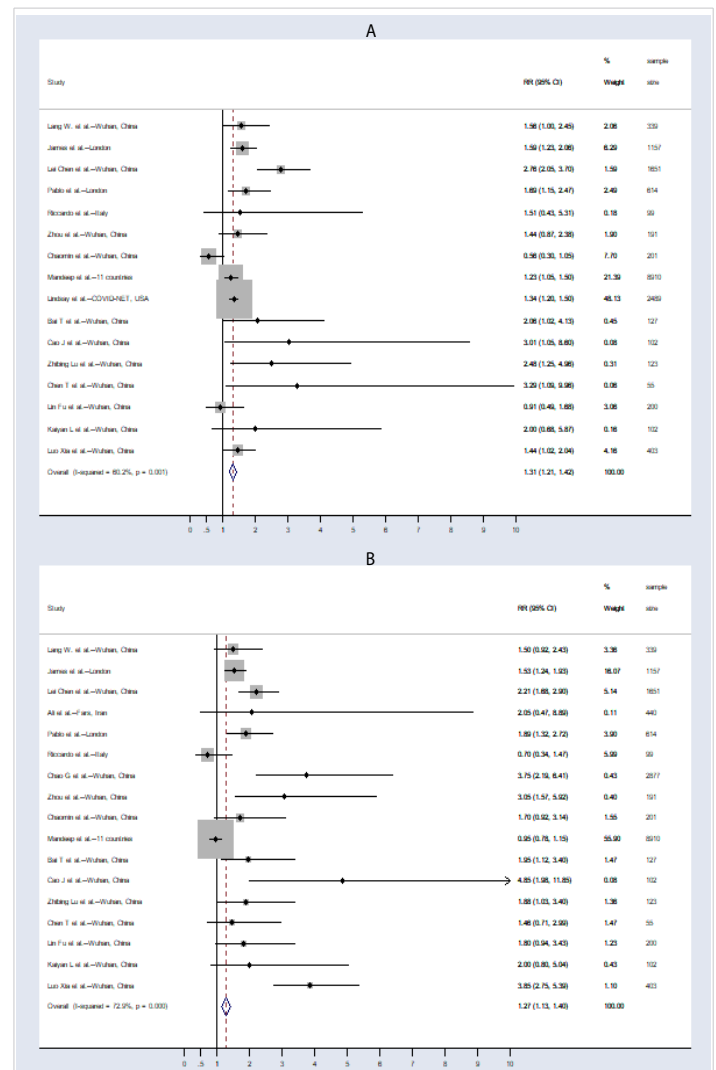

Figure 3: Sensitivity analysis: Removal Giacomo, et al. study reduces association between hypertension and mortality but not the association between male and mortality with COVID-19 outcome.

Discussion

In this systematic review and meta-analysis study, we observed that hypertension were associated with the increased risk of mortality in COVID-19 infections. Meta-regression showed that the association between hypertension and mortality was influenced by sex, which was addressed by the previous severe COVID-19 outcome studies[15]. Further subgroup analysis showed a significantly stronger association in the studies with a higher proportion of male and elderly patients, which is steady with severe and fatal patients in the prior analysis [16].

Although the association between sex and mortality was weaker in the five studies [17–21], meta-analysis shows that the male COVID-19 infected patients were 1.28 times more likely to die. Even though the proportion of male patients was higher (58.8%) than the female patients in the present studies, a male patient had increased risk of dying independent of age. We found similar results with severely infected patients in

studies from China [22,23]. The mean score of all comorbidities in men (3.1) was significantly higher than women (1.8) (p - value < 0.05) [24] while the prevalence of hypertension is 25% in men and 20% in women worldwide [7]. However, the COVID-19 infected male patients had more risk of dying than the female patients probably due to weaker immune function in males with existence chronic condition [25–28].

The hypertensive patients were more likely to have a fatal COVID-19 infection compared to non-hypertensive patients in the present study. It is consistent with the prior studies which illustrated that hypertension causes death among COVID-19 patients [6,15,16]. However, the hypertensive patients were more adversely affected by SARS-CoV-2 virus that enters the epithelial cells passing through angiotensin-converting enzyme 2(ACE2). ACE2 decreases vascular inflammatory action of angiotensin 1-7 [29,30]. Inflammatory storm in infected patients releases cytokines causes systemic immune function damage, which may be a significant cause of multiple organ failure and even death [31].
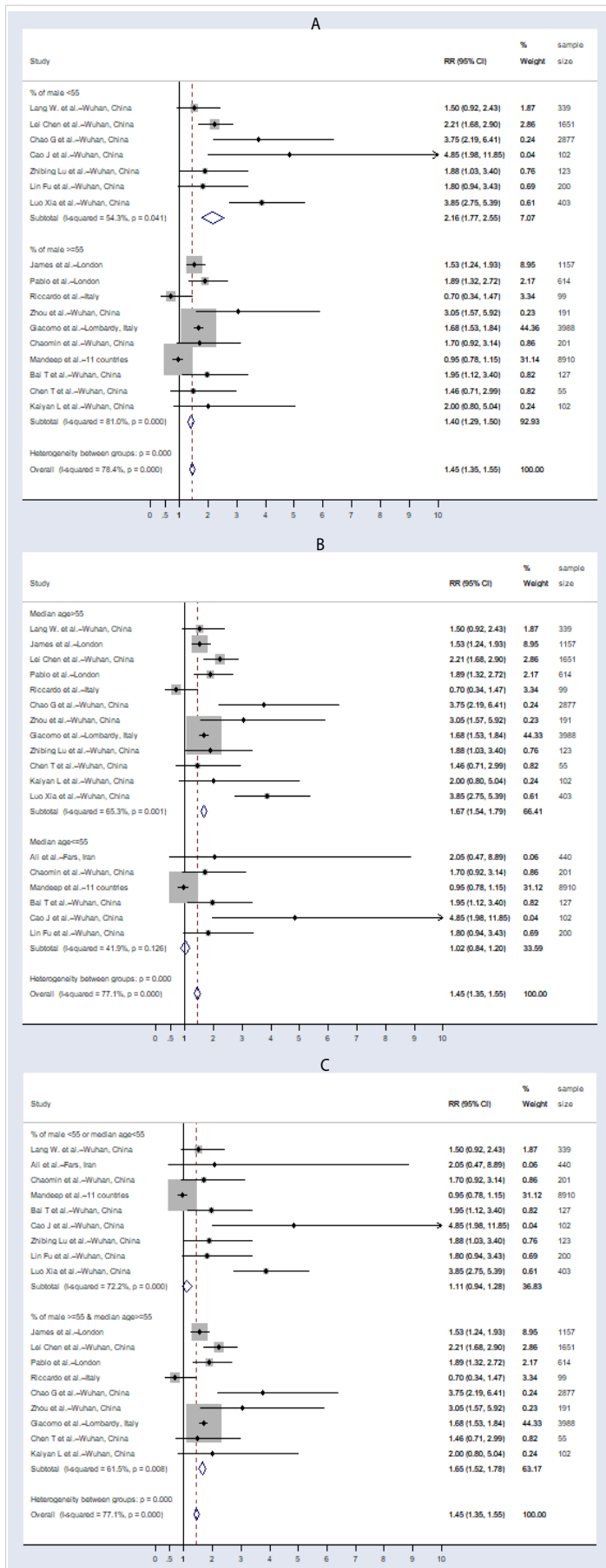
Figure 4: Sub-group analysis showed the association between hypertension and mortality was stronger in studies with (A) single male < 55% (B) single median age > 55 years and (C) combined with male ≥ 55% and age ≥ 55 years.
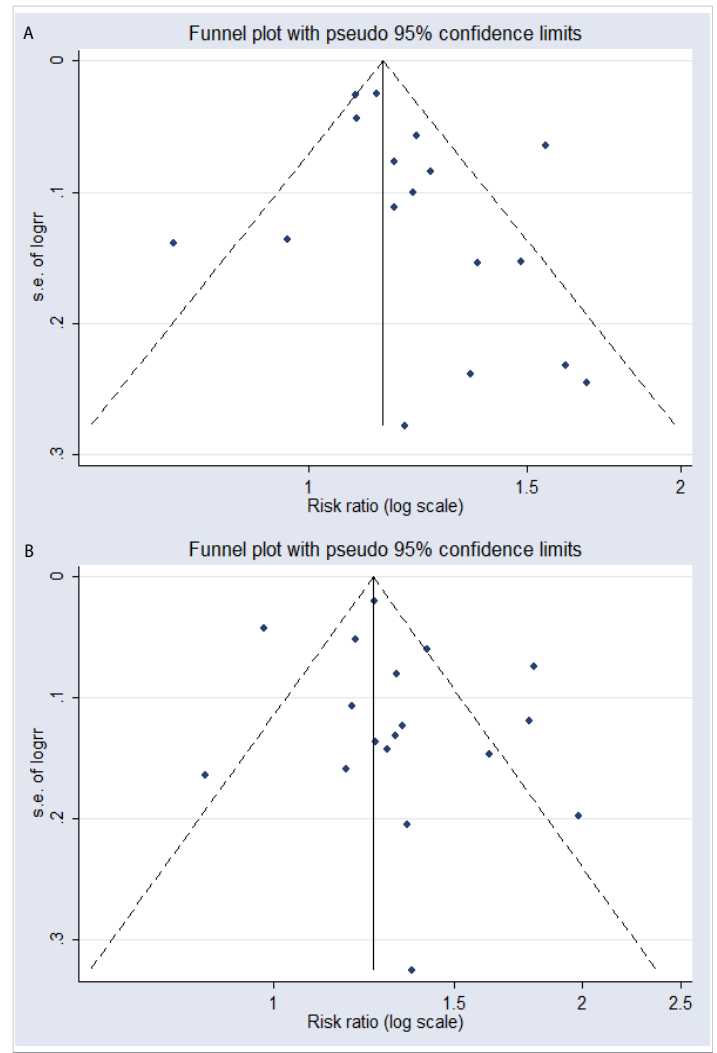

Figure 5: Funnel plot analysis showed a qualitatively symmetrical funnel plot for the association between mortality and (A) male, and (B) hypertension.

Subgroup analysis showed that the increased mortality with COVID-19 disease was more significant in a higher proportion of male > 55 years with hypertensive patient studies. However, sex and age were more explained in the association between mortality of COVID-19 outcome and hypertension because circulating protein expression of ACE2 is higher in older men with hypertensive condition [8,32].

This study has several limitations. Since angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) treatment are used in COVID-19 patients with hypertension, it may affect the outcome. Data on hypertensive medicine or therapy were not included in the selected studies. Almost all of the studies were retrospective and peer-reviewed, however, a few preprints before peer review were also included in the meta-analysis. Included studies were from Asia, Europe and North America, however, most of the studies were from China but from different hospitals, therefore, the sample might not represent COVID-19 patients globally.

In conclusion, hypertensive patients are strongly

associated with higher odds of mortality due to COVID-19 infections which may account for the contradiction in the many studies. The effect of coexistence hypertension on the risk of mortality with COVID-19 patients was more influential in elderly male patients. We should direct more attention to COVID-19 and hypertensive patients, especially in elderly men in the course of treatment to reduce mortality. Further, more comprehensive studies are needed to investigate more detailed information on the association between hypertension and death of COVID-19 patients, particularly in low-middle income countries.

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