Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Association of Cerebrovascular Disease with Adverse Outcomes in COVID-19 Patients: A Meta-Analysis Based on Adjusted Effect Estimates

Jie Xu,* Wenwei Xiao,* Xuan Liang,* Peihua Zhang,* Li Shi,* Ying Wang,* Yadong Wang,† and Haiyan Yang,*

Objective: The aim of this study was to address the association between cerebrovascular disease and adverse outcomes in coronavirus disease 2019 (COVID-19) patients by using a quantitative meta-analysis based on adjusted effect estimates. *Method:* A systematic search was performed in PubMed, Web of Science, and EMBASE up to August 10th, 2020. The adjusted effect estimates were extracted and pooled to evaluate the risk of the unfavorable outcomes in COVID-19 patients with cerebrovascular disease. Subgroup analysis and meta-regression were also carried out. *Results:* There were 12 studies with 10,304 patients included in our meta-analysis. A significant trend was observed when evaluating the association between cerebrovascular disease and adverse outcomes (pooled effect = 2.05, 95% confidence interval (CI): 1.34−3.16). In addition, the pooled effects showed that patients with a history of cerebrovascular disease had more likelihood to progress fatal outcomes than patients without a history of cerebrovascular disease (pooled effect = 1.78, 95% CI: 1.04−3.07). *Conclusion:* This study for the first time indicated that cerebrovascular disease was an independent risk factor for predicting the adverse outcomes, particularly fatal outcomes, in COVID-19 patients on the basis of adjusted effect estimates. Well-designed studies with larger sample size are needed for further verification.

Key Words: COVID-19—Cerebrovascular disease—Adverse outcomes—Meta-analysis—Adjusted effect estimate

Introduction

The disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). Both the morbidity and mortality of COVID-19 were so high that the health system of many countries was on the verge of collapse.[1] To help clinicians better allocate health resources, many researchers devoted themselves to explore the biomarkers and clinic features which might be useful predictors for disease progression.[2−4] Recently, an article published in the International Journal of Stroke by Aggarwal et al.[5] indicated that cerebrovascular disease was associated with increased disease severity in COVID-19 patients. The authors evaluated the common risk estimates by unadjusted effects and found that there was no significant association between cerebrovascular disease and fatal outcomes in COVID-19 patients (odds ratio (OR) = 2.33, 95% confidence interval (CI): 0.77−7.04). Coincidentally, a paper reported by Chen et al.[6] illustrated that cerebrovascular disease might increase the risk of death in COVID-19 patients in univariable analysis (OR = 3.258, 95% CI: 1.658−6.402), but in multivariable analysis, it might not be associated with fatal outcome in COVID-19 patients (OR = 1.379, 95% CI: 0.650−2.926). This suggested that the association between cerebrovascular disease and adverse outcomes in COVID-19 patients might be affected by many confounders such as age, gender, and other

From the *Department of Epidemiology, School of Public Health, Zhengzhou University, No. 100 of Science Avenue, Zhengzhou 450001, China; and †Department of Toxicology, Henan Center for Disease Control and Prevention, Zhengzhou 450016, China.

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Address correspondence to Haiyan Yang, Department of Epidemiology, School of Public Health, Zhengzhou University, No. 100 of Science Avenue, Zhengzhou 450001, China. E-mail: yhy@zzu.edu.cn.

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comorbidities.[7–10] Therefore, this meta-analysis was performed to evaluate the association between cerebrovascular disease and adverse outcomes in COVID-19 patients on the basis of adjusted effect estimates.

Methods

Search strategy

A comprehensive retrieve was conducted in PubMed, Web of Science, and EMBASE up to August 10th, 2020 using the following search terms: "COVID-19", "coronavirus", "SARS-CoV-2", "2019-nCoV", "cerebrovascular disease", "stroke", "cerebral infarction", "brain infarction", "cerebrovascular disorder", "cerebral atherosclerosis", "fatality", "mortality", "death", "severe", "critical", "severity", and "outcome". References to previous similar studies were also considered.

Inclusion and exclusion criteria

Studies were taken into account if they met all of the following criteria: (1) the included population should be patients with confirmed COVID-19; (2) the method must include multivariate analysis such as cox regression, logistic regression, and so on; (3) the results of the study included the association between cerebrovascular disease (stroke, cerebral infarction, brain infarction, cerebrovascular disorder, cerebral atherosclerosis) and the adverse outcomes (severe, critical, and fatal outcomes) in patients with COVID-19; (4) complete and available data were reported in those studies. Studies with larger sample sizes were selected if the exposed population of them originated from the same hospital within an overlapping period. Duplicates, comments, letters, conference records, and editorial were excluded.

Data extraction and quality assessment

Two investigators extracted the following information independently: first author, country, date of data collection, source of data, percentage of cerebrovascular disease patients, adjusted effect estimates and confounders. When a paper reported both multivariable adjusted hazard ratio (HR) and OR, it was preferred to include HR because cox regression took time into account. Two researchers negotiated to resolve it in case of disagreement. The quality of included studies was assessed by investigators according to the Newcastle-Ottawa Scale.[11] The studies with a score above 7 were considered to be high quality.

Statistical analysis

The pooled effects were calculated by multivariable adjusted effect estimates (OR and HR) and 95% CI,

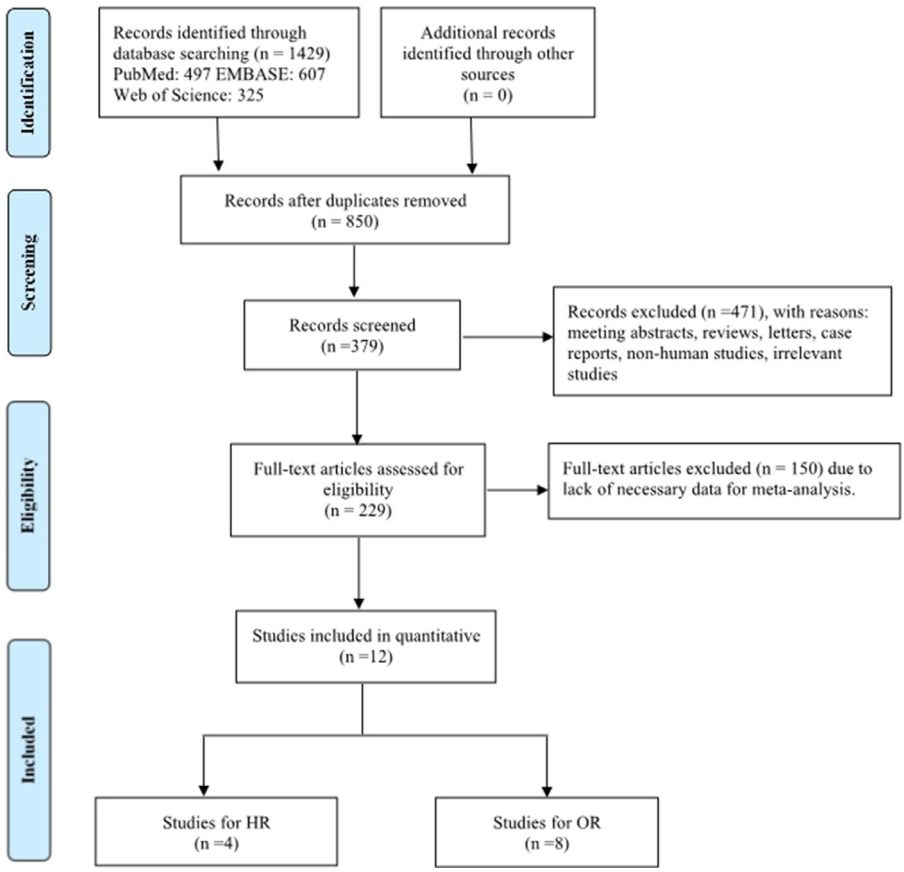

Fig. 1. *Flow diagram of the publication search and selection process.*

Table 1. *Main characteristics of the included studies.*

Author	Source of data	Country	Date of data collection	Patients (n)	Age (years)	Male (%)	Study design	CVA (%)	Adjusted HR/OR	Confounders	NOS
Yan X[17]	Wuhan Third Hospital & Tongren Hospital of Wuhan University	China	Jan 11-Mar 24	1004	62	48.3	R	2.2	OR 2.606 (0.988-6.870)	NLR>11.75, high sensitivity CRP, NT-proBNP, blood urea nitrogen, HTN, respiratory failure, digestive system disease	7
Zhao M[18]	Renmin Hospital of Wuhan University	China	Jan 1-Feb 14	1000	61	46.6	R	3.2	HR 2.1 (1.157-3.809)	HTN, diabetes, CHD, COPD, chronic renal disease, chronic liver disease, malignancy	7
Choi MH[20]	Armed Forces Daegu Hospital	Korea	Mar 5-Mar 18	293	29	73	R	1.7	HR 4.71 (1.13-19.62)	Age, gender, healthcare-acquired infection, ECOG performance status, time from disease confirmation to admission, time from symptom onset to admission and confirmed, Initial symptoms, Initial signs, comorbidities, prior history of drug use, KCDC classification I/Ⅱ, CT score, MuLBSTA, CURB65, pneumonia severity index, age-adjusted charlson comorbidity index	7
Guan WJ[21]	575 hospitals	China	Dec 11-Jan 31	1099	47	58.2	R	1.4	HR 1.73 (0.73-4.04)	NR	8
Magleby R[22]	New York-Presbyterian Hospital/Weill Cornell Medical Center	USA	Mar 30-Apr 30	678	NR	38.93	R	8.11	OR 1.24 (0.54-2.86)	Age, white race, obesity, CAD, congestive heart failure, HTN, COPD, use of oral steroids as an outpatient, days of symptoms prior to admission, symptoms on admission, highest level of supplemental oxygen within 3 hours of arrival to the ED, chest x-ray findings, viral load by nasal pharyngeal swab	8

(*Continued*)

Table 1 (*Continued*)

Author	Source of data	Country	Date of data collection	Patients (n)	Age (years)	Male (%)	Study design	CVA (%)	Adjusted HR/OR	Confounders	NOS
Pettit NN[23]	The University of Chicago Medical Center	USA	Mar 1-Apr 18	238	58.5	47.5	R	5(Stroke)	OR 0.9 (0.1-6.5)	Obesity, age, gender, HTN, diabetes, pulmonary disease, CVD, venous thromboembolism, hyperlipidemia, cancer, kidney disease, CVD	8
Chen J[6]	Tongji Hospital	China	Jan 8-Mar 27	3309	62	49.62	R	3.9	OR 1.25 (0.73-2.13)	Age, gender, HTN, diabetes, CVD, malignancy, CKD, COPD, days from onset to clinics, days from onset to admission	7
Chen F[19]	The Central Hospital of Wuhan	China	Jan 1-Feb 15	660	55	44.7	R	7.9(Cerebral infarction)	OR 4.257 (1.638-11.063)	Age, HTN, SOFA, CRP	7
Hwang JM[24]	Kyungpook National University Hospital and Kyungpook National University Chilgok Hospital	Korea	Feb 1-Mar 25	103	67.62	50	R	4(Stroke)	HR 0.279 (0.021−3.747)	Age, diabetes, chronic lung disease, CVD, alzheimer's dementia	8
Yang Y[25]	Tongji hospital in Wuhan	China	Jan 1-Mar 30	170	66	49	R	9	OR 4.4 (0.99-21.84)	Age, gender, comorbidity (CVD, COPD, CKD, CLD, malignancy), history of surgery, high SAT, high VAT, visceral adiposity, high SMA, high IMF deposition	8
Atkins J L[26]	UK Biobank	UK	Mar 16-Apr 26	268	74.3	30.6	R	4.5(Stroke)	OR 0.93 (0.4-2.17)	Age, gender, ethnicity, education, prevalent disease (CHD, atrial fibrillation, HTN, diabetes (type 2), CKD, depression, dementia, asthma, COPD, osteoporosis, osteoarthritis), previous disease/condition (delirium, pneumonia, falls/fragility fractures)	8

Table 1 (*Continued*)

Author	Source of data	Country	Date of data collection	Patients (n)	Age (years)	Male (%)	Study design	CVA (%)	Adjusted HR/OR	Confounders	NOS
Xiong TY[27]	51 hospitals within Sichuan province	China	Jan 16-Mar 10	472	43	53	R	1.91	OR 4.49 (0.67-29.82)	Age, HTN, hemoglobin, oxygenation index on admission, neutrophils, LDH	7

NLR, neutrophil to lymphocyte ratio; NR, not reported; HTN, hypertension; P, prospective; R, retrospective; HR, hazard ratio; OR, odds ratio; CI: confidence interval; CHD, coronary heart disease; CVA, cerebrovascular disease; CVD, cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney diseases; CLD, chronic liver diseases; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; SOFA, Sequential Organ Failure Assessment; SAT, subcutaneous adipose tissue area; VAT, visceral adipose tissue area; SMA, skeletal muscle area; IMF, intramuscular fat; KCDC, Korea Centers for Disease Control and Prevention; ECOG, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NOS, Newcastle-Ottawa Scale.

assessing the association between cerebrovascular disease and adverse outcomes in COVID-19 patients. Cochran's Q-statistic and I^2 test were conducted to evaluate the heterogeneity among studies. The random-effects model was applied if heterogeneity existed across studies ($I^2 \geq 50\%$, $P < 0.1$), otherwise, the fixed-effects model was adopted.[12] Subgroup analysis and meta-regression were performed to explore the source of heterogeneity. The robustness of the results was assessed by sensitivity analyses.[13] Publication bias was evaluated by Begg's test, Egger's test and Deek's funnel plot.[14–16] Stata V.12.0 software was used to conduct all analyses.

Results

Flow diagram of the publication search and selection process was presented in Fig. 1. Total 1429 documents were initially retrieved, and 850 studies were remained after removing duplications. 379 studies were identified after screening titles and abstracts, and 12 studies with 10,304 cases were included conclusively after full-text review.[6,17–27] Of those, 8 studies reported OR and 4 reported HR, and 8 studies reported the association between cerebrovascular disease and the fatal outcomes. Seven studies came from China, two from America, two from Korea, and one from UK. The main characteristics of the included studies are summarized in Table 1.

The pooled effects in our analysis showed that COVID-19 patients with a history of cerebrovascular disease were more likely to progress to adverse outcomes than patients without a history of cerebrovascular disease (pooled effect = 2.05, 95% CI: 1.34−3.16; I^2 = 50%, Cochran's Q, P = 0.024, random-effects model; Fig. 2A). The results of subgroup analysis grouped by effect values were in keeping with it (OR = 2.19, 95% CI: 1.19−4.05; HR = 2.01, 95% CI: 1.15−3.53; Fig. 2A). In addition, we also conducted a pooled analysis of mortality studies, and the data indicated that an obvious association was also observed between cerebrovascular disease and fatal outcomes (pooled effect = 1.78, 95% CI: 1.04−3.07; I^2 = 60.7%, Cochran's Q, P = 0.013, random-effects model; Fig. 2B). Sensitivity analysis demonstrated that the results were robust (Fig. 3A and B). No source of heterogeneity was found by meta-regression (all $P > 0.05$). No publication bias was found either in Begg's test (P = 0.631, Fig. 4A), Egger's test (P = 0.327, Fig. 4B) or Deek's plot (P = 0.846, Fig. 4C).

Discussion

COVID-19 has caused a worldwide pandemic with its high mortality and infection rates since January, 2020.[28] Identifying risk factors associated with disease progression of COVID-19 is essential to guide clinicians in the use of targeted medications. It has been reported that COVID-19 patients diagnosed in intensive care units have a higher mortality rate than patients confirmed in the ordinary ward, which appeared to be associated with some

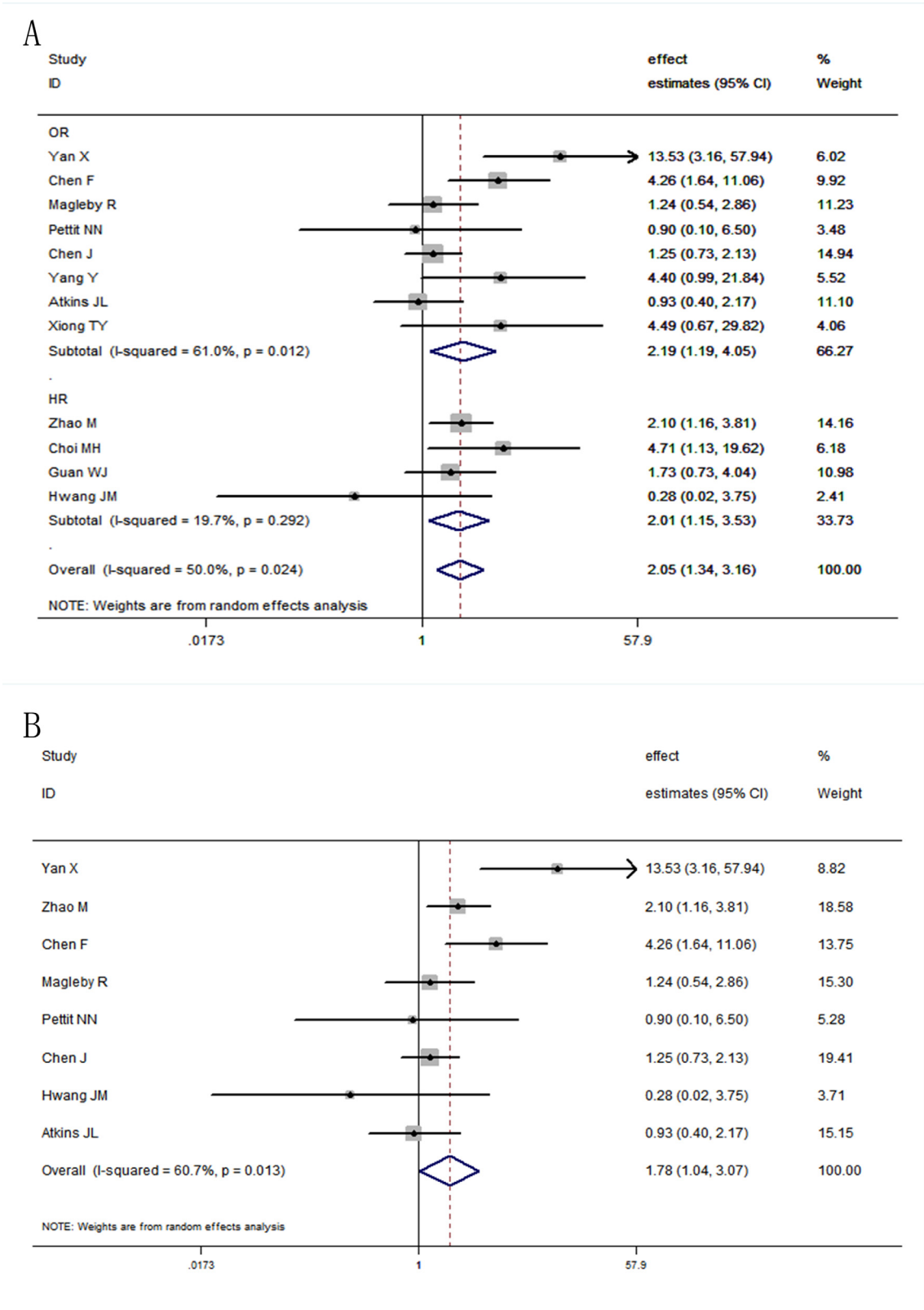

Fig. 2. *(A) Forest plot of adjusted hazard ratios for adverse outcomes associated with cerebrovascular disease in patients with COVID-19. (B) Forest plot of adjusted hazard ratios for in-hospital mortality associated with cerebrovascular disease in patients with COVID-19.*

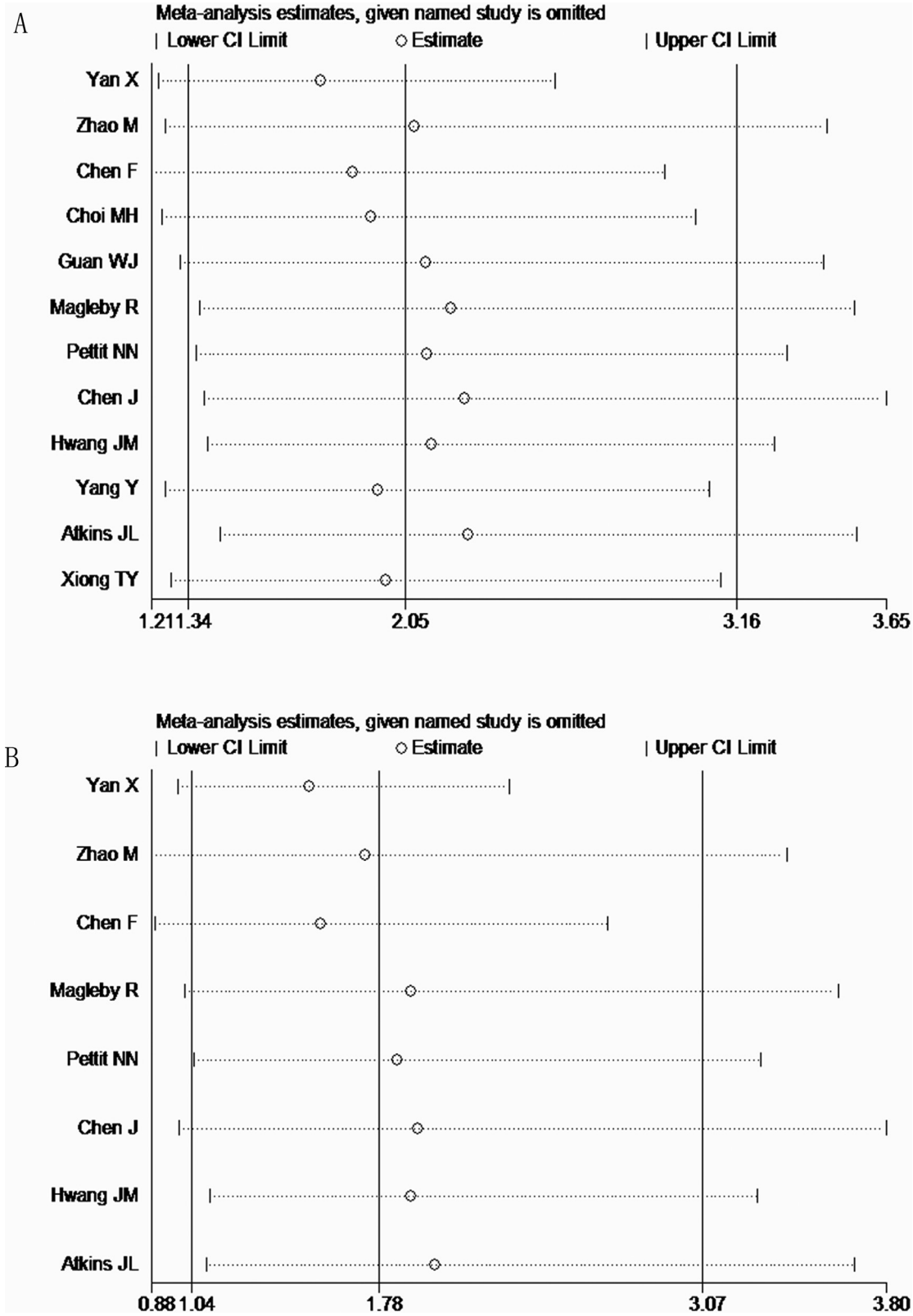

Fig. 3. *Sensitivity analysis.*

comorbidities such as hypertension, diabetes, cardiovascular disease, and so on.[29] Cerebrovascular disease, as a common disease with high mortality, caught the attention of researchers.[30] To our knowledge, several meta-analyses have investigated the association of cerebrovascular disease with the adverse outcomes in COVID-19

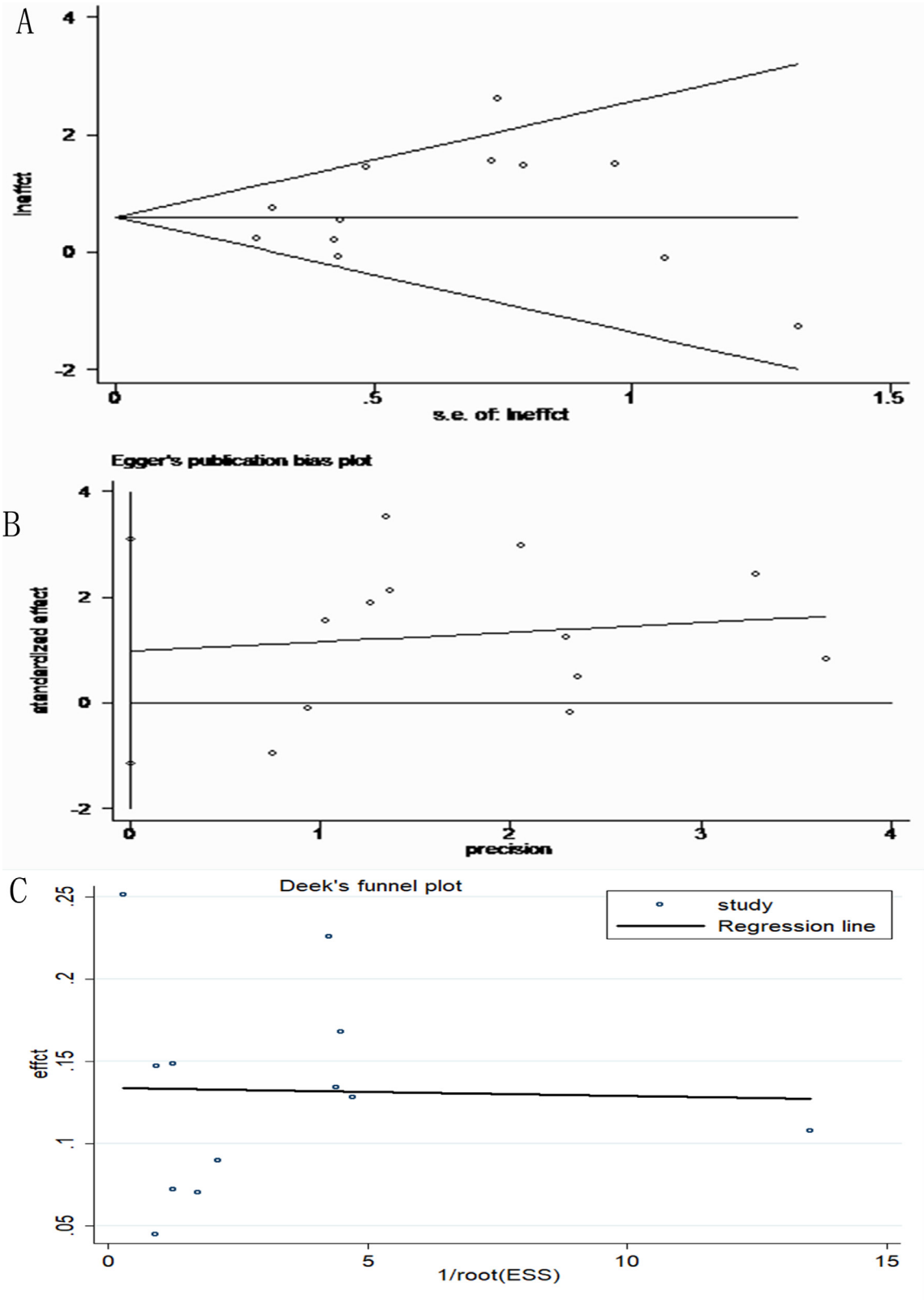

Fig. 4. *(A) Begg's test. (B) Egger's test. (C) Deek's plot.*

patients,[5,31,32] however, the data were uniformly estimated based on unadjusted effect estimates. As reported in previous studies, age, gender and pre-existing disease conditions could affected disease progression of COVID-19,[7–10] and might modulate the association between cerebrovascular disease and the adverse outcomes in COVID-

19 patients. Therefore, it is an urgent need to verify this association by performing a quantitative meta-analysis based on adjusted effect estimates.

Our current meta-analysis based on adjusted effect estimates showed that there was a positive correlation between cerebrovascular disease and unfavorable outcomes, especially fatal outcomes in COVID-19 patients. This suggests that cerebrovascular disease is an independent risk factor for predicting the unfavorable outcomes in COVID-19 patients. Moreover, studies concluded that critically ill COVID-19 patients experiencing cytokine storm and thrombotic complication had a poorer prognosis and increased fatality rate,[33,34] and that stroke might be an expression of a severe form of COVID-19. Therefore, in clinical practice, clinicians should pay more attention to COVID-19 patients with co-existing cerebrovascular disease and timely medications were applied to prevent worse outcomes.

There are still some important limitations in our study. First, our meta-analysis included only 12 studies due to the limitation of the number of published articles. Second, the heterogeneity of our study cannot be ignored. The subgroup analysis and meta-regression were conducted to explore the source of heterogeneity, and it was found in the subgroup analysis that the heterogeneity might originate from different effect values used in different studies, but in the meta-regression, no source of heterogeneity was found. Third, although the selected studies presented the adjusted effect estimates, the adjusted confounders are not completely uniform across studies. Finally, our study failed to establish a causal relationship between cerebrovascular disease history and adverse outcomes in COVID-19 patients on account of the built-in limitations of observational studies. More rigorous studies are needed to further test the causal link.

In summary, our study retrieved all multivariate analyses of the relationship between cerebrovascular disease history and poor prognosis in COVID-19 patients in three databases, and it is the first systematic review and meta-analysis that evaluated the relationship between cerebrovascular disease and adverse outcomes in COVID-19 patients using adjusted effect estimates. The pooled effects suggest that cerebrovascular disease is an independent risk factor for predicting the adverse outcomes, particularly fatal outcomes, in COVID-19 patients. Well-designed with larger sample size are needed for further verification.

Author contributions

W. Y. D. and Y. H. Y. designed the analysis; L.X. and X.W.W. extracted the data; X.J. performed the analysis; X. J. and S. L. contributed to the statistical analyses and interpretation; X. J. drafted the manuscript, which was modified by W. Y. D. and Y. H. Y. All authors read and approved the final manuscript.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Statement of ethics

Not required.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Declaration of Competing Interest

All authors report that they have no potential conflicts of interest.

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