What can the neurological manifestations of COVID-19 tell us : a meta-analysis

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Abstract

Background Covid-19 became a global pandemic in 2019. Studies have shown that coronavirus can cause neurological symptoms, but clinical studies on its neurological symptoms are limited. In this meta-analysis, we aim to gather and discuss COVID-19 various neurological symptoms of infection, and to assess the prevalence of each of the nervous system symptoms, and characterized by neurological in-depth discussions of nervous system damage mechanism, biomarkers and inspection methods, recovery and prognosis, and provide the research behind the potential target and direction. **Methods** We systematically searched all published English literature related to the neurological manifestations of COVID-19 from January 1, 2020 to November 20, 2020 in Pubmed, Embase, and Cochrane library. The keywords used were COVID-19 and terminology related to nervous system performance. All included studies were selected by two independent reviewers using EndNote and NoteExpress software, any disagreement was resolved by consensus or by a third reviewer, and the selected data was then collected for meta-analysis using a random-effects model. **Results** A total of 62 articles (n =32729) were included in the study, and the meta-analysis showed that the most common neurological manifestations of COVID-19 were altered mental status (39% ; 95% CI 0.17-0.64 ; I² 98.59%), encephalopathy (37% ; 95% CI 0.17-0.60 ; I² 97.36%), myalgia(31% ; 95% CI 0.25-0.38; I² 98.79%), headache(30% ; 95% CI 0.22-0.37; I² 99.28%), smell impairment(28% ; 95% CI 99.57% ; I² 0.17-0.39), taste dysfunction (27% ; 95% CI 0.18 -0.38 ; I² 99.35%), acute ischemic stroke (23% ; 95% CI 0.06-0.47 ; I² 99.30%), alteration of consciousness(17% ; 95% CI 0.06-0.31 ; I² 96.78%), dizziness (10% ; 95% CI 0.06-0.15; I² 95.30%), intracerebral haemorrhage (7% ; 95% CI 0.02-0.14 ; I² 93.64%), vision impairment(5% ; 95% CI 0.02-0.10 ; I² 92.73%), seizure(2% ; 95% CI 0.01-0.04 ; I² 84.67%). **Conclusions** Neurological symptoms are common and varied in Covid-19 infections, and a growing number of reports suggest that the prevalence of neurological symptoms may be increasing. In the future, the role of COVID-19 neurological symptoms in the progression of COVID-19 should be further studied, and its pathogenesis and assessment methods should be explored, so as to detect and treat early neurological complications of COVID-19 and reduce mortality.

Introduction

At the end of December 2019, an epidemic of COVID-19 occurred in Wuhan, Hubei Province, China. As the epidemic has spread, cases have been found in many countries. At the time of writing, it has spread to 215 countries and regions, with a total of 84.38 million confirmed cases and 1.83 million deaths. Coronavirus has caused two fatal outbreaks in the past, the first in China in 2003, with a 10 percent mortality rate; The second outbreak was Middle East Respiratory syndrome (MERS) in Saudi Arabia in 2012, with a mortality rate of 35%^[1-2]. Novel Coronavirus was named severe acute respiratory syndrome coronavirus Type 2 (SARS-COV-2). Sars-cov-2 is a single-stranded RNA coronavirus, belonging to the same -coronavirus branch as SARS-COV and MERS-CoV. Its genome sequence is 89.1% similar to the nucleotide sequence of a group of SARS-like coronaviruses. Studies have found that the viral structure and receptor binding domain of SARS-COV-2 are similar to that of SARS-COV, and both of them enter

human cells by binding to ACE2 receptors ^[3-4]. In order to evaluate the genetic variation of SARS-CoV-2, 86 complete or nearly complete genomes were genetically analyzed, and many mutations and deletions were found in both coding and non-coding regions ^[5]. At present, the biological characteristics and genetic variation of SARS-CoV-2 are still not very clear and deserve further study.

Although COVID-19 is typically characterized by respiratory symptoms, numerous clinical studies have shown that patients infected with SARS-CoV-2 are associated with acute injuries to external pulmonary organs, including the heart, digestive tract, liver, kidney and nervous system ^[6-7]. More and more clinical evidence indicates that SARS-CoV-2 may invade the central nervous system. A retrospective analysis of 214 patients with COVID-19 found that 78 (36.4%) had nervous system involvement, and 28.2% of them had severe central nervous system injury ^[8]. Studart-neto A et al. retrospectively analyzed 1208 patients with COVID-19 and found that 89 (7.4%) presented neurological manifestations, including encephalopathy (44.4%), stroke (16.7%), epilepsy (9.0%), neuromuscular disease (5.6%), other acute brain injury (3.4%), and other mild non-specific diseases (11.2%) ^[9]. Takeshi et al. detected SARS-CoV-2 RNA in cerebrospinal fluid specimens, providing direct evidence for the nerve invasiveness of SARS-CoV-2 ^[10]. There are three main types of COVID-19 nervous system involvement: (1) central nervous system involvement, such as dizziness, headache, disturbance of consciousness, acute cerebrovascular disease, and epilepsy; (2) peripheral nervous system involvement, including anosmia, decreased taste, decreased vision, and neuralgia; (3) skeletal muscle injury ^[11-12]. COVID-19 possible mechanisms include: nerve injury by angiotensin-converting enzyme (ACE2) receptor function, blood and break through the blood brain barrier, through the way such as olfactory nerve attack the nervous system ^[13-14].

Neurological manifestations are an extremely important part of the clinical manifestation of COVID-19, but the prevalence, severity, and mechanism of action of neurological symptoms are still not well understood, and the reasons for the differences in the incidence of neurological symptoms reported in different studies remain unclear. The clinical prognosis of COVID-19 neurological injury is poor, and early detection and intervention may be most beneficial. Therefore, understanding the characteristics of neurological impairment of COVID-19 is of positive clinical significance for better epidemic prevention and control, clinical diagnosis and treatment in the future.

Methods

Search strategy and research selection

We searched the following electronic databases for literature published between 1 January 2020 and 20 November 2020: Pubmed, Embase and Cochrane library. The search terms used include: ((severe acute respiratory syndrome coronavirus 2) OR (SARS-CoV-2) OR (2019-nCoV) OR (2019 novel coronavirus) OR (COVID-19) OR (coronavirus) OR (novel coronavirus pneumonia) OR (NCP)) AND ((neurologic manifestations) OR (neurological manifestations) OR (neurologic manifestation) OR (neurologic signs and symptoms) OR (neurological manifestation) OR (neurologic deficits) OR (neurologic deficit) OR (neurologic symptoms) OR (neurologic symptom) OR (neurologic findings) OR (neurologic finding) OR

(neurologic signs) OR (neurologic sign) OR (neurologic dysfunction) OR (neurologic dysfunctions) OR (nervous system diseases) OR (nervous system disease) OR (neurologic disorders) OR (neurologic disorder) OR (neurological disorders) OR (neurological disorder) OR (nervous system disorders) OR (nervous system disorder) OR (neurological complication) OR (neurological complications) OR (nerve function injury)) .

Inclusion and exclusion criteria

The inclusion criteria for this study are as follows: all English literature from 1 January 2020 solstice 20 November 2020 that has been published reporting neurological manifestations of COVID-19 patients. Study types include randomized controlled trials, non-randomized controlled trials, case-control studies, cohort studies, cross-sectional studies and case series. Only those subjects who were diagnosed with SARS-COV-2 infection by real-time reverse transcription polymerase chain reaction or high-throughput sequencing of swab samples or serological or culture analyses were included in the study. Only those studies whose results included specific neurological manifestations were included.

Exclusion criteria included :(1) no clinical manifestations of related neurological symptoms and lack of relevant data;(2) Age<18 years old;(3) Repeated studies;(4) Editorials, reviews, systematic reviews, meta-analyses, comment, animal studies, postmortem studies, etc.(5) Documents not written in English.

Data extraction and quality assessment

A comprehensive and rigorous review of all literature retrieved was conducted by two independent study members according to inclusion and exclusion criteria, and any disagreement between the reviewers was determined by consultation between the two or by a third investigator. Extracting data from each study include: the first author's name, year, country, research design, time and duration, participants details (gender, age, the overall sample size and specific symptoms of patients number) and neurologic manifestations, such as headache, dizziness, altered mental status, stroke, acute cerebrovascular disease, acute ischemic stroke, intracerebral haemorrhage, seizure, myalgia, smell impairment, taste dysfunction, vision impairment, alteration of consciousness and encephalopathy.

The STROBE Statement was used to evaluate the quality of the included studies. It consists of 22 projects and is used to evaluate six main components, including Title and abstract, Introduction, Methods, Results, Discussion, and Other information. Quality evaluations were conducted by two independent researchers, and any differences between them were resolved by discussion or by the intervention of a third researcher.

Statistical analysis

The main purpose of our study is to synthesize the results of several similar studies to provide a quantitative summary. The extracted data details and instructions are presented in tables and figures. We used Stata (version 15.1) for the meta-analysis. I^2 was calculated to assess the level of heterogeneity and

can be divided into four categories: may be unimportant (0-40%), may represent moderate heterogeneity (30-60%), may represent significant heterogeneity (50-90%) and significant heterogeneity (75-100%). In this study, fixed effect model or random effect model was used to calculate the comprehensive prevalence rate and 95% confidence interval. When there was no heterogeneity, fixed effect model was selected; when there was heterogeneity, random effect model was selected. Forest maps are used to visually indicate the magnitude of the effects that the study summarizes and their 95% confidence intervals. Funnel plot and Egger's test were used to assess the publication bias of all literature, and $P < 0.05$ was considered statistically significant.

Results

A total of 3,286 studies were selected from the database, including 2998 in Pubmed, 267 in Embase and 21 in Cochrane Library. After the elimination of repeated studies ($n = 454$), 2,832 studies met the preliminary screening criteria based on titles and abstracts. After preliminary screening, 2687 articles were excluded, and the remaining 145 were screened in accordance with the inclusion and exclusion criteria. After full-text screening, 62 articles ($n = 32729$) were included in the meta-analysis. **Figure 1** shows the Study flow Diagram. All of the studies were published in 2020. Among the included studies, 5 studies were case series, 6 were cohort studies, and 9 were cross-sectional studies. Among the included studies, 34 retrospective studies, 11 prospective studies and 11 multicenter studies were included. The major countries included were 10 studies in Italy, 7 each in China, the United States, and France, 6 in Spain, and 5 in Turkey. **Table 1** shows the details and characteristics of the included studies.

Altered mental status was the most common neurological manifestation (39%; 95% CI 0.17 - 0.64; I^2 98.59%) (7 studies: 17,31,37,38,41,48,74), encephalopathy (37%; 95% CI 0.17 - 0.60; I^2 97.36%) (5 studies: 9,28,48,49,74), myalgia (31%; 95% CI 0.25 - 0.38; I^2 98.79%) (35 studies: 15-22,27,29-30,32,35,37,41,43-45,47,49-51,53-54,58-59, 62-64,68-71,73), headache (30%; 95% CI 0.22 - 0.37; I^2 99.28%) (49 studies: 8-9,15-22,26-32,35,37-41,43-55,58-60, 67-74), smell impairment (28%; 95% CI 0.17 - 0.39; I^2 99.57%) (44 studies: 8-9,15-20,27,29-30,35-45,48-54, 56-61, 63-66,68-71,73), taste dysfunction (27%; 95% CI 0.18-0.38; I^2 99.35%) (33 studies: 8-9,15,17,19-20,27,29-30,36,39-40,43-45,49-53,56-61,63-64,66,69-70,73-74), acute ischemic stroke (23%; 95% CI 0.06 - 0.47; I^2 99.30%) (8 studies: 23-25,33,41,48-49,69), alteration of consciousness (17%; 95% CI 0.06 - 0.31; I^2 96.78%) (7 studies: 8-9,26,37,39,44,55), Dizziness (10%; 95% CI 0.06- 0.15; I^2 95.30%) (19 studies: 8, 15-17 to 39,41,45,21,27,38-50,58,63,67,69), intracerebral haemorrhage (7%; 95% CI 0.02 - 0.14; I^2 93.64%) (8 studies: 9,23-25,28,31,33,48), vision impairment (5%; 95% CI 0.02 - 0.10; I^2 92.73%) (7 studies: 8,17,30,39,46,58,73), seizure (2%; 95% CI 0.01 - 0.04; I^2 84.67%) (13 studies: 8-9,17,26,31,34,38-39,41-42,48-49,69).

The included studies had good methodological quality. **Figure 2** shows a forest map of acute cerebrovascular disease, acute ischaemic stroke, alteration of consciousness, altered mental status, encephalopathy, intracerebral haemorrhage, seizure, stroke, vision impairment, headache, dizziness, myalgia, smell impairment and taste dysfunction. Visual symmetry of funnel plots and Egger's test

showed no publication bias for headache, acute ischemic stroke, intracerebral haemorrhage, seizure, myalgia, smell impairment, taste dysfunction and vision impairment. The funnel plot is shown in **Figure 3**.

Discussion

The characteristics of SARS-CoV-2

SARS-CoV-2 was an enveloped positive single-stranded RNA virus, belonging to the genus B coronavirus [75-76]. The genomic sequence of the infected patients with SARS-CoV-2 has 79.5% genetic similarity to SARS-CoV, about 50% homology to MERS-CoV [77-79], and 96% genetic similarity to bat coronavirus [80]. SARS-CoV-2 contains four structural proteins (spines (S), envelope proteins (E), membrane proteins (M) and nucleocapsid proteins (N)) and 16 non-structural proteins (NSP1 –16). The entry of coronavirus into host cells is mediated by spiking glycoprotein (S protein), so spiking glycoprotein is the key for the entry and infection of coronavirus [81]. Tang X. et al. found a total of 149 mutations in 103 SARS-CoV-2 genomic strains [84]. The most easily altered sequence in the coronavirus genome is the receptor binding domain (RBD) of the S gene [82-83]. Up to now, 13 mutations have been found in Spike proteins. D614G mutation in Spike protein increases infectivity and transduction of a variety of human cell types. D614G mutation also reduces serum neutralization sensitivity of COVID-19 patients during recovery [85-86].

Evidence of neurological damage in COVID-19 patients

Firstly, according to our meta-analysis, the most common neurological manifestations of COVID-19 patients were altered mental status (39%) and encephalopathy (37%). Then, myalgia (31%), Headache (30%), smell impairment (28%), taste dysfunction (27%), acute ischemic stroke (23%), vision impairment (5%) and seizure (2%) were less common. Among them, smell impairment and taste dysfunction appeared earlier. This suggests that SARS-CoV-2 will affect functional areas such as temporal lobe, parietal lobe and occipital lobe, which will lead to clinical manifestations of the nervous system in patients.

Secondly, the etiological evidence are as follows: (1) Evidence related to cerebrospinal fluid: On March 8, 2020, Moriguchi et al. reported evidence of SARS-CoV-2 in cerebrospinal fluid for the first time in Japan [87]. On June 20, 2020, Domingues et al. reported that the SARS CoV-2 virus genome was detected in cerebrospinal fluid and sequenced, and its sequence similarity with that of the world virus was 99.74-100% [88]. (2) Autopsy evidence: Remmelink et al. conducted an autopsy study on August 12, 2020 on 17 adult patients with Covid-19, and the results showed that SARS-CoV-2 RNA was found in 9 out of 11 brain samples [89]. Other studies have also demonstrated that SARS-CoV-2 RNA or viral protein can be detected in the brain, olfactory bulb, trigeminal ganglion, medulla oblongata and cerebellum [90]. At the same time, autopsy results of brain tissue of patients with Covid-19 death showed edema, hemorrhage, infarction, atrophy, encephalitis, olfactory bulb asymmetry, glial cell proliferation, neuron loss or

degeneration, etc. ^[91,107-109].(3) Experimental evidence: Zheng et al. ^[92] found that the primary target organ of SARS-CoV-2 was the lung in the early stage and the brain in the late stage by studying the K18-HCE2 mouse model. At 6 days after infection, immunostaining showed extensive staining in cerebral cortex, caudate nucleus/putamen, thalamus, hypothalamus, ventral striatum, olfactory bulb and other brain regions, as well as sublingual and postlingual nuclei.

Biomarkers reflecting nervous system damage in COVID-19 patients

A prospective study showed that total Tau, GFAP, and NFL protein levels in cerebrospinal fluid were elevated in 63%, 37%, and 16% of patients, respectively, and NFL protein was associated with disease severity, duration of intensive care and level of consciousness ^[110]. Multiple studies on COVID-19 patients with ischemic stroke have shown that the neutrophil-lymphocyte ratio (NLR) is increased in 90% of the patients ^[111], CRP is increased in over 90% of the patients ^[112], and serum ferritin is also increased ^[113], in which serum ferritin can also predict the degree of nerve injury in patients with acute ischemic stroke ^[114]. There was a significant correlation between the decrease of interleukin-6 level and the improvement of olfaction and taste function in COVID-19 patients ^[115]. Elevated serum nerve filament light chain (SNFL) levels in critically ill patients with COVID-19 are closely associated with poor prognosis ^[116].

Examination methods reflecting nervous system damage in COVID-19 patients

In the early stages, acute thromboembolic infarction is the most common intracranial presentation. At present, the most common neurological imaging findings of acute infarction with a large number of blood clots, and intracranial hemorrhage (brain hemorrhage, subarachnoid hemorrhage, subdural hemorrhage or bleeding), the second including leukoencephalopathy, total lack of injury (basal ganglia, globus pallidus, hypothalamus, hippocampus and cortex), meningitis, and encephalitis, corpus callosum lesions, the olfactory bulb lesion, cranial nerve, spinal lesions and long-term changes in diffusion tensor imaging of the brain. Covid-19 is an independent risk factor for acute ischemic stroke, which is a valid indicator of poor prognosis. Meningitis and encephalitis are not very common ^[117-118]. In one study, continuous EEG monitoring was performed in 11 of 16 patients with Covid-19, most of which showed non-specific encephalopathy ^[119].

Mechanisms of nervous system injury in COVID-19 patients

(1) ACE2—ACE2 has been proved to be a functional receptor of SARS-CoV-2, which binds to the ACE2 receptor through its Spike (S) protein C-terminal domain (CTD) ^[93]. The expression profile of ACE2 is very extensive, and it is expressed in various regions of human brain, such as ventricle, motor cortex and posterior cingulate gyrus, middle temporal gyrus, substantia nigra, olfactory bulb, ventrolateral medulla oblongata, nucleus solitarius, vagus nerve, neurons, astrocytes, microglia and oligodendroglia, etc ^[120-121]. Therefore, the nervous system is at risk of SARS-COV-2 infection.

(2) AXL and NRP1 It is worth noting that, in addition to ACE2, recent studies have shown that receptor tyrosine kinase AXL is a new phenotype receptor of choice for SARS-CoV-2, and AXL is widely expressed in almost all human organs, especially in human lung and bronchial epithelial tissues and cells, the expression of AXL is much higher than that of ACE2^[122]. AXL is also found in cells in the brain, including radiating glia, astrocytes, and microglia^[123]. Another cellular mediator, neurociliary protein-1 (NRP1), also promotes the entry of SARS-CoV-2 into host cells, thereby increasing its infectivity. NRPs are involved in a variety of physiological processes, including neuronal development and axon control. Studies have observed high expression of NRP1 in olfactory epithelial cells infected with SARS-CoV-2^[124-125]. Therefore, AXL and NRP1 provide us with new research directions and intervention targets.

(3) Cross-neuronal hypothesis: Results from an animal experiment showed that SARS-CoV-2 may invade the brain retrograde along taste and trigeminal pathways in the early stage of infection^[94]. Some studies also found significant structural changes in olfactory nerve, olfactory bulb, olfactory cortex and other olfactory pathways in the MRI examination of Covid-19 patients, suggesting that SARS-CoV-2 may enter the central nervous system through the olfactory bulb mediated cross-neuronal pathway^[95-96].

(4) Hemogenous transmission and BBB transmission: viruses can infect the central nervous system by infecting BBB endothelial cells, acquiring access or infecting white blood cells^[97]. Perrin et al^[98] found in an in vivo study that SARS-CoV-2 may also invade the central nervous system through the impaired blood-brain barrier. In addition, it has also been found that SARS-CoV can infect monocytes and macrophages and migrate through the blood-brain barrier^[99].

(5) Hypoxia: Patients with COVID-19 are highly hypoxic, and persistent hypoxia can eventually lead to disorders in neurotransmitter metabolism, mitochondrial failure, and intracellular Ca²⁺ accumulation. The immediate consequence is irreversible nerve damage and even neuronal death, which increases the risk of stroke^[100].

(6) Inflammatory response and hypercoagulability: The inflammatory response of severe pneumonia is not limited to lung tissue; when the systemic inflammatory response is activated, its amplification cascade impairs the function of distal organs^[101]. Intravascular coagulation secondary to systemic inflammation is the main cause of thrombosis, bleeding and stroke^[103].

(7) Immune mechanism: After SARS-CoV-2 enters the human body through ACE2, the host triggers an immune response to the virus. When the virus invades the human brain, it will cause immune damage, causing brain damage and acute or chronic inflammation, thus forming a vicious cycle^[102].

Prognosis of nervous system injury in COVID-19 patients

Nervous system damage is closely associated with the mortality of SARS-COV-2 infection, and whether the neurological symptoms are reversible is not yet clear. Patients with COVID-19 who require ICU admission for neurological problems or develop neurological dysfunction in the ICU have significantly

increased mortality^[104]. In one animal study, 4 out of 14 infected mice developed significant respiratory distress and neurological symptoms 2 days after infection, and only the mice showing neurological symptoms died, suggesting that neurological involvement may be a cause of death^[105]. Some studies have confirmed that recovery from acute SARS-CoV-2 infection does not completely clear the virus, and has been found to have a higher potential risk for long-term residual neuropsychiatric and neurocognitive impairments, including depression, obsessive-compulsive disorder, psychosis, Parkinson's disease and Alzheimer's disease^[106]. An experimental animal study has also shown that coronavirus can persist in the central nervous system of its host^[126]. The study results of Helms et al. showed that 36% of severe COVID-19 survivors developed Dysfunction Syndrome^[127], and some studies also reported that patients with severe Dysfunction after the acute phase had significant recovery after active neurological rehabilitation^[128]. In a prospective study, 68.33% of patients developed neurological symptoms during infection with SARS-CoV-2, and 50% recovered 3 months after infection but still had neurological symptoms^[117]. Imaging results of 60 patients after recovery of COVID-19 neurological symptoms suggest that the microstructure and functional brain integrity of the brain may be damaged during the rehabilitation phase, which may require long-term neurological and neuroimaging follow-up^[118].

Advantages and disadvantages of this study

Our meta-analysis, involving 32,729 patients, detailed various common neurologic symptoms in COVID-19 patients and provided a comprehensive view of COVID-19 neurologic symptoms. The results were comprehensive. We started the discussion from the clinical manifestations, and analyzed the evidence, possible mechanism and prognosis of the nervous system injury caused by SARS-CoV-2. We also discussed the biomarkers and examination methods of nervous system injury caused by SARS-CoV-2, providing some valuable suggestions for early identification, monitoring, screening, diagnosis and follow-up of nervous system injury and poor prognosis in patients with COVID-19 and potential targets for future clinical intervention strategies.

This study also has some limitations. Firstly, most of the included literatures were retrospective studies, which may cause some potential bias. Secondly, this study failed to provide an analysis of the correlation between various neurological manifestations and disease severity and mortality. The question of which neurological manifestations are the most insidious and which are the most difficult to recover from is currently unanswered, and more findings are needed in the future. Finally, the high degree of heterogeneity in our study may be due to differences in patient race selection, disease severity, comorbidities, only a few studies specifically assessed neurological symptoms, differences in the number of patients in different studies, or due to differences in publication bias and study methodology.

Conclusion

In conclusion, our study suggests that nervous system expression in COVID-19 is diverse and pervasive, but easily underestimated. Therefore, the long-term pathophysiological results of SARS-CoV-2 neuropathy should be of serious concern to us. At the same time, summarizing the entire symptom

spectrum, biomarkers and examination methods of the disease is conducive to predicting the severity of neurological impairment and providing better suggestions for preventing misdiagnosis, early diagnosis, preventing disease transmission, early intervention treatment, evaluation of therapeutic effect and follow-up. In the future, more clinical and experimental studies should be carried out to provide strong evidence to support clinical practice, and further explore the role of nervous system symptoms in the incidence of COVID-19 and its possible mechanism, so as to reduce mortality, reduce disease severity, control disease progression and prevent possible long-term nervous system complications.

Declarations

1.Ethics approval and consent to participate: Not applicable.

2.Consent for publication: Not applicable.

3.Availability of data and materials: Not applicable.

4.Competing interests: The authors declare that they have no competing interests.

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6.Authors' contributions:

ZH and HY proposed the research idea. HY completed the data analysis and paper writing, and was a major contributor in writing the manuscript. BX and ZT were responsible for literature retrieval and data extraction. HJ finished the quality evaluation. All authors read and approved the final manuscript.

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Table

Due to technical limitations, Table 1 is only available as a download in the supplementary files section.

Figures

Figure 1

Study flow diagram

Figure 2

Forest map of acute cerebrovascular disease—acute ischaemic stroke—alteration of consciousness—altered mental status—encephalopathy—intracerebral haemorrhage—seizure—stroke—vision impairment—headache, dizziness, myalgia—smell impairment and taste dysfunction.

Figure 3

Funnel plot

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.pdf](#)