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.

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Risk of ischemic stroke in patients with COVID-19 infection: A systematic review and meta-analysis

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ABSTRACT

An ongoing global pandemic, the coronavirus disease 2019 is posing threat to people all over the world. The association between COVID-19 and the risk of ischemic stroke remains unclear. This study systematically reviewed published studies and conducted meta-analysis to evaluate the association between the risk of ischemic stroke and COVID-19. This study was conducted according to guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The protocol used in this study had been registered in the International Prospective Register of Systematic Reviews. EMBASE, PubMed, Cochrane Library and Web of Science were searched from 1st December 2019–19th February 2021. This systematic review and meta-analysis analysed the combined effect estimations based on odds ratios (OR) with the random-effects model. Four studies were screened from 31,634 participants including 171 COVID-19 positive patients with ischemic stroke were included. The mean age of COVID-19 positive patients with ischemic stroke was 69.45 years (Range: 63–77 years) and the male patients were 56%. Countries covered by these articles were USA, Italy and France. Three of the articles were retrospective cohort studies and one was prospective cohort study. Our analysis revealed that the risk of ischemic stroke (combined OR: 2.41; 95% CI: 1.08–5.38) was significantly increased. Four included studies were significantly heterogeneous ($I2 = 75.2\%$, $P = 0.007$). Significant association between the risk of ischemic stroke and COVID-19 was observed in the North America group (combined OR: 2.90; 95% CI: 0.45–18.80, $I2 = 89.60\%$, $P = 0.002$). This study found that the risk for ischemic stroke was increased in COVID-19 patients, especially in patients from North America. Further studies with larger sample sizes that include different ethnic populations are required to confirm our analysis.

1. Introduction

A novel corona virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019 (Mao et al., 2020; Zhu et al., 2020). It is now well-known that SARS-CoV-2 can cause a series of acute respiratory syndromes including pneumonia and these syndromes are collectively termed corona virus disease 2019 (COVID-19) according to the World Health Organization. Although COVID-19 affects the respiratory system, it can also cause damage to other systems, such as the immune system and the nervous system (Siow et al., 2021). The COVID-19 has been associated with many neurological complications including strokes (Montalvan et al., 2020). Indeed, previous studies found that 78 of 214 COVID-19 patients from Wuhan, China experienced neurological complications (Mao et al., 2020; Wang et al., 2020). As the most serious form of neurological complications, strokes can be mainly categorized into hemorrhagic strokes and ischemic strokes (Nannoni et al., 2020). To the best of our knowledge, the association between the risk of ischemic stroke and COVID-19 remains inconclusive. While studies pointed out that COVID-19 was a risk factor for the ischemic stroke (Dhamoon et al., 2021; Perry et al., 2020), other studies suggested that COVID-19 posed an independent risk to the acute ischemic stroke (Bekelis et al., 2020;

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Belani et al., 2020; Katz et al., 2020; Qureshi et al., 2021). To resolve this contradiction, we systematically reviewed published studies and conducted meta-analysis to evaluate the association between the risk of ischemic stroke and COVID-19.

2. Methods

This study was conducted according to guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). The protocol used in this study had been registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021244691).

2.1. Search strategy

Databases used in this study included the EMBASE, PubMed, Cochrane Library and Web of Science. MeSH terms and search keywords used were: (COVID-19) OR (COVID 19) OR (COVID-19 Virus Disease) OR (COVID 19 Virus Disease) OR (COVID-19 Virus Diseases) OR (Disease, COVID-19 Virus) AND ((Ischemic Stroke) OR (Ischemic Strokes) OR (Stroke, Ischemic) OR (Ischemic Stroke) OR (Ischemic Strokes) OR (Stroke, Ischemic) OR (Acute Ischemic Stroke) OR (Acute Ischemic Strokes) OR (Ischemic Stroke, Acute) OR (Stroke, Acute Ischemic)). Two authors Yanhua Cui (YHC) and Tianbai Li (TBL) screened all titles and abstracts independently. Any disagreements were discussed with a third evaluator Zhao-fei Yang (ZFY) or resolved through consensus.

2.2. Eligibility criteria

Identified articles were further selected based on the following criteria: observational cohort studies, studies reporting on a minimum of ten patients aged $\geq$ 18 years; the studies on COVID-19 patients with and ischemic stroke, studies published from 1st December 2019–19th February 2021.

2.3. Excluded criteria

We excluded all studies conducted on animals and reported only hemorrhagic stroke, cerebral venous thrombosis. Other exclusion criteria included publications on patient cohorts previously reported, non-English articles, full-texts unavailable, non-original research papers (systematic reviews, editorials commentaries, opinion papers, letters, protocols, reports, book chapters), non-clinical characteristics reported, as well as COVID-19 diagnosis but no reporting of ischemic stroke as a complication.

2.4. Data extraction

Two authors YHC and TBL independently extracted data from each study based on eligibility criteria and excluded criteria. Any disagreements between these two authors (YHC and TBL) were discussed with a third evaluator ZFY or by consensus. We extracted data about the name of authors, year, study design, country, continent, age, sex, sample size, the number of COVID-19 positive patients with or without ischemic stroke, the number of COVID-19 negative patients with or without ischemic stroke.

2.5. Assessment of quality

Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of all included observational cohort studies. All studies were evaluated based on their outcome, selection and comparability. Two authors YHC and TBL evaluated all included studies independently and discussed discrepancies by consensus.

2.6. Data analysis

To determine the correlation between ischemic stroke and COVID-19, odds ratios (OR) and confidence intervals (CI) were assessed. To assess the heterogeneity between studies, the Cochran's Q test was performed. The heterogeneity was estimated by calculating the I^2 with levels of 0% (absent), 25% (low), 50% (moderate) and 75% (high). The random effect model was used when the severe heterogeneity had $I^2 >$ 50%, otherwise the fixed effect model was applied. A P-value less than 0.05 was defined as statistic significant. Subgroup analyses were performed according to the type of continent, number of sample size, study design and NOS score. Moreover, sensitivity analysis was conducted by deleting each study individually and thus the quality and consistency of results were evaluated. Begg's test was used to analysis the publication bias. In this study, statistical analyses were performed using the Stata software package (version 15.1).

3. Results

3.1. Study selection

A total of 1191 publications was identified in the initial literature search. Among these studies, 497 articles were from PubMed, 375 articles were from EMBASE, 313 articles were from Web of Science and 6 articles were from Cochrane Library, and 406 duplicated articles were removed. Thus, we identified 785 unique papers and selected 51 papers for full-text review after reviewing the title and abstract. We excluded 47 articles based on the exclusion criteria. Finally, we included 4 eligible studies in our systematic review and meta-analysis. The flowchart showing the systematic screening and process of selection is reflected in Fig. 1.

3.2. Quality assessment and baseline characteristics

We summarized the main characteristics of included articles in Table 1 The mean age of COVID-19 positive patients with ischemic stroke was 69.45 years (Range: 63–77 years) and the male patients were 56%. Countries covered by these articles were USA, Italy and France. Three of the articles were retrospective cohort studies and one was prospective cohort study. The study quality indicated by the score of NOS was ranged from 7 to 8 (Table S1).

3.3. Overall analysis of the correlation between the risk of ischemic stroke and COVID-19

We analysed the combined effect estimations based on OR with the random-effects model (Fig. 2). We found that the risk of ischemic stroke (combined OR: 2.41; 95% CI: 1.08–5.38) was significantly increased. Four included studies were significantly heterogeneous (I2 = 75.2%, P = 0.007).

3.4. Subgroup analyses of correlation between the risk of ischemic stroke and COVID-19

We conducted subgroup analyses based on the continent (North America or Europe), sample size (>500 or <500), study design (prospective, retrospective) and NOS score (7, 8) in Fig. 3. Significant association between the risk of ischemic stroke and COVID-19 was observed in the North America group (combined OR: 2.90; 95% CI: 0.45–18.80, I2 = 89.60%, P = 0.002), but not in the Europe group (combined OR: 2.29; 95% CI: 1.22–4.29, I2 = 0.00%, P = 0.79); Significant association between the risk of ischemic stroke and COVID-19 was also observed in studies with sample size > 500 (combined OR: 2.90; 95% CI: 0.45–18.80, I2 = 89.60%, P = 0.002), but not in studies with sample size < 500 (combined OR: 2.29; 95% CI: 1.22–4.29, I2 = 0.00%, P = 0.79); Moreover, significant association between the

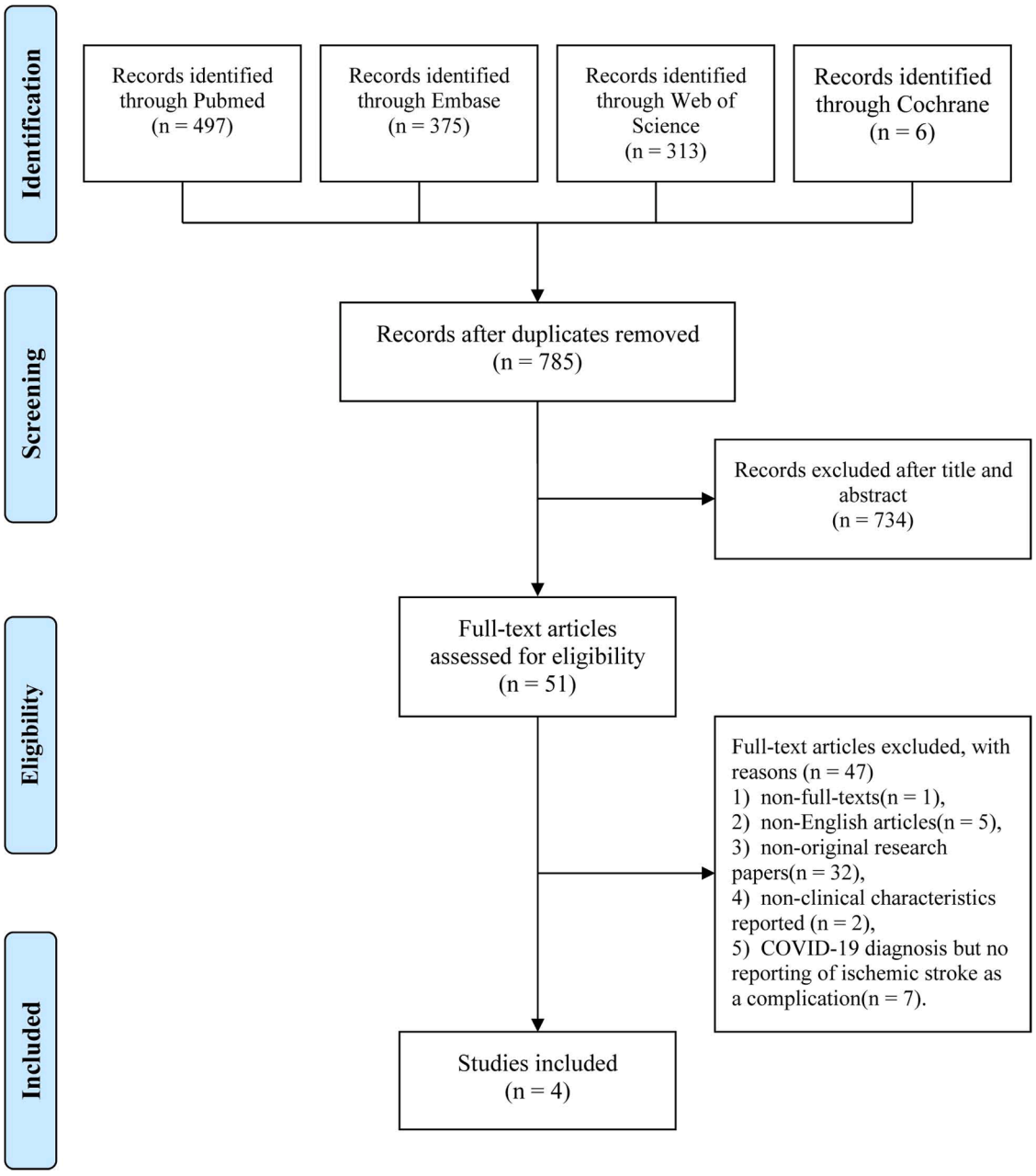

Fig. 1. The process of study selection shown in the PRISMA flowchart.

Table 1
Baseline features of COVID-19 patients with ischemic stroke.

Study	Year	Study Design	Country	Continent	Age	Sex (Male %)	Sample size (n)	IS in COVID-19 (+)	COVID-19 (+) (n)	IS in COVID − 19 (-)	COVID-19 (-)
Qureshi	2021	retrospective cohort	USA	North America	68.8	44.7	27676	103	8163	199	19513
Benussi	2020	retrospective cohort	Italy	Europe	77	50	173	35	56	50	117
Merkler	2020	retrospective cohort	USA	North America	69	58	3402	31	1916	3	1486
Helms	2020	prospective cohort	France	Europe	63	81.3	383	2	150	1	233

Abbreviations: IS, Ischemic Stroke, COVID-19,Coronavirus Disease 2019

risk of ischemic stroke and COVID-19 was further observed in retrospective studies (combined OR: 2.39; 95% CI: 0.99–5.45, I2 = 82.90%, P = 0.003). In addition, we also assessed the quality of studies based on the NOS score. We found that there was no significant association between the risk of ischemic stroke and COVID-19 studies with a score of 7 (combined OR: 1.53; 95% CI: 0.88–2.67, I2 = 63.60%, P = 0.10) or 8

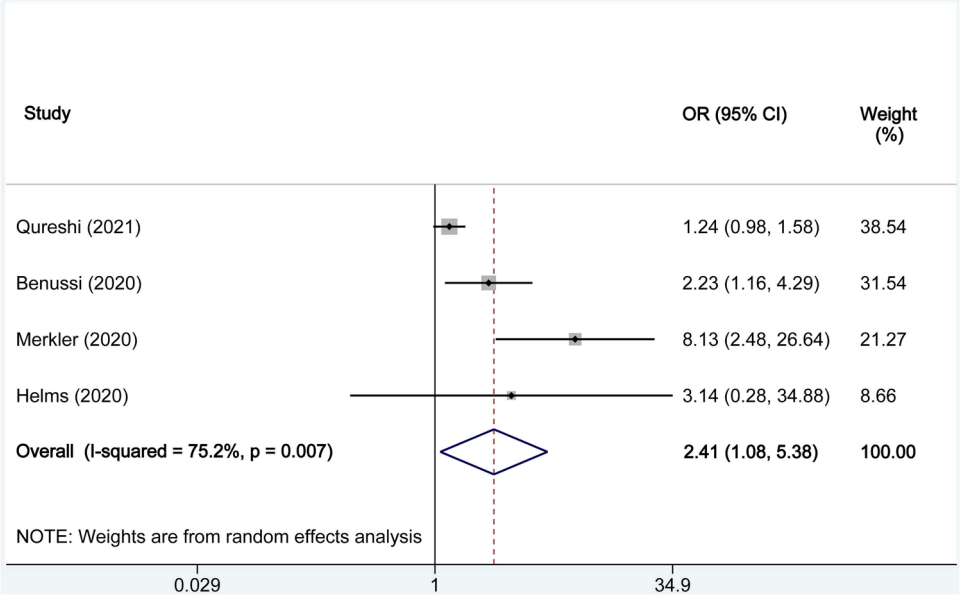

Fig. 2. Forest plots indicating COVID-19 and the risk of ischemic stroke. The X axis represents odds ratios (OR) for each individual study. Square size represents individual study weight. Bar represents 95% confidence interval (CI); diamond represents combined OR. Abbreviations: OR, odds ratios; CI, confidence intervals.

(combined OR: 6.75; 95% CI: 2.33–19.57, I2 = 0.0%, P = 0.48).

3.5. Sensitivity analysis

We next confirmed whether modification of the inclusion criteria had affected the final results using the sensitivity analysis. By excluded single study sequentially, we analysed the effect of each study on the pooled results and found no significant changes in the final results (Fig. S1). Thus, our meta-analysis had validated rationality and reliability.

3.6. Publication bias

To assess publication bias, we performed Begg's test and examined the funnel plot symmetry (Fig. S2). We observed no publication bias with the Begg's test (Z = 0.73, P = 0.67). In addition, all studies had CIs within 95% and were evenly distributed around the vertical.

4. Discussion

This study analyzed the associations between the risk of ischemic stroke and COVID-19 with a systematic review and meta-analysis. This is the first study comprehensively analysed the relationship between the risk of ischemic stroke and COVID-19 when previous studies failed to draw consistent conclusions. This meta-analysis showed that the risk of ischemic stroke was positively associated with COVID-19. Specifically, COVID-19 might have increased the risk of ischemic stroke by 1.4-fold.

Moreover, we found that the increased risk of ischemic stroke was associated with COVID-19 in retrospective cohort studies or studies with COVID-19 participants in North America but not elsewhere. This might be explained by the high risk of ischemic stroke among COVID-19 participants from USA and a low risk of ischemic stroke among COVID-19 participants from Italy and France. As we know that blacks have almost twice the risk of having a stroke for the first time as whites (Virani et al., 2020). Blacks have the highest death rate from stroke (Mozaffarian et al., 2016). Furthermore, a high percentage of COVID-19 patients are black people in the USA (Tai et al., 2021). These reasons may be the high risk of ischemic stroke among COVID-19 participants from USA. Studies with smaller sample size also failed to demonstrate an association between the risk of ischemic stroke and COVID-19 probably due to insufficient data for statistical analysis.

Several mechanisms had been proposed to explain the association between the risk of ischemic stroke and COVID-19. The first possible mechanism is the cytokine storm occurred in response to COVID-19 (Chen et al., 2020; Guzik et al., 2020; Zakeri et al., 2020). Indeed, increased levels of proinflammatory cytokines such as interleukine-1β (IL-1β), IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, granulocyte-macrophage colony-stimulating factor, interferon-γ, and monocyte chemotactic protein 1 were associated with the risk of multiple organ dysfunction in patients with COVID-19 (Huang et al., 2020; Mehta et al., 2020; Ojo et al., 2020). In addition, the increased levels of C-reactive protein and IL-6 might also contribute to the increased risk of acute ischemic stroke (Tzoulaki et al., 2007; Zakeri et al., 2020). Another possible mechanism for COVID-19-induced ischemic stroke is the activated innate immune system and the coagulation induced by infection with SARS-CoV-2 (Beyrouti et al., 2020; Campbell and Kahwash, 2020; Majidi et al., 2020; Sweid et al., 2020; Yaghi et al., 2020). In fact, the level of D-dimer was increased in COVID-19 patients with acute ischemic stroke, suggesting that COVID-19 may cause an acute systemic inflammatory response and lead to a procoagulant state (Grau et al., 2010; Merad and Martin, 2020; Wang et al., 2020). Inflammatory cytokines can cause endothelial activation which refers to the procoagulant state of the endothelial cells of blood vessels (Ojo et al., 2020). Thrombin, the serine protease which regulates blood coagulation, can be released by activated endothelial cells and is normally controlled by natural anticoagulants. Uncontrolled thrombin in the blood stream can activate platelets and lead to thrombosis which increases the risk of stroke (Beyrouti et al., 2020; Tang et al., 2020). Moreover, the antiphospholipid antibody syndrome (APS), an autoimmune disorder featured by excess formation of blood clot, might be another mechanism that associated COVID-19 with the ischemic stroke (Beyrouti et al., 2020; Zhang et al., 2020). The APS is mainly classified by an increased level of primary antiphospholipid antibodies including the lupus anticoagulant and aβ2GPI immunoglobulin M or immunoglobulin G antibodies. One study reported that 14 patients were tested positive for lupus anticoagulant and 5 patients were positive for β2GPI immunoglobulin M or immunoglobulin G antibodies among 56 COVID-19 patients (Harzallah et al., 2020; Ojo et al., 2020). Therefore, the level of antiphospholipid antibodies might be a good indicator for COVID-19 patients in predicting the risk of ischemic stroke. However, more studies are required to clarify the

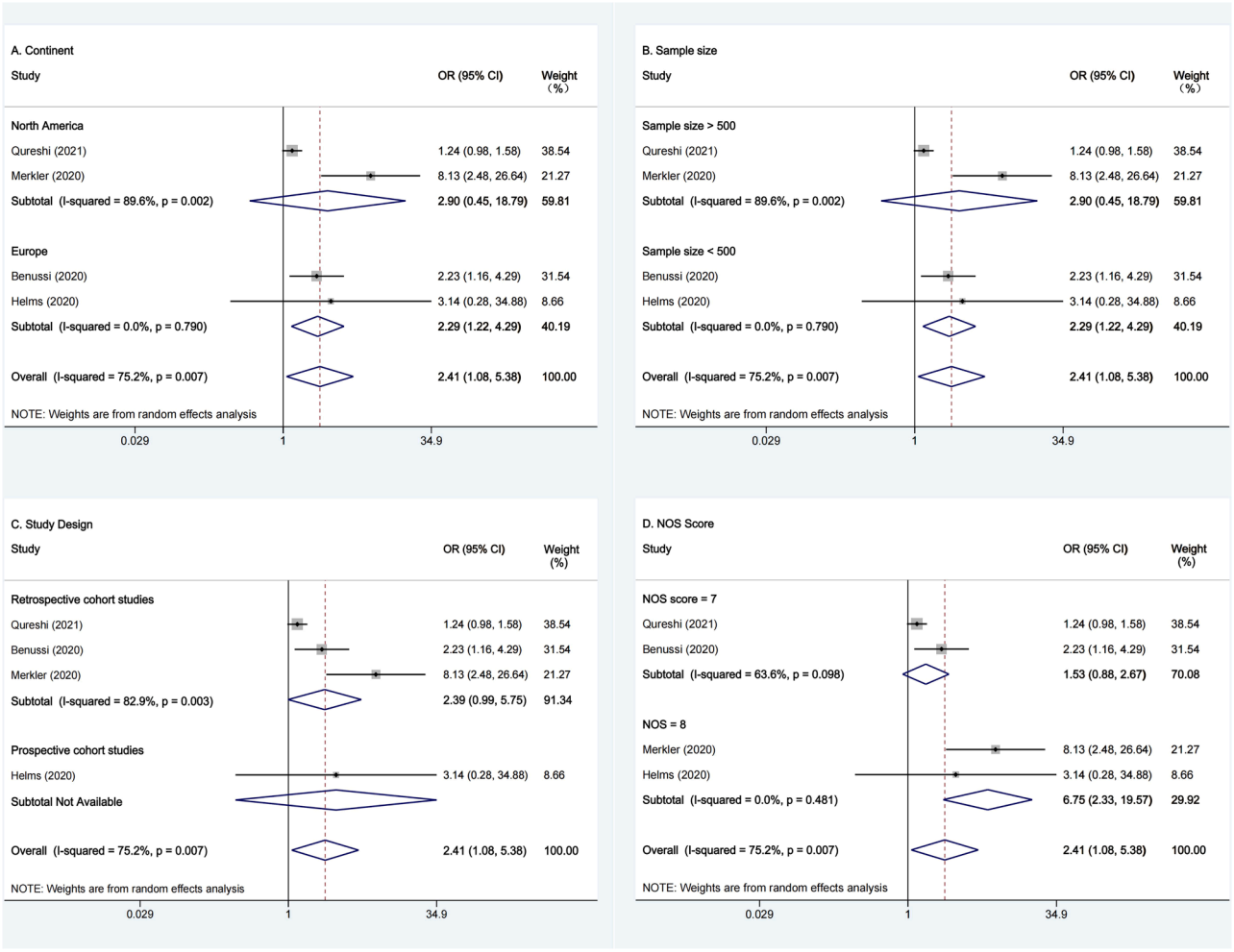

Fig. 3. Subgroup Analyses Forest plots of the risk of ischemic stroke and COVID-19. (A) Subgroup Analyses Forest plots of the risk of ischemic stroke and COVID-19 based on continent; (B) Subgroup Analyses Forest plots of the risk of ischemic stroke and COVID-19 based on sample size; (C) Subgroup Analyses Forest plots of COVID-19 and risk of ischemic stroke for study design; (D) Subgroup Analyses Forest plots of the risk of ischemic stroke and COVID-19 based on NOS Score; The X axis represents odds ratios (OR) for each individual study; Square size represents individual study weight. Bar represents 95% confidence interval (CI); diamond represents combined OR. Abbreviations: OR, odds ratios; CI, confidence intervals; NOS, Newcastle–Ottawa Scale.

contribution of antiphospholipid antibodies to increase the risk of ischemic stroke in COVID-19 patients.

Our study has some strengthens. First, we analysed cohort studies instead of case report or case series. Second, we also considered the generalizability by including studies from different countries. Third, multiple analyses including the publication bias analysis, sensitivity analysis and subgroup analysis, were conducted to evaluate the combined effect size estimation.

Our study has some limitations. First, although we analysed four studies, the sample size remained small. Second, the language bias that favor English exists in this study. Therefore, further studies with larger sample sizes that include different ethnic populations are required to confirm our analysis.

5. Conclusions

Our meta-analysis showed a strong correlation between the increased incidence rate of ischemic stroke and COVID-19, especially in North America COVID-19 patients. Further study is required to develop effective treatments to decrease the ischemic stroke risk in COVID-19 patients.

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CRediT authorship contribution statement

Yanhua Cui, Taibai Li and Zhaofei Yang searched literatures and performed data extraction. Yanhua Cui and Bing Zhao analyzed the data, drafted and finalized the manuscript. Song Li revised the manuscript. Wei-dong Le designed the study concept and revised the manuscript. All authors have approved the final article.

Acknowledgments

Not applicable.

Declaration of Conflicts of interest

All authors declared no financial or other conflicts of interest involved.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2021.12.011.

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