



# Cerebrovascular disease is associated with the risk of mortality in coronavirus disease 2019

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Received: 10 May 2020 / Accepted: 21 June 2020 / Published online: 30 June 2020  
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Dear Editor,

Recently, the paper by Wang et al. demonstrated a significant relationship between cerebrovascular disease and patients with severe coronavirus disease 2019 (COVID-19) (OR = 3.89, 95% CI: 1.64–9.22,  $P = 0.002$ ) in a meta-analysis based on three published studies [1]. To our knowledge, there have been several published articles reporting the association between cerebrovascular disease and the risk of mortality in COVID-19 patients [2–6]. However, the conclusions are not consistent. Therefore, it is required to clarify the association of the cerebrovascular disease with the risk of mortality in COVID-19 patients by using a systematically quantitative meta-analysis.

Relevant studies were extracted by systematic retrieval of PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) up to date to April 30, 2020. The searching terms used were as follows: “coronavirus” or “COVID-19” or “SARS-CoV-2” or “2019-nCoV” and “clinical” and “mortality” or “outcome.” Duplicate results were removed. All studies were evaluated for eligibility by two independent reviewers (Ying Wang and Li Shi). Inclusion criteria are the following: (1) studies reporting extractable data on a past history of cerebrovascular disease in laboratory-confirmed COVID-19 patients and (2) compared patients between survivors and non-survivors. Exclusion criteria are as follows: (1) reviews and case reports and (2) non-survivor subgroup was not included in the study. Odds ratio (OR) with its 95% confidence intervals (CI) was applied to estimate the combined effects. Heterogeneity was evaluated with the  $I^2$

test. A fixed-effects model was selected to compute the combined effects if there was no obvious heterogeneity among studies ( $I^2 \leq 50\%$ ). Otherwise, a random-effects model was applied [7]. The possibility of publication bias was checked by using Egger’s test and Begg’s test [8]. Sensitivity analysis was carried out by excluding studies successively [9]. The statistical analysis was carried out using the Stata 11.2 (StataCorp, College Station, TX), and the  $P$  value  $< 0.05$  was considered to be statistically significant.

We found a total of 966 records, and 741 remained after the removal of duplicates. Forty-two records remained after reading the title and abstract. After reading the full text, we excluded 34 studies that did not report a past history of cerebrovascular disease and finally included eight articles for our meta-analysis. Included studies grouped into survival and non-survival groups (six articles), recovered and non-survival groups (one article), and discharged and non-survival groups (one article). The essential characteristics are presented in Table 1.

Seven studies compared cerebrovascular disease in non-survival vs. survival patients with a total of 1374 confirmed COVID-19 patients including 392 (28.5%) non-survival cases. A past history of cerebrovascular disease was reported in 126 patients (9.2%), of whom 70 (55.6%) patients were classified as non-survivors. Besides, one study by Chen et al. individually provided a hazard ratio (HR) (HR = 4.28, 95% CI: 1.07–8.94) for cerebrovascular disease and mortality of COVID-19 patients [10].

Our meta-analysis showed that cerebrovascular disease was significantly associated with an increased risk of mortality in COVID-19 patients on the basis of a fixed-effects model (OR = 4.78, 95% CI: 3.24–7.03,  $P < 0.001$ ) (Fig. 1a). Heterogeneity was not observed presently ( $I^2 = 22.4\%$ ,  $P = 0.251$ ). The sensitivity analysis indicated that the combined OR did not change significantly after deleting each study one by one. Although the combined OR was declined (OR = 3.319, 95% CI: 1.98–5.57,  $P < 0.001$ ) after deleting Li Juyi et al.’s study [5], the result still indicated that cerebrovascular

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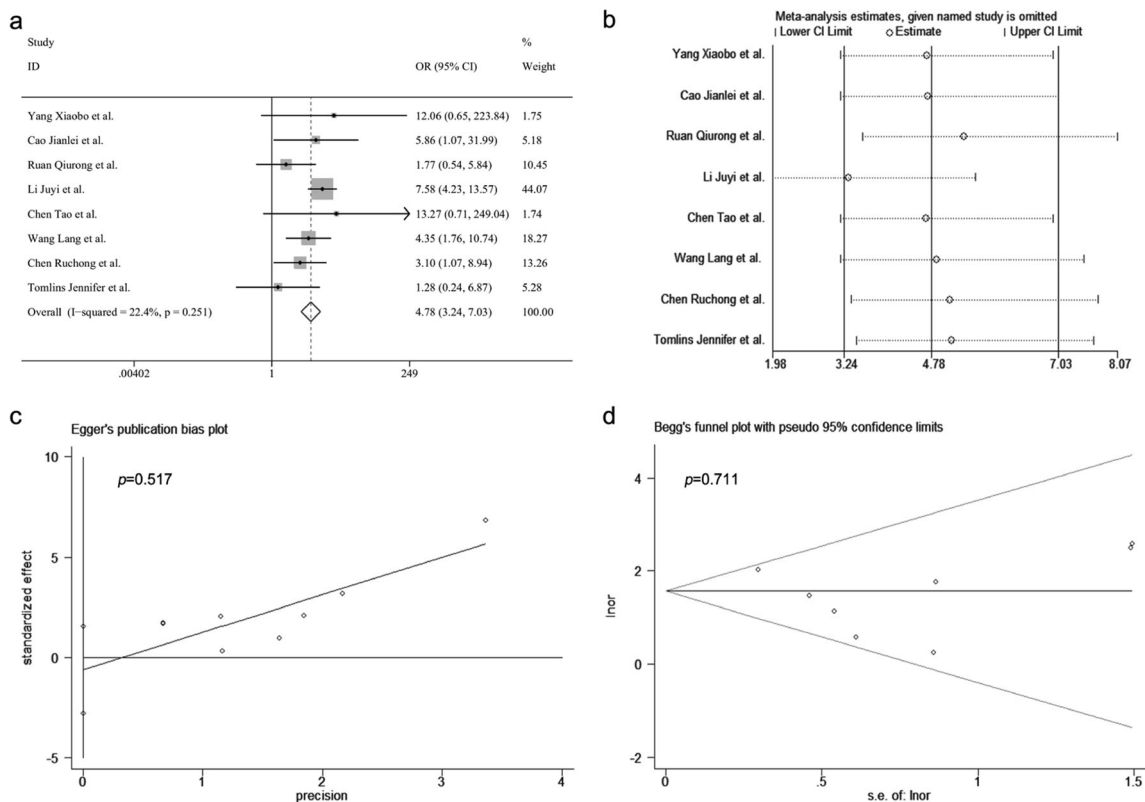
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**Table 1** Characteristics of the included studies

Authors	Location	Group	Samples	Non-survival patients			Survival patients		
				Age	Male	Cerebrovascular/ n	Age	Male	Cerebrovascular/ n
Yang Xiaobo et al. (PMID: 32105632)	China	Survival vs. non-survival	52	64.6 (11.2)	21 (66%)	7/32	51.9 (12.9)	14 (70%)	0/20
Cao Jianlei et al. (PMID: 32239127)	China	Survival vs. non-survival	102	72 (63–81)	13 (76%)	3/17	53 (47–66)	40 (47%)	3/85
Ruan Qiurong et al. (PMID: 32253449)	China	Discharged vs. non-survival	150	67 (15–81)	49 (72%)	7/68	50 (44–81)	53 (65%)	5/82
Li Juyi et al. (PMID: 32324209)	China	Survival vs. non-survival	362	72 (64.5–82)	50 (65%)	37/77	65 (57.5–71)	139 (48%)	31/285
Chen Tao et al. (PMID: 32217556)	China	Recovered vs. non-survival	274	68 (62–77)	83 (73%)	4/113	51 (37–66)	88 (55%)	0/161
Wang Lang et al. (PMID: 32240670)	China	Survival vs. non-survival	339	76 (70–83)	39 (60%)	10/65	68 (64–74)	127 (46%)	11/274
Chen Ruchong et al. (PMID: 32304772)	China	Survival vs. non-survival	1950	69 (51–86)	30 (60%)	6/50	NR	NR	NR
Tomlins Jennifer et al. (PMID: 32353384)	UK	Survival vs. non-survival	95	77 (72–85)	12 (60%)	2/20	74 (56–82)	48 (64%)	6/75

All values are *n* (%), mean (SD), and median (IQR)  
NR not reported



**Fig. 1** Odds ratio (OR) with its 95% confidence intervals (CI) for cerebrovascular disease (a), sensitivity analysis for cerebrovascular disease (b), publication bias assessment: Egger's test (c) and Begg's test (d)

disease was associated with an increased risk of mortality in COVID-19 patients (Fig. 1b). Hence, we can consider our result to be robust. The results of Egger's test ( $P = 0.517$ ) (Fig. 1c) and Begg's test ( $P = 0.711$ ) (Fig. 1d) indicated there was no publication bias presently.

To our knowledge, a previous meta-analysis by Aggarwal et al. did not observe a significant association between a past history of cerebrovascular disease and the risk of mortality in COVID-19 patients based on two published studies (OR = 2.33, 95% CI: 0.77–7.04) [11]. However, in our present meta-analysis based on eight published studies, the cerebrovascular disease was identified to be significantly associated with an increased risk of mortality in COVID-19 patients. Some patients with COVID-19 have neurological symptoms, such as headache, anosmia, dysgeusia, dizziness, and impaired consciousness [12]. There is evidence that SARS-CoV-2 has neuro-invasive abilities and might spread from the respiratory system to the central nervous system [13, 14]. COVID-19 may also predispose cerebrovascular diseases due to inflammation, hypoxia, and diffuse intravascular coagulation [15]. Thus, clinicians should strengthen the monitoring of COVID-19 patients with the cerebrovascular disease.

This study has several limitations. Firstly, except for one article from the UK, most of the articles came from China. Secondly, some patients had more than one coexisting illness in our included studies. Hence, our conclusion needs to be treated with caution and further analyses including more studies are needed to verify our findings.

**Funding information** This work was supported by a grant from the National Natural Science Foundation of China (grant number 81973105).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** Not Applicable.

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