Clinical research

Hypertension, diabetes mellitus, and cerebrovascular disease predispose to a more severe outcome of COVID-19

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Abstract

Introduction: The world is currently facing the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The total number of cases of coronavirus disease 2019 (COVID-19) is rising daily and no vaccine has yet been approved. While the pathophysiology behind the virus is still being studied, many possible several risk factors using small sample sizes have been found.

Material and methods: We conducted a pooled analysis using several databases such as Medline, Scopus, Wangfang, Web of Science, Research Square, medrxiv, and Google Scholar to identify studies reporting severe and non-severe groups of COVID-19 patients. The odds ratios as well as the 95% confidence intervals for hypertension, diabetes, and cerebrovascular disease leading to severe COVID-19 were calculated using R-software.

Results: Fifty-three articles were used for our analysis and they involved 30,935 confirmed cases of COVID-19 from several countries across the world. The odds ratio for severe COVID-19 in hypertensive patients, diabetics, and patients with a history of cerebrovascular disease was 2.58 (95% confidence interval (CI): 2.16–3.08, from 53 studies), 2.17 (95% CI: 1.72–2.74, from 44 studies), and 2.63 (95% CI: 1.80–3.85, from 25 studies), respectively.

Conclusions: Our analysis confirms that patients with hypertension, diabetes, or cerebrovascular disease are at a higher risk of a severe outcome of COVID-19. It is thus vital for physicians to identify the main risk factors for a severe outcome of this disease.

Key words: hypertension, diabetes, cerebrovascular disease, stroke, severity, COVID-19, SARS-CoV-2, coronavirus 2019, meta-analysis, pooled analysis.

Introduction

In December 2019, several patients in Wuhan, China, were admitted with symptoms of "pneumonia of unknown etiology". Over the next few days, the Chinese Centre for Disease Control and Prevention (CDC) started to investigate the possible causes of these new and strange presentations. A new virus was finally identified and found to belong to the family of coronavirus (CoV) which also included severe acute respiratory syndrome coronavirus (SARS-CoV), discovered in 2002, and the Middle East respiratory syndrome coronavirus (MERS-CoV) which appeared in 2012 [1–3].

The virus was called severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and the disease it can cause was called coronavirus disease 2019 (COVID-19) [1]. As SARS-CoV-2 continued to spread over China and over different countries, the World Health Organization declared it as a pandemic. Almost a year later, it has infected about 85,892,625 people causing 1,857,399 deaths worldwide [1, 3, 4]. Since many countries have limited health care resources and intensive care units [3], many researchers studied early data to find possible risk factors that can lead to a more severe outcome of this virus [1, 5–13]. Analysis of SARS-COV-2 showed that the virus engages the angiotensin-converting enzyme 2 (ACE2) as a receptor to penetrate human cells [14]. The enzyme is present in multiple systems including the cardiovascular system. Diabetics have marked hyperglycemia which leads to inflammatory as well as coagulation imbalance [15], which potentiates the replication of the virus [16]. Hypertension and diabetes are also the two most important risk factors among patients with cerebrovascular disease. COVID-19 offers hypercoagulable and possible hypoxic states in some patients which could lead to more severe outcomes in patients with a prior history of cerebrovascular disease [17]. The severity of these three risk factors for the progress of COVID-19 patients was tested and confirmed using limited population groups during the first 4 months of the pandemic [12, 18, 19]. We hereby sought to expand and strengthen the understanding and risks using a larger population sample via a pooled analysis.

Material and methods

We used the guidelines set up by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to conduct a meta-analysis [20] (Figure 1). Our search team consisted of two groups. Each group first independently searched Medline, Scopus, Wangfang database, Web of Science, Research Square, medrxiv, and Google Scholar databases using the keywords "COVID-19", "coronavirus 2019", "2019-nCoV", "SARS-CoV-2", "hypertension", "diabetes", "diabetes mellitus", "cerebrovascular disease", and "stroke". Articles published between 1st December 2019 and 15th October 2020 were included in our selection. We were able to evaluate studies published in English, French, Chinese, and Spanish.

Studies needed to report two groups: one severe and one non-severe. Based on previous studies [7, 12, 19, 21–26] and since there are multiple guideline protocols in different countries, severity

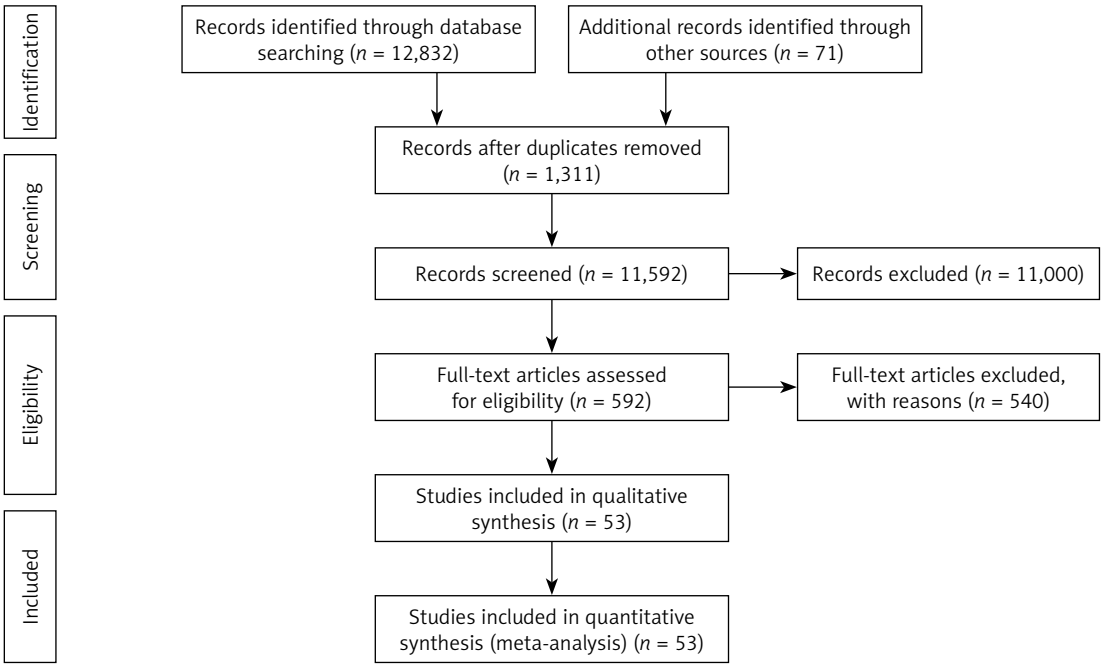

Figure 1. PRISMA flow-diagram

was defined depending on either clinical presentation during their hospitalizations and laboratory findings [27–30], admission in intensive care unit [31], use of mechanical ventilation [32] or patients ranked using radiological findings [33]. The studies also had to include at least one of the three risk factors being studied by our team. We excluded studies that did not provide the raw table of data, case series, and case reports, meta-analyses and also had a very small sample size ($n < 10$).

The articles that met the initial search criteria were further assessed by their abstracts and full texts. Each researcher presented his/her search results and discussed it with his/her group [22, 34, 35]. Eventually, each group made its own list and discussed together with the team to draft a final inclusion list. Disagreements were resolved by a consensus from all the researchers involved.

Statistical analysis

Statistical analysis was performed using R software (version 4.0.3) (https://www.r-project.org/). We used the meta-package to study our data and a forest plot was also extrapolated [36]. The heterogeneity of our study was assessed via Higgins's I^2 test [37]. The fixed-effect model was applied if the I^2 was less than 50% and, the random-effect model was used for I^2 greater or equal to 50% for our study. The study was conducted in compliance with the Declaration of Helsinki and no ethical approval was required [38].

Results

Our initial search yielded 12,903 studies. They were first filtered off based on the title and abstract. Finally, 592 articles were reviewed for their full texts. We initially chose 77 studies and finally after careful evaluation and further discussions, 53 articles that matched our criteria of selection for hypertension [14, 27, 28, 30, 32, 33, 39–85], 44 articles that compared the presence of diabetes [27, 28, 30, 32, 33, 39–50, 52–56, 58–61, 63, 64, 66-69, 71–76, 80, 81, 83–85], and 25 articles that reported the risk of patients with a prior cerebrovascular disease with a severe and non-severe outcome [27, 28, 33, 40, 44-47, 53, 55, 58–61, 64, 66, 69, 71, 73–75, 80–83] were retained for our analysis.

Hypertension

A total of 7,031 patients formed the severe group and 23,904 patients formed the non-severe group in our selection. 2,514 severe patients also had a history of hypertension while 3,537 patients in the non-severe group had hypertension. The odds ratio for a hypertensive patient to have a severe outcome of COVID-19 was 2.58 (95% confidence interval (CI): 2.16–3.08, heterogeneity: I^2 = 80%, $p < 0.01$) (Figure 2).

Diabetes

Our analysis found 6,327 severe cases and 22,071 non-severe cases amongst which 1,622 and 2,548 had a history of diabetes, respectively with an odds ratio of 2.17 (95% CI: 1.72-2.74, heterogeneity: I^2 = 81%, $p < 0.01$) (Figure 3).

Cerebrovascular disease

Three hundred and seventy-three patients with a history of cerebrovascular disease developed a severe outcome of COVID-19 out of the 4,361 severe cases reported in total, compared to 481 of the 12,809 non-severe cases. Their odds ratio was estimated at 2.63 (95% CI: 1.80–3.85, heterogeneity: I^2 = 63%, $p < 0.01$) (Figure 4).

Discussion

Our study provides an update on the impact of hypertension, diabetes, and cerebrovascular disease on the severity of COVID-19. It is one of the largest pooled analyses, to our knowledge, that includes these three risk factors. We used 53 studies that covered 30,935 confirmed cases of COVID-19 from several countries, classified as severe and non-severe ones.

The findings closely confirm early studies such as the study involving 2,552 patients conducted by Lippi *et al.* who found that the risk of severe COVID-19 is increased by almost 2.5 with a history of hypertension [12] while Del Sole *et al.* reported values of 2.24 among 2,794 patients [25]. Similar higher risks have been previously linked among patients with diabetes and cerebrovascular diseases. Aggarwal *et al.* studied previously published reports totaling 2,564 patients and found that the odds ratio of severity among diabetes was 2.60 (95% CI: 1.96–3.45) [7]. Their team also published another early pooled analysis involving four studies and reported that patients with a prior history of cerebrovascular disease are at 2.5 higher risk of ending with a more severe outcome of COVID-19 [19].

While the increased risks of severity in patients with hypertension, diabetes, and cerebrovascular disease can now be statistically established, there are multiple theories and possible pathways concerning their pathophysiology. Huang *et al.* suggested that there may be an imbalance of various inflammatory cytokines in COVID-19 which may be more severe in hypertensive patients. Higher levels of multiple factors such as IL-6, IL-7, and granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor α have also been reported to be involved in the various pathophys-

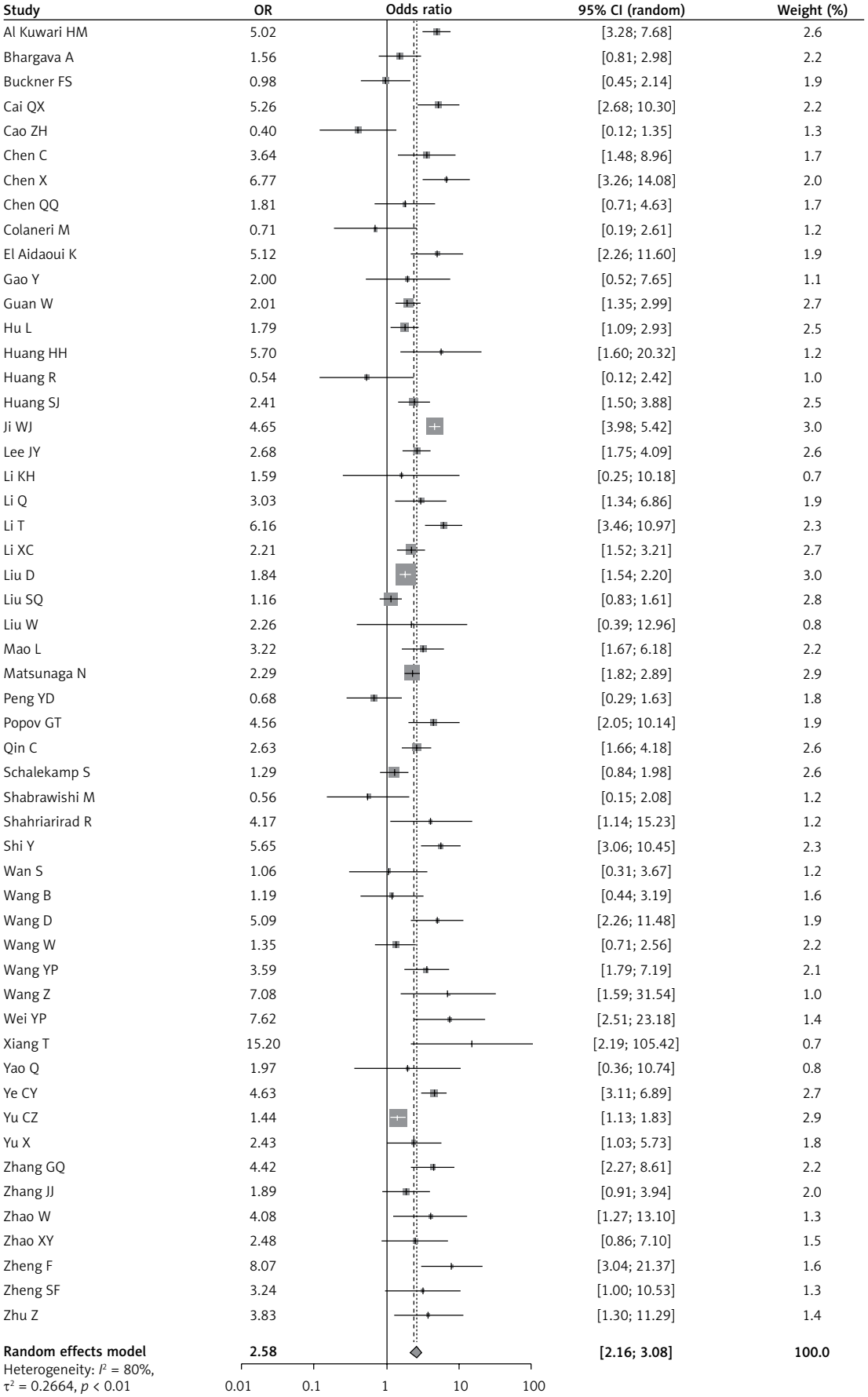

Figure 2. Hypertension and severity of COVID-19

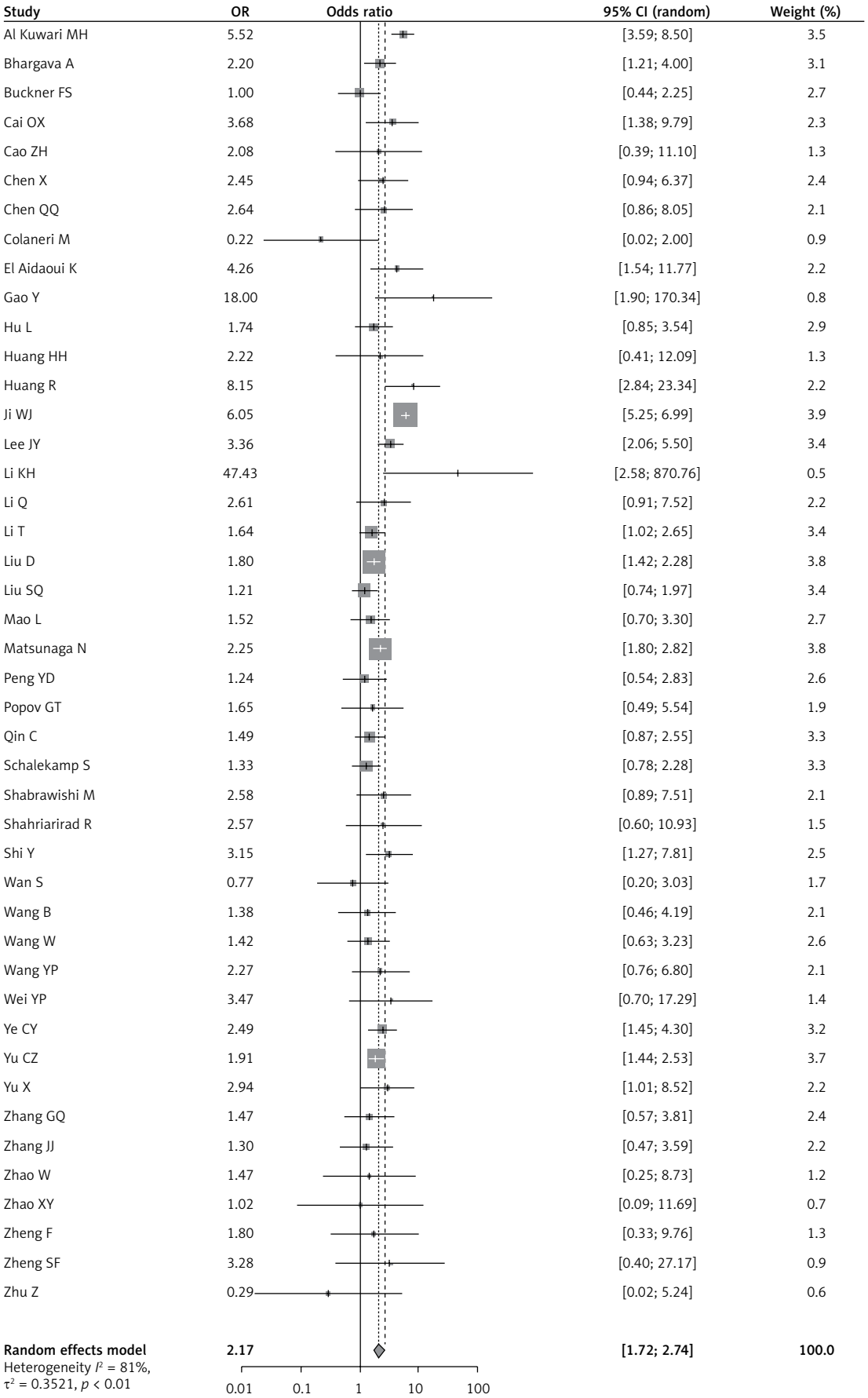

Figure 3. Diabetes and severity of COVID-19

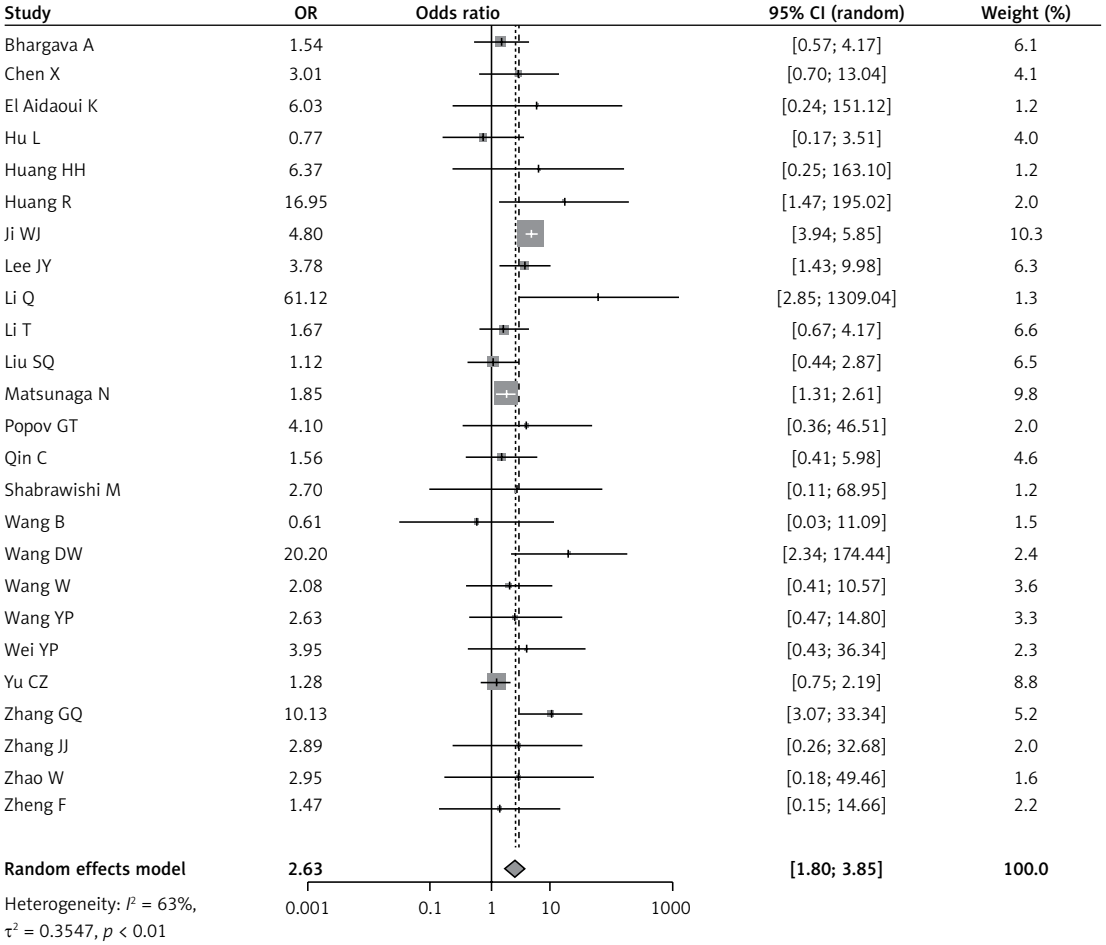

Figure 4. Cerebrovascular disease and severity of COVID-19

iologic pathways of hypertension. Their presence in COVID-19 patients can thus trigger a more severe outcome and also increase the risk of cytokine storms [14, 86, 87]. The possible link between the Renin-Angiotensin-Aldosterone System and COVID-19 has also been suggested [88]. The SARS-CoV-2 has an S spike protein (S-protein) that can bind to ACE2 receptors [89]. This allows the virus to enter the host cells. The viral and receptor complex is then endocytosed. This eventually leads to a lower number of the receptors and a higher level of Angiotensin II [90].

Several very similar pathways have also been hypothesized for diabetic patients. The higher levels of multiple pro-inflammatory conditions and the often co-accompanying obesity with diabetes can both lead to a more severe progression of COVID-19 [7, 91]. A study by Barron *et al.* found that there was also a higher risk of mortality in both type 1 and type 2 diabetics who were diagnosed with COVID-19 [92]. In their analysis, Wang *et al.* hypothesized that since the surfactant production and the vascular beds in diabetics are often affected, they typically have a poor pulmonary function [93]. They also hypothesized that the high sugar level and lower insulin level can affect multiple innate immune responses that can lead to an impaired function of cells responsible for improving an immune protection in the alveoli and impact the proper formation of Th1 and Th2 cells. These make diabetics more prone to multiple pulmonary infections as they will have a slower and weaker response to combat them [93–101]. Further research should also be encouraged from hospitals to publish data on diabetics having different anti-diabetic treatments so that the relationship between anti-diabetic treatments and severity of COVID-19 can also be explored in the future [102]. During the pre-COVID-19 era, several patient groups were also associated with higher risks and worse outcome of diabetic ketoacidosis [103]. Research comparing changes in severity and mortality in those specific patient groups can also help physicians prioritize their resources for a better clinical outcome.

The higher risks of severe COVID-19 in patients with a history of cerebrovascular disease have been linked with several possible pathophysiological pathways. Most stroke patients have underlying conditions such as diabetes and hypertension. They are also chronically using multiple drugs that can lead to multiple pathways in the pathogenesis of SARS-CoV-2. Several cases of new onset of stroke

have also been reported in COVID-19 patients. A study by Merkler *et al.* found that COVID-19 had a 7.6 times higher risk of causing a new stroke than an influenza infection [104]. Fifi *et al.* warned that there are many new cases of stroke in young patients who initially presented with mild respiratory symptoms [105]. As COVID-19 is associated with multiple laboratory changes that can predispose previous and new patients with cerebrovascular insults, physicians need to be on the watch-out for neurological changes and symptoms [106–108].

Since COVID-19 is a new disease, the progress in understanding the impact and risk factors, as well as changes in management protocols of at-risk patients, have been done in a step-by-step manner based on findings from multiple cellular studies and pooled analyses. Initially, there were several arguments for and against the continued use of ACEI and ARBs among hypertensive patients, diabetics and also patients with a history of cerebrovascular disease [109, 110]. Both the European Society of Hypertension and the American Heart Association advised that these medications should not be discontinued as the benefits outweigh the risks [111]. Protocols involving the use and effects of corticosteroids among diabetics were also evaluated. High doses lead to a rise in blood glucose levels in up to 80% of diabetics who were COVID-19 positive and were associated with a higher mortality rate. With the higher severity of COVID-19, the use of anti-diabetic medications such as DPP4 Inhibitors and their effects are currently being studied [112–114]. While multiple changes have been established in the effective management of new cases of stroke in COVID-19 positive patients, guidelines for COVID-19 patients with a past history of cerebrovascular disease have followed the hypertensive and the diabetic protocols due to their close relationship in the pathophysiology [115–124].

In conclusion, our study provided a fresh view with a larger sample size on three main risk factors that can cause COVID-19 patients to have a severe outcome from the disease. We strongly believe that these preliminary reports can help physicians prioritize their limited healthcare resources and be prepared in advance for any severe outcome of the disease.

Conflict of interest

The authors declare no conflict of interest.

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