

Short Communication

Comparative Impact of Cerebrovascular and Cardiovascular Diseases to Other Comorbidities in COVID-19 Poor Outcomes: A Systematic Review and Meta-Analysis

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- Clinical characteristics
- Cerebrovascular diseases

Abstract

Background: Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease that presents from mild cases to severe forms. Comorbidities, especially cardiovascular diseases, were associated with poor outcome. The virus uses angiotensin converting enzyme 2 (ACE-2) receptor to invade cells. Cerebrovascular diseases have a more conflicting relationship with ACE-2 regulation. The objective of this study was to evaluate the impact of Cerebrovascular and Cardiovascular diseases to Non-cardiovascular diseases (Chronic pulmonary obstructive diseases, chronic kidney diseases, cancer, liver diseases, etc) and compare Cerebrovascular diseases to Other cardiovascular diseases (Cardiac diseases, hypertension and diabetes) in COVID-19 poor outcomes.

Methods: We searched PubMed, EMBASE and Scopus including english language studies from 2020. We selected studies considering COVID-19 patients with poor outcome (severe form and non-survivors patients). Then we compared the prevalence of cerebrovascular diseases x Non-cardiovascular diseases; all cardiovascular diseases x Non-cardiovascular diseases and cerebrovascular diseases x other cardiovascular diseases. The Cerebrovascular diseases were included in all cardiovascular and excluded in other cardiovascular diseases groups.

Results: We found 1155 studies, including 18 studies in the quantitative analysis (meta-analysis). Cerebrovascular diseases and All Cardiovascular diseases were more frequent than Non-cardiovascular diseases in COVID-19 poor outcome. [RR 1.39 CI 95% (1.20-1.63), $p < 0.0001$, $I^2 = 15\%$, fixed effects; RR 1.10 CI 95% (1.01-1.21), $p = 0.04$, $I^2 11\%$, fixed effects]. The prevalence of cerebrovascular diseases was disproportionately increased even when compared to other cardiovascular diseases. [RR 1.34 CI 95% (1.13-1.60), $p = 0.001$, $I^2 57\%$, random effects].

Conclusion: Cerebrovascular and cardiovascular diseases were more frequent in COVID-19 patients with poor outcomes than Non-cardiovascular diseases. Also, cerebrovascular diseases were disproportionately represented in poor outcome than other cardiovascular diseases. We consider that Clinicians should be aware that a cerebrovascular disease is an important risk factor for severe disease and deaths in COVID-19 pandemic.

ABBREVIATIONS

COVID-19: Coronavirus Disease 2019; ACE-2: Angiotensin Converting Enzyme 2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic infectious disease of the lower respiratory tract. In mild cases, common symptoms are fever and cough. In severe cases, patients may develop acute respiratory distress syndrome and multi-organ failure, leading to intensive care unit admissions, mechanical ventilation and death [1,2].

Previous studies showed that people with chronic underlying diseases had a greater risk of developing severe COVID-19 and a higher mortality rate. The most common comorbidities associated with poor prognosis were cardiovascular diseases: hypertension, diabetes, cardiac and cerebrovascular diseases [3-6].

Coronavirus uses angiotensin converting enzyme 2 (ACE-2) receptor to promote cell invasion. Hypertension, diabetes and heart failure were associated with ACE-2 upregulation and, hence, may justify worse clinical outcomes in these patients [7,8].

However, cerebrovascular diseases have a more conflicting relationship with ACE-2. In acute stroke, human and animal

studies showed a decrease in serum ACE-2 activity. That was not related to arterial pressure. This phenomenon was accompanied by an increase in brain activity of this enzyme. Nevertheless, after three days, a rebound increase in serum ACE-2 levels activity was seen[9,10].

Considering ACE-2 relevance in COVID-19, we hypothesized cardiovascular diseases would be more important than other comorbidities to predict COVID-19 poor prognosis. Particularly, as cerebrovascular diseases have a conflicting relationship with ACE-2, the objective of this study was to evaluate the impact of Cerebrovascular and Cardiovascular diseases to Non-cardiovascular diseases (Chronic pulmonary obstructive diseases, chronic kidney diseases, cancer, liver diseases, etc) and also compare Cerebrovascular diseases to Other cardiovascular

diseases (Cardiac diseases, hypertension and diabetes) in COVID-19 poor outcomes.

MATERIALS AND METHODS

We used the Preferred Reporting Items for Systematic Review and Meta-Analysis PRISMA statement as a reference [11]. The review protocol was not previously registered. We performed a comprehensive systematic literature search using Pubmed, Embase and Scopus, including English language studies published in 2020. The systematic literature search was finalized on April 18th, 2020. The screening included a Boolean expression with the following key-words: ("COVID-19" OR "SARS-CoV-2" OR "Coronavirus disease 2019" OR "novel coronavirus") AND ("clinical findings" OR "clinical characteristics" OR "clinical features" OR "neurological manifestations" OR "retrospective*")

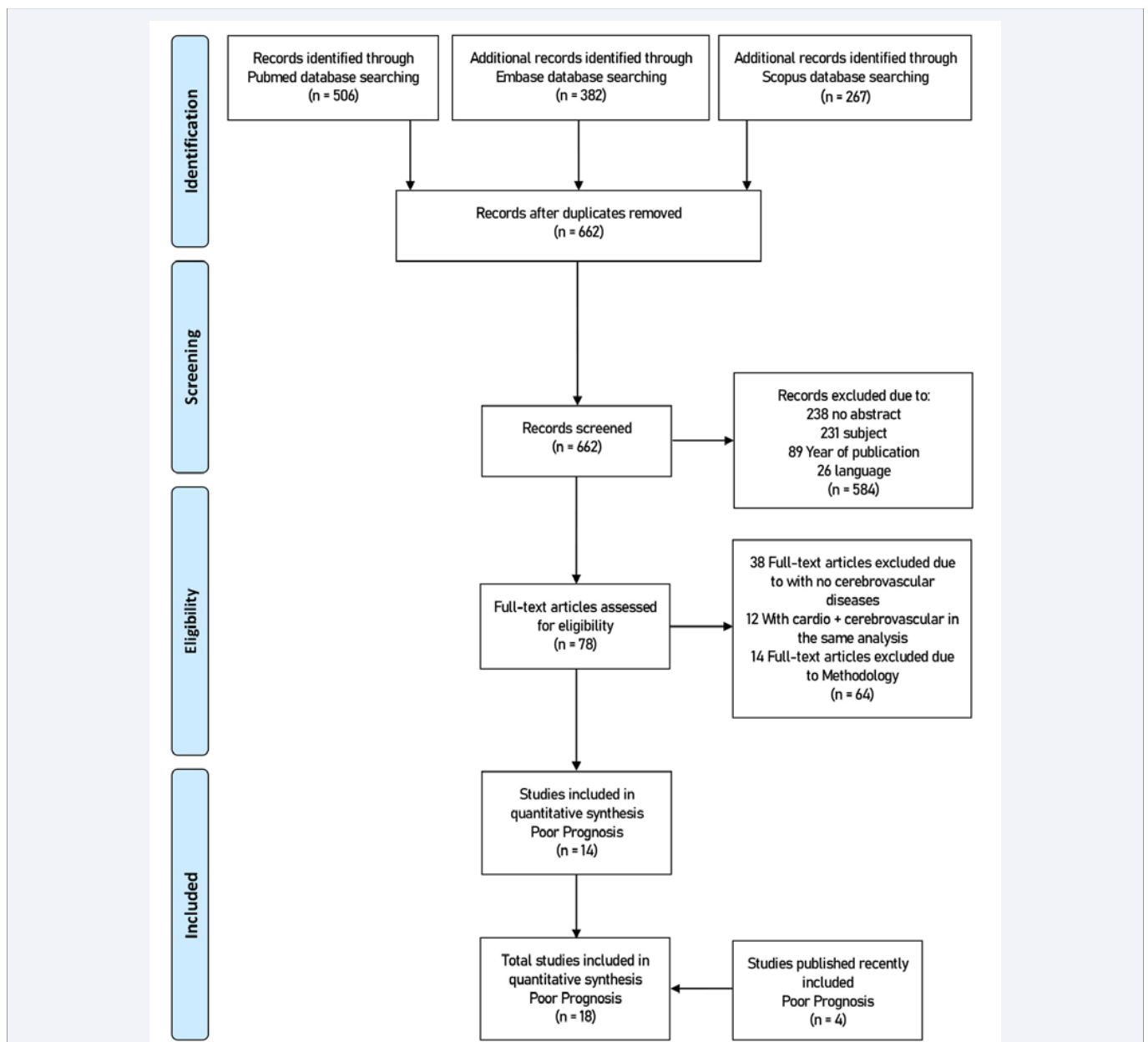


Figure 1 Flowchart diagram shows full screen of the meta-analysis following eligibility criteria based on PRISMA statement.

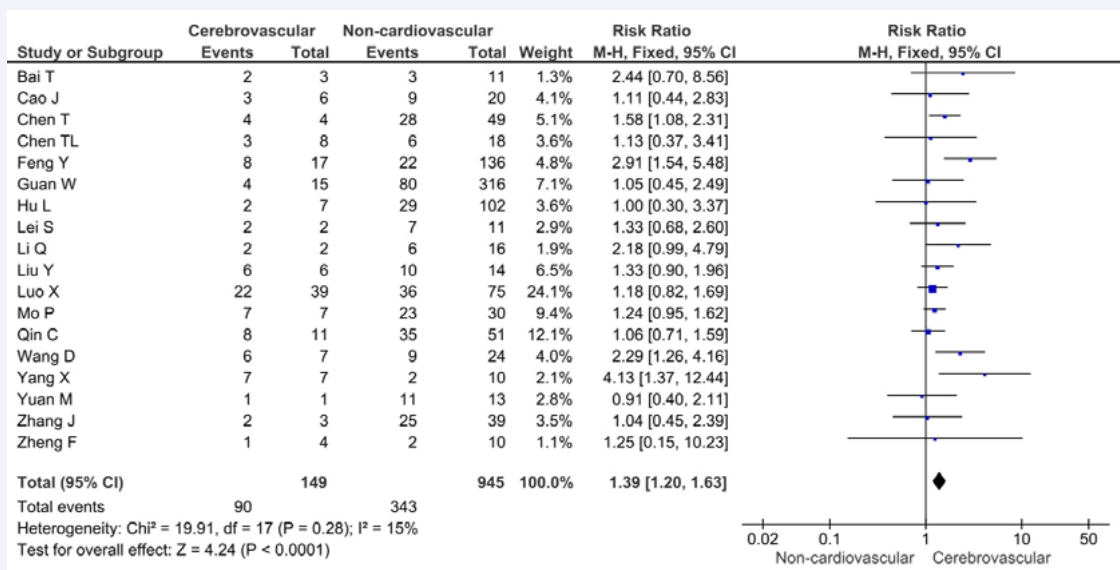


Figure 2 Forest Plot shows the prevalence of Cerebrovascular diseases x Non-cardiovascular diseases in patients diagnosed with COVID-19.

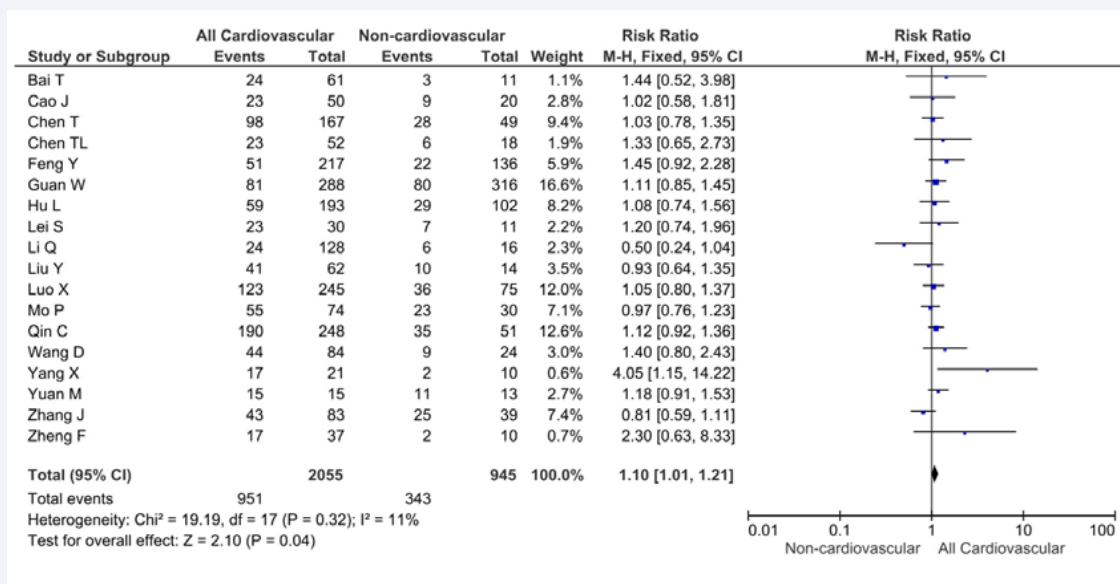


Figure 3 Forest plot shows the prevalence of All cardiovascular diseases x Non-cardiovascular diseases in patients diagnosed with COVID-19.

OR “observational*” OR “cerebrovascular*”). We selected studies considering COVID-19 patients with poor outcome, defined as a combined endpoint of death or severe disease. We defined “severe disease” as patients that required mechanical ventilation and intensive care unit admission. Data extracted from selected studies were: first author, year, number of patients, sample, age, sex, comorbidity and clinical outcome. No method was used to assess the risk of bias in individual studies.

We compared the prevalence of comorbidities in patients diagnosed with COVID-19 that presented poor outcome (severe form and non-survivors patients) in four groups: Cerebrovascular diseases; All cardiovascular diseases (cardiac diseases, cerebrovascular diseases, hypertension and diabetes); Non-cardiovascular diseases (Chronic pulmonary obstructive

diseases, chronic kidney diseases, cancer, liver diseases, etc) and Other cardiovascular diseases (Cardiac diseases, hypertension and diabetes), excluding cerebrovascular diseases from this group.

The risk ratio (RR) was the principal summary measure. We used the I² statistics to assess the heterogeneity. The fixed effect model was performed if i² was up to 50%. Otherwise, we preferred the random effect model.

RESULTS AND DISCUSSION

After initial database searching, we found 1155 studies, excluding 493 duplicates. After screening the title/abstract, 584 records were excluded: 238 for no abstract available, 231 for different subject, 89 for publication year before 2020 and 26

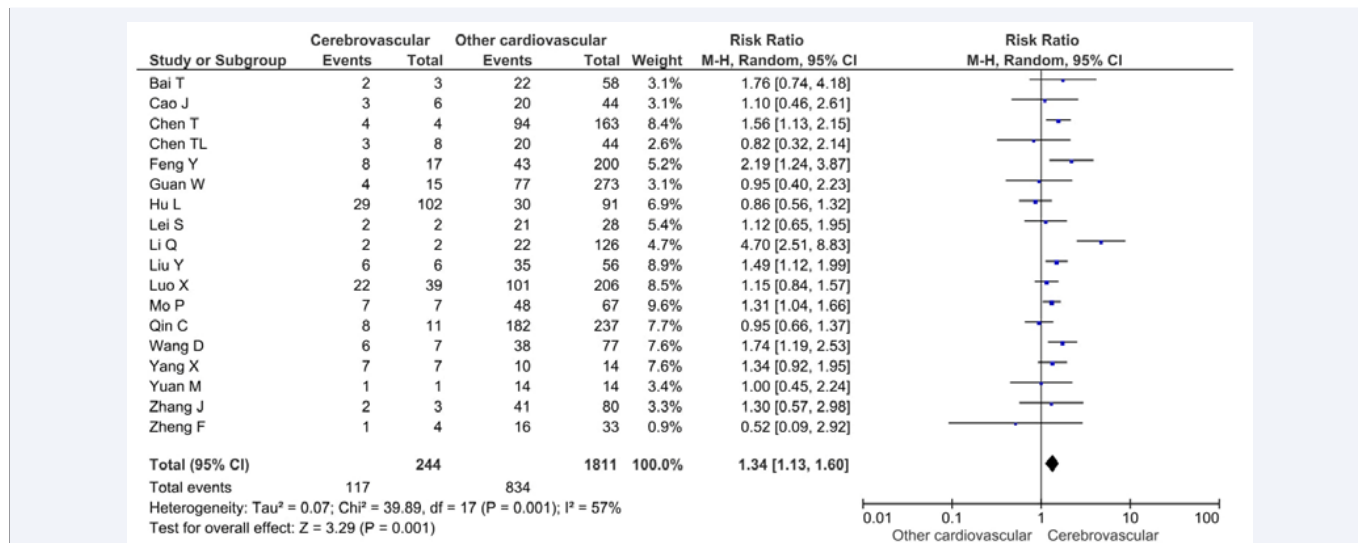


Figure 4 Forest plot shows the prevalence of Cerebrovascular diseases x Other Cardiovascular diseases in patients diagnosed with COVID-19.

Table 1: Characteristics of studies in patients diagnosed with COVID-19 with poor outcomes (Severe cases and Non-survivors).

Study	Year	Country	Sam- ple	Age	Sex		All cardiovascular		Cerebrovascular		Non-cardiovascular		Study Type
					Men	Women	Poor Outcome	Total	Poor Ou- tcome	Total	Poor Out- come	Total	
Bai T, et al	2020	China	127	55	80	47	24	61	2	3	3	11	Case series
Cao J, et al	2020	China	102	54	53	49	23	50	3	6	9	20	Case series
Chen T, et al	2020	China	274	62	171	103	98	167	4	4	28	49	Case series
Chen TL, et al	2020	China	55	74	34	11	23	52	3	8	6	18	Case series
Feng Y, et al	2020	China	406	59	223	183	32	217	1	17	22	136	Case series
Guan W, et al	2020	China	1099	47	640	459	81	288	4	15	80	316	Case series
Hu L, et al	2020	China	323	61	166	157	59	193	2	7	29	102	Case series
Lei S, et al	2020	China	34	55	14	20	23	30	2	2	7	11	Case series
Li Q et al	2020	China	325	51	167	158	24	128	2	2	6	16	Case series
Liu Y et al	2020	China	109	55	59	50	41	62	6	6	10	14	Case series
Luo X et al	2020	China	403	53	193	210	123	245	22	39	36	75	Case series
Mo P et al	2020	China	155	54	86	69	55	74	7	7	23	30	Case series
Qin C et al	2020	China	452	58	235	217	190	248	8	11	35	51	Case series
Wang D, et al	2020	China	138	56	75	65	44	84	6	7	9	36	Case series
Yang X, et al	2020	China	52	59	35	17	17	21	7	7	2	10	Case series
Yuan M, et al	2020	China	27	60	12	15	15	15	1	1	11	13	Case series
Zhang J, et al	2020	China	140	57	71	69	43	83	2	3	25	39	Case series
Zheng F, et al	2020	China	161	45	80	81	17	37	1	4	2	10	Case series

with no English language. After assessing the full-text article, 64 studies were excluded: 38 had no measuring of cerebrovascular diseases, 12 showed cardiovascular and cerebrovascular diseases in the same analysis and 14 studies with no proper methods. Finally, we included 14 studies in the quantitative analysis (meta-analysis) representing patients diagnosed with COVID-19 with poor outcome. After the screening we included 4 more studies that were published recently. Figure 1 represents study selection in a flow diagram.

Our meta-analysis included 18 studies published in 2020, all from China, published in 2020, including a total of 4382 confirmed COVID patients, 149 with history of cerebrovascular diseases (3,4%), medium age 55 years. All were retrospective observational studies (case series). Study characteristics are shown in Table 1.

Cerebrovascular diseases and all cardiovascular diseases were more frequent than Non-cardiovascular diseases in COVID-19 poor outcome. [RR 1.39 CI 95% (1.20-1.63), $p < 0.0001$, $I^2 = 15\%$, fixed effects; RR 1.10 CI 95% (1.01-1.21), $p = 0.04$, $I^2 11\%$, fixed effects]. We found that Cerebrovascular diseases prevalence was disproportionately increased in poor outcome COVID-19 patients, even when compared to Other cardiovascular diseases [RR 1.34 CI 95% (1.13-1.60), $p = 0.001$, $I^2 57\%$, random effects]. Figures 2,3 and 4 represents statistics in the forest plots.

Cardiovascular diseases are common in general population. Hence, our goal was to evaluate if cardiovascular and cerebrovascular diseases would be not only frequent, but also disproportionately represented in poor outcome in COVID-19 patients.

We found only Chinese articles and the median age of our patients was 55 years. Thus, we chose the chinese prevalence of diseases in 50-69 years old people as a baseline to comparison. Data from the Global Burden of Disease database is represented In Table 2 [12]. The total prevalence of all cardiovascular diseases is higher than the combined prevalence of the non-cardiovascular comorbidities in our meta-analysis (cancer + kidney + liver + lung diseases). These differ from the Chinese prevalence [12]. However, cardiovascular diseases were even more frequent in poor outcome COVID-19 patients, suggesting they were disproportionately represented in this population. Our finding is consistent with another meta-analysis that reported an increased risk for severe cases of COVID-19 in patients with cardiovascular disorders [13].

We also found that cerebrovascular diseases were disproportionately represented in poor outcome COVID-19 patients, being associated with severe disease and deaths in the COVID-19 pandemic [14]. In our meta-analysis, cerebrovascular diseases were even more disproportionately represented in poor outcome COVID-19 than any other comorbidity, including other cardiovascular diseases.

This study has some limitations, including no risk of bias or subgroup analysis. All the studies were from the same country area in China with no broad geographic approach. Also, the studies included only retrospective case series which infers less quality to the evidence. There were no specifications to the type of cerebrovascular or cardiovascular disease in this analysis. It's

Table 2: Prevalence of cardiovascular diseases, cerebrovascular diseases and non-cardiovascular diseases in China in 50-69 years-old – Cases per 100.000 (Global Burden of Diseases).

Cardiovascular diseases	14.933
Stroke	5.080
Diabetes	11.429
Total Cardiovascular diseases (Stroke included)	31.442
Neoplasm	2.770
Cirrhosis and other chronic liver diseases	40.030
Chronic kidney disease	14.876
Chronic obstructive pulmonary diseases (COPD)	8.234
Total Non-cardiovascular diseases	65.910

also important to consider that some important commorbidities for progressive and severe forms of COVID-19 as smoking, pregnancy and old age as other risky conditions were not included in the outcomes [15]. We consider a need for prospective studies associated with COVID-19 outcomes.

CONCLUSION

Cerebrovascular and Cardiovascular diseases were more frequent in COVID-19 patients with poor outcomes than Non-cardiovascular diseases. Also, cerebrovascular diseases were even more disproportionately represented in poor outcome than other cardiovascular diseases in COVID-19 patients. We consider that Clinicians should be aware that cerebrovascular diseases are an important risk factor for severe disease and deaths in COVID-19 pandemic.

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