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

Yuanyuan He, Xiaojie Bai, Tiantian Zhu, Jialin Huang and Hong Zhang*

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 aimed to summarize the various neurological manifestations that occurred in COVID-19 patients and calculate the incidence of various neurological manifestations. At the same time, we further explored the mechanism of nervous system injury and prognosis in COVID-19 patients in combination with their nervous system manifestations. This study provides a reference for early clinical identification of COVID-19 nervous system injury in the future, so as to achieve early treatment and reduce neurological sequelae.

Methods: We systematically searched all published English literature related to the neurological manifestations of COVID-19 from January 1, 2020, to April 30, 2021, in Pubmed, Embase, and Cochrane Library. The keywords used were COVID-19 and terminology related to the 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 were then collected for meta-analysis using a random-effects model.

Results: A total of 168 articles (n = 292,693) were included in the study, and the meta-analysis showed that the most common neurological manifestations of COVID-19 were myalgia (33%; 95%CI 0.30–0.37; I² = 99.17%), smell impairment (33%; 95%CI 0.28–0.38; I² = 99.40%), taste dysfunction (33%; 95%CI 0.27–0.39; I² = 99.09%), altered mental status (32%; 95%CI 0.22–0.43; I² = 99.06%), headache (29%; 95%CI 0.25–0.33; I² = 99.42%), encephalopathy (26%; 95%CI 0.16–0.38; I² = 99.31%), alteration of consciousness (13%; 95%CI 0.08–0.19; I² = 98.10%), stroke (12%; 95%CI 0.08–0.16; I² = 98.95%), dizziness (10%; 95%CI 0.08–0.13; I² = 96.45%), vision impairment (6%; 95%CI 0.03–0.09; I² = 86.82%), intracerebral haemorrhage (5%; 95%CI 0.03–0.09; I² = 95.60%), seizure (4%; 95%CI 0.02–0.05; I² = 98.15%), encephalitis (2%; 95%CI 0.01–0.03; I² = 90.36%), Guillain-Barré Syndrome (GBS) (1%; 95%CI 0.00–0.03; I² = 89.48%).

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, to detect and treat early neurological complications of COVID-19 and reduce mortality.

Keywords: COVID-19, SARS-CoV-2, Neurologic manifestations, The prevalence rate

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 more than 200 countries and regions, with a total
of 187,637,579 confirmed cases and 4,066,292 death. 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 is similar to that of SARS-COV, and both of them enter human cells by binding to ACE2 receptors [3, 4]. 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%), another 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 nervous 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 the olfactory nerve attack the nervous system [13, 14].

Since nervous system manifestations are an important part of COVID-19 patients’ clinical manifestations, early detection and treatment of nerve injury in COVID-19 patients is of great significance for their prognosis and reduction of neurological sequelae. This study aims to further summarize the incidence and characteristics of various nervous system manifestations in COVID-19 patients, and explore the mechanism and prognosis of nervous system injury in combination with nervous system manifestations, so as to provide positive clinical significance for better epidemic prevention and control and 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 April 30, 2021: Pubmed, Embase and the 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) OR (neurologic sign) OR (neurologic dysfunction) OR (neurologic symptoms) OR (neurologic findings) OR (neurologic symptom) OR (neurologic signs and symptoms) OR (neurologic manifestation) OR (neurologic signs and symptoms) OR (neurologic manifestation) OR (neurologic deficit) OR (neurologic deficits) OR (neurologic deficit) OR (neurologic symptoms) OR (neurologic 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 solstices 30 April 2021 that has been published reporting neurological manifestations of COVID-19 patients. Studying types include 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 by high-throughput sequencing of swab samples 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 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 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, intracerebral hemorrhage, seizure, myalgia, smell impairment, taste dysfunction, vision impairment, alteration of consciousness, encephalitis, encephalopathy and Guillan-Barré Syndrome (GBS).

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
Our study synthesizes 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. I² was calculated to assess the level of heterogeneity and can be divided into four categories: maybe unimportant (0–40%), may represent moderate heterogeneity (30–60%), may represent significant heterogeneity (50–90%) and significant heterogeneity (75–100%). In this study, a fixed-effect model or random-effect model was used to calculate the comprehensive prevalence rate and 95% confidence interval. When there was no heterogeneity, the fixed effect model was selected; when there was heterogeneity, a 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 8812 studies were selected from the database, including 5789 in Pubmed, 2971 in Embase, and 52 in the Cochrane Library. After eliminating duplicate studies (n = 1916), 6896 studies met the preliminary screening criteria based on titles and abstracts. After excluding review, meta analysis, case report, age < 18, animal experiment and literature with inconsistent research contents (n = 6483), the remaining 413 articles were screened according to the inclusion and exclusion criteria. After the full-text screening, 168 articles (N = 292,693) were included in the meta-analysis. Figure 1 showed the Study Flow Diagram. All of the studies were published in 2020 and 2021. Among the included studies, 6 studies were case–control studies, 10 studies were case series, 13 were cohort studies, and 25 were cross-sectional studies. 104 retrospective studies, 36 prospective studies and 29 multicenter studies were included. Major countries included were 29 studies in the USA, 20 in Italy, 17 in Spain, 15 in France, 15 in China and 12 in Turkey. Table 1 showed the details and characteristics of the included studies.

Myalgia(33%; 95%CI 0.30–0.37; I² = 99.17%) (86 studies), smell impairment(33%; 95%CI 0.28–0.38; I² = 99.40%) (106 studies), taste dysfunction(33%; 95%CI 0.27–0.39; I² = 99.09%) (80 studies) and altered mental status(32%; 95%CI 0.22–0.43; I² = 99.06%) (18 studies) were the most common neurological manifestations of COVID-19. Headache(29%; 95%CI 0.25–0.33; I² = 99.42%) (123 studies), encephalopathy(26%; 95%CI 0.16–0.38; I² = 99.31%) (23 studies), alteration of consciousness(13%; 95%CI 0.08–0.19; I² = 98.10%) (19 studies), stroke(12%; 95%CI 0.08–0.16; I² = 98.95%) (47 studies), dizziness(10%; 95%CI 0.08–0.13; I² = 96.45%) (50 studies), vision impairment(6%; 95%CI 0.03–0.09; I² = 86.82%) (14 studies), intracerebral haemorrhage(5%; 95%CI 0.03–0.09; I² = 95.60%) (21 studies) and seizure(4%; 95%CI 0.02–0.05; I² = 98.15%) (47 studies) were the next most common. The less common neurological manifestations were encephalitis(2%; 95%CI 0.01–0.03; I² = 90.36%) (14 studies) and Guillan–Barré Syndrome (GBS) (1%; 95%CI 0.00–0.03; I² = 89.48%) (12 studies).

In all the included literature, 16 studies grouped and analyzed the neurological characteristics according to the severity of COVID-19. Through meta-analysis, we concluded that there was no significant difference in the incidence of headache(16%; 95%CI 0.11–0.22; I² = 94.05% VS 16%; 95%CI 0.10–0.23; I² = 97.77%) between the severe group and the non-severe group, and the incidence of dizziness(12%; 95%CI 0.07–0.18; I² = 88.28% VS 9%; 95%CI 0.04–0.16; I² = 96.05%) and seizure(3%; 95%CI 0.01–0.06; I² = 83.80% VS 1%; 95%CI 0.00–0.03; I² = 86.05%) was higher, while myalgia(21%; 95%CI 0.13–0.29; I² = 97.82% VS 24%; 95%CI 0.16–0.32; I² = 98.39%), smell impairment(8%; 95%CI 0.05–0.13; I² = 87.77% VS 13%; 95%CI 0.08–0.18; I² = 92.34%) and taste dysfunction(9%; 95%CI 0.05–0.14; I² = 90.24% VS 14%; 95%CI 0.10–0.20; I² = 93.21%) were less. Table 2
Fig. 1 The Study flow Diagram
### Table 1  The details and characteristics of the included studies

| Study                  | Design   | Country | Case | Male(%) | Age (mean) | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations 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| Study | Design | Country | Case | Male(%) | Age (mean) | Neurologic manifestations |
|-------|--------|---------|------|---------|------------|--------------------------|
|       |        |         |      |         |            |                          |
|        |        |         |      |         |            | Headache                  |
|        |        |         |      |         |            | Dizziness                 |
|        |        |         |      |         |            | Altered mental status     |
|        |        |         |      |         |            | Intracerebral hemorrhage  |
|        |        |         |      |         |            | Seizure                   |
|        |        |         |      |         |            | Stroke                    |
|        |        |         |      |         |            | Myalgia                   |
|        |        |         |      |         |            | Smell impairment          |
|        |        |         |      |         |            | Taste dysfunction         |
|        |        |         |      |         |            | Vision impairment         |
|        |        |         |      |         |            | Alteration of consciousness|
|        |        |         |      |         |            | Encephalopathy            |
|        |        |         |      |         |            | Encephalitis               |
|        |        |         |      |         |            | Guillain-Barré Syndrome   |
|        |        |         |      |         |            | (GBS)                     |
| Imen Kacem et al. [30] | RS | Tunisia | 646 | 53.9 | 421.7 | 279 | / | / | / | / | 241 | 245 | 238 | 48 | / | / | / | / |
| B.C. Yoon et al. [31] | RS | USA | 26 | 61.5 | 636 | 2 | / | 14 | 11 | 1 | 2 | / | / | / | / | / | / |
| Chaolin Huang et al. [32] | PS | China | 41 | 73 | 49 | 3 | / | / | / | / | 18 | / | / | / | / | / | / |
| Manuel Requena et al. [33] | PS | Spain | 2050 | 56 | 665 | / | / | / | / | 4 | / | 21 | / | / | / | / | / | / |
| Jennifer A. Frontera et al. [34] | PS * | USA | 4491 | 66 | 71 | / | / | / | / | / | 74 | 84 | / | / | / | / | 309 | / | 3 |
| Timothée Klopfenstein et al. [35] | RS | France | 54 | 33 | 47 | 44 | / | / | / | / | / | 40 | 54 | / | 4 | / | / | / |
| Maryam Jalevi et al. [36] | PS | Iran | 92 | 67.4 | 5294 | 20 | / | / | / | / | / | 57 | 22 | 15 | / | / | / | / |
| David García-Aznar et al. [37] | CSS | Spain | 104 | 36.5 | 567 | 104 | 3 | 10 | / | / | / | 44 | 67 | / | 6 | / | / | / |
| Samar Ilraf Sr et al. [38] | CSS | PAK | 350 | 70 | 495 | 21 | 12 | / | / | / | 1 | / | / | 5 | / | / | 7 | / | 3 | 1 |
| Aamir Makda et al. [39] | CSS | PAK | 114 | 54.4 | 51 | 18 | 20 | / | / | / | 1 | / | / | 9 | 9 | 2 | 10 | / | / |
| Pedro Augusto Sampaio Rocha-Filho et al. [40] | CSS | Brazil | 73 | 63 | 58 | 47 | / | / | / | / | / | 28 | 29 | / | / | / | / | / |
| Abdelkader Mahummedi et al. [41] | RS * | Italy | 108 | 64 | 69 | 13 | 4 | 64 | 6 | 10 | 34 | 13 | 2 | / | / | / | / | / | / |
| Antoine Guilmot et al. [42] | PS | Belgium | 15 | 80 | 62 | / | / | / | / | / | 2 | / | / | 2 | / | / | / | / | / | / |
Table 1 (continued)

| Study                                      | Design | Country   | Case | Male(%) | Age (mean) | Neurologic manifestations |
|--------------------------------------------|--------|-----------|------|---------|------------|---------------------------|
|                                            |        |           |      |         |            | Headache                  |
|                                            |        |           |      |         |            | Dizziness                  |
|                                            |        |           |      |         |            | Altered mental status     |
|                                            |        |           |      |         |            | Intercerebral haemorrhage  |
|                                            |        |           |      |         |            | Seizure                    |
|                                            |        |           |      |         |            | Stroke                     |
|                                            |        |           |      |         |            | Myalgia                    |
|                                            |        |           |      |         |            | Smell impairment           |
|                                            |        |           |      |         |            | Taste dysfunction           |
|                                            |        |           |      |         |            | Vision impairment          |
|                                            |        |           |      |         |            | Alteration of consciousness|
|                                            |        |           |      |         |            | Encephalopathy              |
|                                            |        |           |      |         |            | Encephalitis                |
|                                            |        |           |      |         |            | Guillain-Barré Syndrome (GBS) |
| Jerome R. Lechien et al. [43]             | RS     | Belgium   | 2013 | 34      | 395        | 1411 / / / / / / 1244     |
| Sara Mariotto et al. [44]                  | RS     | Italy     | 107  | 76.6    | 658        | 12 / / / / / / 16          |
| Claudia Liguori et al. [45]                | PS     | Italy     | 103  | 57.3    | 55         | 40 / / / / / / 25          |
| Antonina Amelia [46]                       | RS     | Italy     | 78   | 52.6    | 53.7       | 52 / / / / / / / /         |
| Nao Yan et al. [47]                       | RS, cohort study | China | 1682 | 48.9    | 50         | 216 / / / / / / 311        |
| Elodie Meppiel et al. [48]                 | RS     | France    | 222  | 61.3    | 65         | 24 / / / / / / / /         |
| Hisham Salahuddin et al. [49]              | RS     | USA       | 574  | 48.1    | 62.83      | 82 / / / / / / 80          |
| Rishu Garg et al. [50]                     | CSS    | India     | 106  | 61      | 4907       | 24 / / / / / / 20          |
| Adalberto STUDART-NEU et al. [9]           | RS     | Brazil    | 89   | 61.8    | 574        | 3 / / / / / / 2           |
| M Petrocelli et al. [51]                   | Cohort study | Italy | 301  | 25      | 436        | 133 / / / / / / 128        |
| Daniel J Lee et al. [52]                   | CSS    | Toronto   | 56   | 41.1    | 38         | 10 / / / / / / / /         |
| Yujie Liang et al. [53]                    | RS     | China     | 86   | 51.2    | 255        | 12 / / / / / / / /          |
| Timothée Klopfenstein et al. [54]         | RS     | France    | 70   | 41      | 57         | 51 / / / / / / 41          |
| Weixi Xiong et al. [55]                    | RS, cohort study | China | 917  | 55      | 487        | 2 / / / / / / 10           |
| Jerome R. Lechien et al. [56]              | RS     | Europe    | 417  | 36.9    | 369        | / / / / / / / / 357         |
| Study                            | Design     | Country | Case | Male(%) | Age (mean) | Neurologic manifestations | Intercerebral hemorrhage | Seizure | Stroke | Myalgia | Smell impairment | Taste dysfunction | Vision impairment | Alteration of consciousness | Encephalopathy | Encephalitis | Guillain-Barré Syndrome (GBS) |
|----------------------------------|------------|---------|------|---------|------------|---------------------------|----------------------------|---------|--------|---------|----------------|-----------------|-----------------|---------------------------|----------------|-------------|----------------------|
| Yonghyun Lee et al. [57]          | RS         | Korea   | 3191 | 36.4    | 44         | /                          | /                          | /       | /      | /       | /              | /               | /               | /                         | /              | /           | /                     |
| Ömer Karadaş et al. [58]          | PS         | Turkey  | 239  | 55.6    | 46.46      | 64                         | 16                         | /       |       | /       | /              | /               | /               | /                         | /              | /           | 1                     |
| Benoit Tudrej et al. [59]         | CSS        | France  | 816  | 35      | 45         | 359                        | /                          | /       |       | /       | 166            | 156             | 188             | /                         | /              | /           | /                     |
| Luigi Angelo Vara et al. [60]     | RS         | Italy   | 72   | 37.5    | 49.2       | 30                         | /                          | /       |       | /       | /              | /               | /               | /                         | /              | /           | /                     |
| Valeria Dell’Era et al. [61]      | CSS        | Italy   | 355  | 54.1    | 50         | /                          | /                          | /       | /      | /       | /              | /               | /               | 389                        | 353            | /           | /                     |
| Luis Antonio Díaz et al. [62]     | RS         | Chile   | 7016 | 50      | 40         | 3040                       | /                          | /       | /      | /       | /              | 3082            | /               | /                         | /              | /           | /                     |
| Ruth Levinson et al. [63]         | RS         | Israel  | 42   | 54.8    | 34         | 20                         | 9                          | /       |       | /       | 24             | 14              | 15              | /                         | /              | /           | /                     |
| Paolo J. Fantozzi et al. [64]     | RS, cohort | Italy   | 111  | 52.3    | 57         | /                          | /                          | /       | /      | /       | /              | /               | /               | /                         | /              | /           | /                     |
| Andy Jian Kai Chua et al. [65]    | Cohort     | Singapore | 31   | /       | /          | /                          | /                          | /       | /      | /       | /              | /               | /               | /                         | /              | /           | /                     |
| Alvaro Beltrán-Corbellini et al. [66] | Case-control study | Spain | 79   | 60.8    | 616        | /                          | /                          | /       | /      | /       | /              | 25              | 28              | /                         | /              | /           | /                     |
| Giacomo Spinato et al. [67]       | RS         | UK      | 202  | 48      | 56         | 86                         | 28                         | /       | /      | /       | /              | /               | /               | /                         | /              | /           | /                     |
| Nitesh Gupta et al. [68]          | PS         | India   | 200  | 58      | 40.03      | 22                         | /                          | /       | /      | /       | /              | 54              | 1               | /                         | /              | /           | /                     |
| Marco Luigi et al. [69]           | RS         | Italy   | 213  | /       | 70.2       | 10                         | 3                          | /       | /      | /       | 6              | 2               | 20              | 13                         | 6              | /           | 86                    |
| Erdal Sakallı et al. [70]         | Questionnaire | Turkey | 172  | 48.8    | 378        | 17                         | /                          | /       | /      | /       | /              | 16              | 18              | 11                         | /              | /           | /                     |
| Study                  | Design          | Country | Case | Male(%) | Age (mean) | Neurologic manifestations | Study Design | Country | Case | Male(%) | Age (mean) | Neurologic manifestations |
|------------------------|-----------------|---------|------|---------|------------|---------------------------|--------------|---------|------|---------|------------|--------------------------|
| Eva Aménez et al. [71] | RS,CS           | Spain   | 15-49 | 57.5    | 69         | 133 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Yhui Huang et al. [72] | RS              | China   | 34    | 41.2    | 56.24      | 2 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Souheil Zayet et al. [73] | RS         | France  | 70    | 41      | 57         | 51 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Tyler Scullen et al. [74] | RS,CS         | USA     | 27    | 52      | 598        | 2 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Ling Mao et al. [8]    | RS,CS           | China   | 214   | 40.7    | 52.7       | 28 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Brad Tyson et al. [75] | RS              | USA     | 71    | 47      | 79         | 5 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Alex Carignan et al. [76] | Case−control study | Canada  | 134   | 47.8    | 57.1       | 87 / / / / / / / / / / / / |              |         |      |         |            |                          |
| D. Hornuss et al. [77] | Case−control study | Germany | 45    | 55.6    | 56         | 10 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Firouzeh Heidari et al. [78] | CS    | Iran    | 23    | 34.8    | 37.4       | / / / / / / / / / / / / |              |         |      |         |            |                          |
| Kevin N. Shef et al. [79] | PS,cohort study | USA     | 20    | 85      | 80         | / / / / / / / / / / / / |              |         |      |         |            |                          |
| Carol H. Yan et al. [80] | CSS           | USA     | 59    | 49.2    | 39         | / / / / / / / / / / / / |              |         |      |         |            |                          |
| A. Mahammedi et al. [81] | RS *          | USA     | 135   | 64      | 68.2       | / / / / / / / / / / / / |              |         |      |         |            |                          |
| A. Radmanesh et al. [82] | RS,CS        | USA     | 242   | 62      | 68.7       | / / / / / / / / / / / / |              |         |      |         |            |                          |
| E. Lin et al. [83]     | RS              | USA     | 278   | 59      | 718        | / / / / / / / / / / / / |              |         |      |         |            |                          |
| Francois Lersy et al. [84] | RS,CS       | France  | 58    | 66      | 62         | 3 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Rajesh Benny et al. [85] | RS *          | India   | 100   | 63      | 57         | 21 / / / / / / / / / / / / |              |         |      |         |            |                          |
| Study                        | Design     | Country  | Case | Male(%) | Age (mean) | Neurological manifestations |
|-----------------------------|------------|----------|------|---------|------------|-----------------------------|
|                            |            |          |      |         |            | Headache | Dizziness | Altered mental status | Intracerebral haemorrhage | Seizure | Stroke | Myalgia | Smell impairment | Taste dysfunction | Vision impairment | Alteration of consciousness | Encephalopathy | Encephalitis | Guillain-Barré Syndrome |
| Deusdedit Branda³o Neto et al. | PS         | Brazil   | 655  | 35.3    | 37.7       | 143 | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Eman M. Khedr et al.        | RS, case–control study* | Egypt    | 439  | 54.5    | 62.8       | /   | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Shin-Woo Kim et al.         | RS *       | Korea    | 2254 | 35.8    | 58         | 378 | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Xiaolong Yao et al.         | RS         | China    | 2474 | 49.9    | 61         | /   | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| G.-u Kim et al.             | RS         | Korea    | 172  | 66      | 54         | 32  | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Nathan J Brendish et al.    | RS, cohort study | Korea    | 197  | 57.4    | 68         | 73  | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| L. Cleret de Langavant et al. | RS        | France   | 26   | 73.1    | 583        | 11  | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Carlos DF de Souza et al.   | RS,CSS     | Brazil   | 9807 | 47.5    | 70.21      | 1980 | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Daniel Schoinfeld et al.    | RS         | Argentina| 207,079 | 50    | 429        | 9,939 | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Raphael L. Tuna et al.      | RS,CSS     | Brazil   | 55   | 68      | 612        | /   | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Souheil Zayet et al.        | RS         | France   | 95   | 16.8    | 398        | 74  | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Souheil Zayet et al.        | RS         | France   | 62   | 39      | 56         | 48  | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Seyed Hadi Samimi Ardastani et al. | CSS * | Iran    | 311  | 71.7    | 47         | 45  | /         | /         | /         | /         | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   | /   |
| Study                      | Design                 | Country      | Case  | Male(%) | Age (mean) | Neurological manifestations | Neurocognitive manifestations | Vision | Alteration of consciousness | Headache | Dizziness | Alteration of consciousness | Alteration of consciousness | Alteration of consciousness | Alteration of consciousness | Alteration of consciousness | Alteration of consciousness | Alteration of consciousness |
|---------------------------|------------------------|--------------|-------|---------|------------|-----------------------------|------------------------------|--------|-----------------------------|--------|------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Andrea Pilotto et al.     | RS                     | Italy        | 147   | 49      | 73.1       | 2                           |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Anne Schneider et al.     | RS                     | Germany      | 87    | 44.8    | 37         | 26                          |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Shaista Alam et al.       | RS                     | USA          | 17    | 56.8    | 61         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Behnam Sabayan et al.     | CS                     | Iran         | 15    | 80      | 65         |                             |                             |        |                             |        |            |                             |                             |                             |                             |                             |                             |                             |
| Study                          | Design | Country | Case | Male(%) | Age (mean) | Neurologic manifestations                                      |
|-------------------------------|--------|---------|------|---------|------------|----------------------------------------------------------------|
|                              |        |         |      |         |            | Headache            | Dizziness  | Altered mental status | Intracerebral haemorrhage | Seizure | Stroke | Myalgia | Smell impairment | Taste dysfunction | Vision impairment | Alteration of consciousness | Encephalopathy | Encephalitis | Guillain-Barré Syndrome (GBS) |
| Shensee Samuels et al. [111]  | RS     | USA     | 1537 | 47.4   | 51        | 219 / / / 6 / / / | 439 / / / | 60 / / / / / / /  |
| Javier Trigo et al. [112]     | RS     | Spain   | 576  | 56.7   | 67.2       | 137 / / / / / | 139 / / / | 146 / / / / / / /  |
| Eric M. Lioia et al. [113]    | RS     | USA     | 509  | 55.2   | 58.5       | 192 / / / 4 / 7 | 228 / / | 58 / 81 / / / 162 1 / |
| Javier A. Membrilla et al. [114] | CSS | Spain   | 45   | 37.8   | 404        | 39 / / / / / | 23 / / / | 28 / / / / / / /  |
| Alfonso Goppolia et al. [115] | PS     | Italy   | 73   | 71.2   | 69.75      | 29 / / / / / / | / / / / | / / / / / / /  |
| Sarah L.M. Janus et al. [116] | RS     | Netherlands | 88  | 27.3   | 83.5       | 17 / / / / 1 / | / / / / | / / / / / / /  |
| Porto-Teleeta et al. [117]    | RS     | USA     | 4491 | 1 / /   | / / / / / / | 539 629 / / / | / / / / | / / / / / / /  |
| Alberto J. Guillén Martinez et al. [118] | RS     | Spain   | 126  | 50.4   | 514.6      | 63 / / / / / | / / / / | 79 75 / / / / / /  |
| Aline Mendes et al. [119]     | RS,CSS | Switzerland | 265 | 43     | 85.9       | / / / / / / | / / / / | / / / / / / /  |
| Sara Radmard et al. [120]     | RS     | USA     | 33   | 60.6   | 56.1       | / / / / / / | 9 5 / / | / / / / / / /  |
| Russell R. Kempker et al. [121]| RS     | USA     | 51   | / / /   | / / / / / / | / 28 26 27 / / / | / / / / | / / / / / / /  |
| Study                        | Design | Country     | Case | Male(%) | Age (mean) | Neurologic manifestations                                                                 |
|-----------------------------|--------|-------------|------|---------|-----------|------------------------------------------------------------------------------------------|
|                            |        |             |      |         |           | **Headache** | **Dizziness** | **Altered mental status** | **Intercerebral haemorrhage** | **Seizure** | **Stroke** | **Myalgia** | **Smell impairment** | **Taste dysfunction** | **Vision impairment** | **Alteration of consciousness** | **Encephalopathy** | **Encephalitis** | **Guillain-Barré Syndrome (GBS)** |
| Patrick Dawson et al. [122] | RS     | USA         | 42   | 53      | 21        | 32       | /             | /             | /                     | /         | 24         | 18         | 24   | /          | /          | /          | /                  | /          | /          |                       |
| Vanessa Oliveira et al. [123]| RS *   | Portugal     | 1261 | 51.3    | 70        | 169      | 8            | /             | /                     | /         | 19         | 114        | 52   | 47         | /          | 122        | /                  | /          | /          |                       |
| Stéphane Kremer et al. [124]| RS *   | France       | 64   | 67      | 65        | 10       | /             | /             | /                     | /         | 1          | 17         | 2    | 47         | /          | /          | /                  | /          | /          |                       |
| Nicola Rifo et al. [125]    | RS     | Italy        | 1760 | 64.9    | 64        | 3        | /             | 49            | /                     | /         | 10         | 37         | /    | /          | /          | /          | /                  | /          | /          |                       |
| Priya Anand et al. [126]    | PS     | USA         | 74   | 57      | 64        | 13       | 5             | 39            | /                     | /         | 15         | 14         | 18   | 2          | /          | /          | 3                  | 26         | /          |                       |
| Fernando Daniel Flores Silva et al. [127]| PS,CSS | Mexico       | 1072 | 65      | 53.2      | 76       | 4             | 11            | /                     | /         | 9          | 9          | 75   | 11         | /          | /          | /                  | 2          | /          |                       |
| Juan Carlos Garcia-Monco et al. [128]| PS     | Spain       | 100  | 62      | 63.5      | 44       | 36            | /             | /                     | 2         | 43         | /          | /    | /          | /          | /          | 9                  | /          | /          |                       |
| Carlos Manuel Romero-Sánchez et al. [129]| RS     | Spain       | 841  | 56.2    | 66.42     | 119      | 51            | /             | 3                     | 6         | 11         | 145        | 41   | 52         | /          | /          | /                  | 1          | /          |                       |
| Emad Nader Eskandar et al. [130]| RS *  | USA         | 4711 | 53.3    | 66.3      | /         | /             | 258            | /                     | /         | 26         | 55         | /    | /          | /          | /          | /                  | /          | /          |                       |
| Aravinthan Varatharaj et al. [131]| PS     | UK          | 153  | 48      | 71        | /         | 39            | /             | 9                     | /         | 57         | /          | /    | /          | /          | /          | 9                  | 7          | /          |                       |
| Study                        | Design | Country | Case | Male(%) | Age (mean) | Neurologic manifestations |
|-----------------------------|--------|---------|------|---------|------------|---------------------------|
| Xudong He et al. [132]      | RS     | China   | 77   | 49.4    | 56         | 4 9 / / / 18 1 / / / / / / |
| Suman Kushwaha et al. [133] | CSS    | India   | 14   | 50      | 415        | 4 / / / 5 2 / 2 / / / / / / 1 |
| Alberto Romagnolo et al. [134]| RS     | Italy   | 344  | 59.3    | 615        | / / / / 6 7 / / / / / / / / |
| Sonia M. D. Brucki et al. [135]| RS     | Brazil  | 63   | 50.8    | 60         | 1 / / / 5 25 / / / / / / / 1 |
| Denise Battaglini et al. [136]| RS     | Italy   | 94   | 78.7    | 616        | / / / / 2 3 / / / / / / / / |
| Sofía Portela-Sánchez et al. [137]| PS    | Spain   | 71   | 70.4    | 69         | / / / / 3 6 16 / / / / 15 / / / / |
| Mehran Ghafarifard et al. [138]| RS     | Iran    | 361  | 59.3    | 619        | 109 34 41 4 10 8 174 69 69 / / 11 / / / 1 |
| David T. Chuang et al. [139]| RS     | USA     | 56   | 43      | 692        | 7 / / 2 6 18 / / / 3 25 / / / / |
| Man Amanat et al. [140]     | PS     | Iran    | 873  | 63.7    | 6071       | 110 104 / / / / 217 / / / / / / / / / / / / |
| Siyuan Fan et al. [141]     | RS     | China   | 86   | 62.8    | 666        | 8 6 / / / 6 15 / / / / / / / / / / / / |
| Giovanna Travi et al. [142]| RS     | Italy   | 901  | 51.7    | 64         | 39 / / / 19 53 / / / / / / / / / / / / |
| Hatice Yüksel et al. [143]| RS     | Turkey  | 204  | 58.5    | 67.22      | 28 32 139 / 27 22 / / / / 132 / / / / |
| Study                          | Design   | Country   | Case | Male(%) | Age (mean) | Neurologic manifestations                                                                 |
|-------------------------------|----------|-----------|------|---------|------------|------------------------------------------------------------------------------------------|
| Verena Rass et al. [144]      | PS, cohort study * | Austria | 135  | 61      | 56         | Headache / Dizziness / Altered mental status / Intracerebral haemorrhage / Seizure / Stroke / Myalgia / Smell impairment / Taste dysfunction / Vision impairment / Alteration of consciousness / Encephalopathy / Encephalitis / Guillain-Barré Syndrome (GBS) |
| Marco H. Carcamo Garcia et al. | PS, CSS | Peru     | 199  | 43      | 43         | 143 / 68 / 1 / 1 / 92 / 80 / 81 / 17 / 7 / / / / |
| Juan Carlos García-Monzo et al. [146] | PS, CSS | Spain    | 35   | 71      | 66         | 3 / 2 / 3 / / / / / / / / |
| David García-Azorín et al. [147] | RS * | Spain     | 233  | 54.9    | 61.1       | 30 / 55 / 27 / 63 / 41 / / / / / / / / |
| David García-Azorín et al. [148] | RS, cohort study | Spain     | 576  | 56.6    | 67.19      | 137 / 11 / 98 / 3 / / / 139 / 146 / / / / / / / / |
| Ummehan Ermis et al. [149]    | PS, CSS | Germany   | 53   | 60      | 63         | 11 / 6 / / / / / / / / / 14 / 8 / / / / / 2 / / / / |
| Andrea Giorgianni et al. [150] | RS | Italy     | 26   | 46.1    | 70.6       | 1 / 3 / / / / / / / / / / / / / / / 1 / / / / |
| A. Patel et al. [151]         | RS | UK        | 141  | 58.9    | 456        | / / / / / / / / / / / / / / / / / / / / / / |
| Fatemeh Sadat Mirfazeli et al. [152] | RS | Iran      | 201  | 100     | 5184       | 80 / 4 / 2 / 68 / 66 / / / / / / / / |
| Fatilet Altin et al. (153)     | PS * | Turkey    | 81   | 50.6    | 54.16      | / / / / / / / / / / / / / / / / / / / / / / |
| Kugananthan Ramasamy et al. [154] | RS | Malaysia  | 145  | 62.1    | 43         | 8 / / / / / / / / / 31 / 34 / / / / / / / / / / |
### Table 1 (continued)

| Study                          | Design       | Country | Case | Male(%) | Age (mean) | Neurologic manifestations | Headache | Dizziness | Altered mental status | Intracerebral haemorrhage | Seizure | Stroke | Myalgia | Smell impairment | Taste dysfunction | Vision impairment | Alteration of consciousness | Encephalopathy | Encephalitis | Guillain-Barré Syndrome (GBS) |
|-------------------------------|--------------|---------|------|---------|------------|---------------------------|----------|-----------|------------------------|---------------------------|---------|--------|---------|---------------------|-----------------|------------------------|-----------------------------|-----------------|-------------|-----------------------------|
| Alberto Paderno et al.        | PS, cohort   | Italy   | 151  | 37      | 45         | /             | /         | /         | /                      | /                         | /       | /      | /       | 126                 | 135             | /                      | /                           | /               | /           | /                            |
| Marlene M. Speeth et al.      | PS, CSS      | USA     | 103  | 48.5    | 46.8       | /             | /         | /         | /                      | /                         | /       | /      | /       | 63                  | 67              | /                      | /                           | /               | /           | /                            |
| Kunal Thakur et al.           | PS           | India   | 250  | 57.6    | /          | 124          | /         | /         | /                      | /                         | 98      | 179    | 79      | /                   | /               | /                      | /                           | /               | /           | /                            |
| Muge Özçelik et al.           | PS, cohort   | Turkey  | 116  | 50      | 5724       | 43           | 37        | /         | /                      | /                         | /       | 44     | 48      | /                   | /               | /                      | /                           | /               | /           | /                            |
| Elif Elbol et al.             | RS           | Turkey  | 155  | 42.2    | 36.3       | /             | /         | /         | /                      | /                         | /       | 55     | 25      | /                   | /               | /                      | /                           | /               | /           | /                            |
| Jerome R. Lechen et al.       | RS           | France  | 86   | 34.9    | 41.7       | 42           | /         | /         | /                      | /                         | /       | 30     | 53      | /                   | /               | /                      | /                           | /               | /           | /                            |
| G. O’Sullivan et al.          | RS, case–control study | Ireland | 102  | 23      | 44.1       | 36           | /         | /         | /                      | /                         | /       | 45     | 4       | /                   | /               | /                      | /                           | /               | /           | /                            |
| Edith L. Graham et al.        | PS           | USA     | 50   | 34      | 43.7       | 32           | 20        | /         | /                      | /                         | 30      | 37     | 32      | 9                   | /               | /                      | /                           | /               | /           | /                            |
| Kate Gregorijevic et al.      | RS           | Australia | 106 | 40.6    | 843        | 7            | 7         | /         | /                      | /                         | /       | /      | /       | /                   | /               | /                      | /                           | /               | /           | /                            |
| Hao Lv et al.                 | RS *         | China   | 196  | 44.9    | 506        | 11          | /         | /         | /                      | /                         | /       | 26     | 16      | 9                   | /               | /                      | /                           | /               | /           | /                            |
| Agathe Nouchi et al.          | CSS          | France  | 390  | 51.8    | 505        | 148         | /         | /         | /                      | /                         | /       | 129    | 130     | /                   | /               | /                      | /                           | /               | /           | /                            |
| Shima Shahjoue et al.         | PS *         | USA     | 432  | 57.6    | 657        | /            | /         | 91        | /                      | 323                        | /       | /      | /       | /                   | /               | /                      | /                           | /               | /           | /                            |
| Study                                      | Design | Country       | Case | Male(%) | Age (mean) | Neurologic manifestations                                                                 |
|-------------------------------------------|--------|---------------|------|---------|-----------|------------------------------------------------------------------------------------------|
|                                           |        |               |      |         |           | **Headache** | **Dizziness** | **Altered mental status** | **Intracerebral hemorrhage** | **Seizure Stroke** | **Myalgia** | **Smell impairment** | **Taste dysfunction** | **Vision impairment** | **Alteration of consciousness** | **Encephalopathy** | **Guillain-Barré Syndrome (GBS)** |
| Patricia Bustos et al. [167]              | RS     | Chile         | 458  | 47.4    | 46.35     | 216 | / | / | / | / | / | 281 | / | / | / | / | / | / |
| Adnan A. Mubarak et al. [168]            | RS     | Kingdom of Saudi Arabia | 1022 | 60.9    | / | 520 | / | / | / | / | / | 605 | 542 | 525 | / | / | / | / |
| Egehan Salepci et al. [169]              | CSS    | Turkey        | 223  | 50.7    | 51 | 59 | 5 | / | / | / | / | 113 | 71 | 77 | / | / | / | / |
| J. Zhang et al. [170]                    | RS/cohort study | China | 663  | 48.4    | 55.6 | 20 | 23 | / | / | / | / | / | 63 | / | / | / | / | / | / |
| Alberto Paderno et al. [171]             | CSS    | Italy         | 508  | 56      | 55 | 198 | / | / | / | / | / | / | 283 | 321 | / | / | / | / |
| Izquierdo-Dominguez A et al. [172]       | PS, CSS * | Spain    | 846  | 52.7    | 56.8 | / | / | / | / | / | / | 454 | 442 | / | / | / | / |
| Alma Tostmann et al. [173]               | RS     | The Netherlands | 21.1 | /       | 64 | / | / | / | / | / | / | 57 | 37 | / | / | / | / |
| Mata Rosaria Barlioni et al. [174]       | RS *   | Italy         | 179  | 50.3    | 41 | 73 | / | / | / | / | / | 84 | / | / | / | / | / | / |
| Elisabeth Nimchnitt-Becerra et al. [175] | PS     | Spain         | 1043 | 36.4    | 39 | 782 | / | / | / | / | / | 719 | 826 | 718 | / | / | / | / |
| Brian E. Dixon et al. [176]              | RS     | USA           | 368  | 44.4    | / | / | / | / | / | / | / | 117 | 94 | 105 | / | / | / | / |
| Eman M. Khedr et al. [177]               | RS     | Egypt         | 55   | 50.9    | 515 | 21 | 9 | / | / | / | / | / | / | / | 2 | / | / | / | 2 |
| Pınar Sayın et al. [178]                 | RS     | Turkey        | 52   | 69.2    | 61.32 | / | / | / | / | / | / | 21 | 19 | / | / | / | / | / | / |
| Study                        | Design    | Country | Case | Male(%) | Age (mean) | Neurological manifestations | Neurologic manifestations          | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations | Neurologic manifestations |
|-----------------------------|-----------|---------|------|---------|------------|-----------------------------|------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Eric J. Chow et al. [179]  | RS        | USA     | 48   | 22.9   | 43         | 20                          | Headache, Dizziness, Anorexia, Decreased Intake, Seizures, Stroke, Miosis, Myalgia, Taste Impairment | Vision Impairment          | Alteration of Consciousness | Alteration of Consciousness | Alteration of Consciousness | Alteration of Consciousness | Alteration of Consciousness |
| Altunisik E et al. [180]    | RS        | Turkey  | 51   | 56.9    | 5278       | 9                           | Headache, Dizziness, Anorexia, Decreased Intake, Seizures, Stroke, Miosis, Myalgia, Taste Impairment | Vision Impairment          | Alteration of Consciousness | Alteration of Consciousness | Alteration of Consciousness | Alteration of Consciousness | Alteration of Consciousness |
Table 2 The details and characteristics of the 16 included studies divided into severe and non-severe groups

| Study                          | Severe | Non-severe |
|-------------------------------|--------|------------|
|                              | Case   | Headache  | Dizziness | Seizure | Myalgia | Smell impairment | Taste dysfunction | Case   | Headache  | Dizziness | Seizure | Myalgia | Smell impairment | Taste dysfunction |
| Ling Mao et al. [8]           | 88     | 15        | 17        | 1       | /       | 3           | 3               | 126    | 13        | 19        | /       | /       | 8           | 9               |
| Antoine Guilmot et al. [42]  | 9      | /         | /         | 1       | /       | /           | /               | 6      | /         | 1         | /       | 2       | /           | /               |
| Nitesh Gupta et al. [68]      | 32     | 13        | /         | /       | /       | /           | /               | 168    | 9         | /         | /       | /       | /           | /               |
| François Lersy et al. [84]    | 47     | 1         | /         | 3       | /       | /           | /               | 11     | 2         | /         | 3       | /       | /           | /               |
| Rajesh Benny et al. [85]      | 47     | 8         | /         | 9       | /       | 7           | 2               | 53     | 13        | /         | 9       | /       | 3           | 6               |
| Daniel Schonfeld et al. [94]  | 5652   | 1168      | /         | 60      | 1002    | 380         | 320             | 41,703 | 12,517    | /         | 223     | 9572    | 5893         | 4508             |
| Caizheng Yu et al. [110]      | 864    | /         | /         | 31      | /       | /           | /               | 799    | /         | /         | /       | 26      | /           | /               |
| Shena Samuels et al. [111]    | 147    | 21        | /         | /       | 30      | /           | /               | 346    | 26        | /         | 3       | 86      | /           | /               |
| Eric M. Liotta et al. [113]   | 134    | 43        | 40        | /       | 56      | 11          | 17              | 375    | 149       | 111       | 4       | 172     | 47           | 64               |
| Carlos Manuel Romero-        | 329    | 38        | 17        | 4       | 44      | 9           | 13              | 512    | 81        | 34        | 2       | 101     | 32           | 39               |
| Sánchez et al. [129]          |        |           |           |         |         |             |                 |        |           |           |         |         |              |                 |
| Xudong He et al. [132]        | 23     | 3         | 4         | /       | 8       | /           | /               | 54     | 1         | 5         | /       | 10      | /           | /               |
| Mehran Ghaffari et al. [138]  | 233    | 60        | 22        | 7       | 101     | 42          | 41              | 128    | 49        | 12        | 3       | 73      | 27           | 28               |
| Man Amanat et al. [140]       | 299    | 24        | 29        | /       | 75      | /           | /               | 574    | 86        | 75        | /       | 142     | /           | /               |
| Egehan Salepci et al. [169]   | 45     | 11        | 4         | /       | /       | 6           | 12              | 178    | 48        | 1         | /       | /       | 65           | 65               |
| J. Zhang et al. [170]         | 409    | 13        | 21        | /       | 30      | /           | /               | 254    | 7         | 2         | /       | 33      | /           | /               |
| Altunisik E et al. [180]      | 11     | 4         | /         | /       | /       | /           | /               | 40     | 5         | 5         | /       | 3       | 3           | /               |

Of all the included literatures, 16 studies grouped neurologic features based on COVID-19 severity. We focused on five neurologic manifestations of headache, dizziness, seizure, myalgia, smell impairment, and taste dysfunction.
shows the details and characteristics of the 16 included studies divided into severe and non-severe groups. Included studies had good methodological quality (Figs. 2, 3, 4, 5).

**Discussion**

According to our meta-analysis, the most common neurological manifestations of COVID-19 patients were myalgia (33%), smell impairment (33%), taste dysfunction (33%) and altered mental status (32%). It can be seen that both the central nervous system and peripheral nervous system will be involved after patients are infected with SARS-CoV-2. At the same time, considering the difference between symptoms and diseases, our study can conclude that the most common central nervous system symptoms are altered mental status (32%), headache (29%), alteration of consciousness (13%), and dizziness (10%). The most common central nervous system (CNS) disorders were encephalopathy (26%), stroke (12%), intracerebral haemorrhage (5%), seizure (4%), and encephalitis (2%). The most common symptoms of peripheral nervous system (PNS) impairment were myalgia (33%), smell impairment (33%), taste dysfunction (33%) and vision impairment (6%). Guillain-Barre Syndrome (GBS) occurs in approximately 1% of peripheral nervous system disorder.

In addition, COVID-19 involvement in the peripheral nervous system includes other manifestations, such as cranial neuropathy and neuromuscular joint disease, etc. However, since only a few studies have reported such cases, and most of these studies were case reports, these less frequent COVID-19 peripheral nervous system manifestations were not included in this study. In the future, as more and more of these studies are reported, we can conduct further research.

Among 168 studies that were finally included in the meta-analysis, 123 studies discussed the incidence of headache, 106 studies discussed smell impairment, 86 studies discussed myalgia, and 80 studies discussed taste dysfunction. In our opinion, this also indirectly indicates that COVID-19 patients have symptoms of headache, smell impairment, myalgia and smell impairment earlier and have more cases, which is worthy of further study and discussion, to provide a diagnosis and treatment direction for early intervention in the future.

In 16 of the included studies, patients were divided into severe and non-severe groups for detailed analysis according to the severity of COVID-19 infection in patients. We found that the most studied neurological manifestations in this literature were headache, dizziness, seizure, myalgia, smell impairment and taste dysfunction. Our results showed that there was no significant difference in the incidence of headache between the two groups, both at 16%; the incidence of dizziness and seizure in the severe COVID-19 group was higher than that in the non-severe group (12% VS 9%, 3% VS 1%, respectively). The incidence of myalgia, smell impairment and taste dysfunction in the severe COVID-19 group was lower than that in the non-severe group, which was 21% VS 24%, 8% VS 13%, 9% VS 14%, respectively. However, considering that the severity of COVID-19 disease is not classified the same according to different prevalence periods of COVID-19 and its prevalence in different countries, our statistical data may be biased to a certain extent, and the statistical results may lack a certain scientific nature. At the same time, there are still limited studies on various neurologic characteristics of COVID-19 under different severity, which deserves more research and exploration.

We also found that altered mental status, encephalopathy, and alteration of consciousness were reported separately, but they may be related to each other. Through reading different literature, we found that different researchers have different definitions of the above three aspects. Josef Anrather et al. [181] argue that altered mental status (e.g., confusion, disorientation, emotional restlessness and lethargy) can be collectively referred to as encephalopathy. Emad Nader Eskandar et al. [130] suggested that if there was evidence of cognitive impairment (e.g., confusion, disorientation, agitation or delirium) or impaired arousal (e.g., lethargy or dullness), the patient can be included in the altered mental status cohort. In another study, altered mental status was defined as including personality, behavior, cognition, and consciousness changes; encephalopathy, encephalitis; catatonia, mania, anxiety or depression, etc. [131]. We recognize that there may be overlapped parts among altered mental status, encephalopathy and alteration of consciousness, but they can all indicate that the central nervous system of patients is damaged, so their clinical reference value is not affected.

**Associations between neurologic manifestations and mechanisms of nervous system injury in patients with COVID-19**

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) [182]. The expression profile of ACE2 is very extensive, and it is expressed in various regions of the human brain, such as the ventricle, motor cortex and posterior cingulum gyrus, middle temporal gyrus, substantia nigra, olfactory bulb, contralateral medulla oblongata, nucleus solitaries, vagus nerve, neurons, astrocytes, microglia and oligodendroglia, etc. [183, 184]. Therefore, the nervous system is at risk of SARS-COV-2 infection. The mechanism
Fig. 2 Forest maps of neurological manifestations. a Headache, b myalgia, c smell impairment, d taste dysfunction, e dizziness, f seizure, g stroke, h encephalopathy, i intracerebral haemorrhage, j alteration of consciousness, k altered mental status, l vision impairment, m Guillain-Barré Syndrome (GBS) and n encephalitis. After the heterogeneity test, the results in figures a–n all suggest that there was significant heterogeneity among the selected literature in this study.
of nervous system injury in COVID-19 patients includes cross-neuronal hypothesis, homogenous transmission and BBB transmission, hypoxia, inflammatory response and hypercoagulability and immune mechanism as well. In the following sections, we will analyze and discuss the relationship between the neurological manifestations we have studied and the corresponding mechanisms of neurological damage.

**Altered mental status and alteration of consciousness**

The altered mental status and alteration of consciousness of COVID-19 patients may be a systemic consequence of the over-activation of the body’s immune response or may be caused by the direct invasion of the nerves by SARS-COV2 [185, 186]. Hypoxia, organ dysfunction, the need for large doses of sedatives, and prolonged isolation may also contribute to consciousness changes [181].

**Headache and dizziness**

Headaches and dizziness can be caused by a variety of causes. One reason may be the large and rapid increase of inflammatory cytokines, including IL-1, IL-6, and TNFα, after infection. It can also cause pain if the virus invades the nervous system directly and damages the nerve. Hypoxia leads to the accumulation of acid in brain cells, swelling, and interstitial edema, resulting in cerebral vasodilation or cerebral blood flow obstruction, etc., which is also considered as one of the potential mechanisms of causing headache [185].

**Myalgia**

Because there are ACE2 receptors in skeletal muscle [187], direct cytotoxicity caused by the interaction between SARS-CoV-2 and ACE2 in skeletal muscle should be considered. Secondly, muscle injury
Fig. 3  Funnel plots. a Headache, b myalgia, c smell impairment, d taste dysfunction, e dizziness, f seizure, g stroke, h encephalopathy, i intracerebral haemorrhage, j alteration of consciousness, k altered mental status, l vision impairment, m Guillain-Baré Syndrome (GBS) and n encephalitis. After the bias test, the visual symmetry of the funnel plot and Egger's test showed that the publication of myalgia, taste dysfunction, encephalopathy and vision impairment was unbiased
may be related to the harmful immune response mediated by infection and the increase of pro-inflammatory cytokines [8]. Elevated concentrations of C-reactive protein and D-dimer in the blood may induce the expression of a strong immune response, leading to direct immune-mediated nerve and muscle injury [188]. At the same time, prolonged mechanical ventilation or the use of neuromuscular blockers in patients with severe COVID-19 infection is also closely related to the progression of critical myopathy [189].

Smell impairment and taste dysfunction
Studies have shown that the anosmia of most COVID-19 patients has nothing to do with rhinorrhea or nasal obstruction, and may be related to the transmission of the virus through olfactory nerve epithelial cells and further invasion of the olfactory bulb and central nervous system [43, 190]. It has been reported that higher levels of angiotensin can induce the apoptosis effect of neural stem cells [191], reducing the number of nerve cells migrating to the olfactory bulb, resulting in reduced replacement of

Fig. 4 Forest plots of the severe and non-severe groups. a Headache, b dizziness, c seizure, d myalgia, e smell impairment, f taste dysfunction in severe group and a’ headache, b’ dizziness, c’ seizure, d’ myalgia, e’ smell impairment, f’ taste dysfunction in the non-severe group. After the heterogeneity test, the results in figures a/a’ to f/f’ all suggest that there was significant heterogeneity among the selected literature in this study.
new neurons in the olfactory bulb, and interference with the smell. Animal experiments have shown that SARS-CoV-2 may invade the brain retrograde along with taste and trigeminal nerve pathways in the early stage of infection, causing lesions such as taste disturbance [192].

**Encephalopathy and encephalitis**

Patients with COVID-19 may develop many types of encephalopathy. The combination of SARS-CoV-2 virus and ACE2 receptor increases peripheral vascular resistance, leading to a significant and rapid increase in blood pressure, triggering a cascade reaction that leads to the destruction of blood–brain barrier integrity, cerebral hyperperfusion, and cerebral edema, leading to the development of hypertensive encephalopathy [193, 194]. Hypoxia, insufficient energy supply, or overall insufficiency after severe brain injury can progress to hypoxic-ischemic encephalopathy. Steatosis, liver function damage, or cardiovascular dysfunction after COVID-19 infection may induce the occurrence of hepatic encephalopathy, which may be related to direct liver damage of SARS-CoV-2 or the side effects of some drugs [195, 196]. In addition, recent studies have found an increased incidence of acute renal damage after SARS-CoV-2, and the
pathophysiological mechanism remains unclear, which may also be caused by an inflammatory response, ACE/ACE2 imbalance, or dysfunction of other organs (such as the heart). When patients have renal insufficiency, the body cannot completely discharge toxins and regulate the concentration of cytokines normally, and the brain homeostasis will be destroyed, leading to uremic encephalopathy [197]. When SARS-CoV-2 enters the human body through ACE2, the human body immediately generates an immune response. When the virus invades the brain, it will cause immune damage and lead to the attack of encephalitis [198]. Encephalitis may also be associated with blood–brain barrier disruption and cytokine surges [199].

**Stroke and intracerebral hemorrhage**

SARS-CoV-2 directly invades the nerve through ACE2 receptors and deregulation of blood pressure is the
potential mechanism of COVID-19 stroke [200, 201]. Continuous hypoxia in COVID-19 patients will eventually lead to disorders in neurotransmitter metabolism and mitochondrial failure, causing irreversible nerve damage and increasing the risk of stroke [202]. Studies have shown that increased inflammatory markers such as IL-2, IL-6, macrophage inflammatory protein 1-α or coagulation dysfunction in patients with severe COVID-19 may increase the likelihood of stroke compared with moderate patients [200]. After the SARS-CoV-2 virus binds to the ACE2 receptor, it can lead to increased blood pressure, which may lead to hypertensive crisis in severe cases and increase the risk of intracranial hemorrhage [188].

Seizure
The process of SARS-CoV-2 virus replication in host cells disrupts neuronal function and manifests as seizures, convulsions, and loss of consciousness [203]. The increase of pro-inflammatory mediators may contribute to epileptic seizures, which in turn enhance the production of cytokines such as IL-1B and TNFα [204]. After
the destruction of the blood–brain barrier, inflammatory factors and viral particles flood into the central nervous system, leading to brain damage that can lead to epileptic seizures [188].

**Guillain-Barré Syndrome (GBS)**
Guillain–Barre syndrome (GBS) is an increasing occurrence in patients with COVID-19, a typical viral autoimmune nervous system disease caused by a strong immune response, which includes a range of polyneuropathy characterized by acute motor weakness, mild to moderate paresthesia, cranial nerve involvement, and muscle or nerve root pain [205]. At present, large sample studies on GBS are still lacking, and most researchers express their views in the form of case reports.

**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 [206]. Multiple studies on COVID-19 patients with ischemic stroke have shown that the neutrophil–lymphocyte ratio (NLR) is increased in 90% of the patients [207], CRP is increased in over 90% of the patients [208], and serum ferritin is also increased [209], in which serum ferritin can also predict the degree of nerve injury in patients with acute ischemic stroke [210]. There was a significant correlation between the decrease of interleukin-6 level and the improvement of olfaction and taste function in COVID-19 patients [211]. Elevated serum nerve filament light chain (SNFL) levels in critically ill patients with COVID-19 are closely associated with poor prognosis [212].

**Examination methods reflecting nervous system damage in COVID-19 patients**
In our study, stroke incidence was 12%, intracerebral hemorrhage 5%, encephalopathy 26% and encephalitis 2%. Studies have shown that patients with COVID-19 with acute neuroimaging abnormalities are more likely to have an ischemic stroke. Neuroimaging features of these patients are not invariable but are predominated by acute ischemic infarction, intracranial hemorrhage, and leukoencephalopathy [81]. COVID-19 is an independent risk factor for acute ischemic stroke and a valid indicator of poor prognosis. Meningitis and encephalitis are not very common [213, 214]. In one study, continuous EEG monitoring was performed in 11 of 16 patients with COVID-19, most of whom presented with nonspecific encephalopathy [215]. At the same time, some studies also found significant structural changes in the olfactory nerve, olfactory bulb, olfactory cortex and other olfactory pathways in 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 [94, 95]. The relationship between COVID-19 imaging changes and neurological symptoms requires more research.

**Prognosis of nervous system injury in COVID-19 patients**
Nervous system damage is closely associated with the morality 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 [216]. 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 [217]. 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 neuroscientist impairments, including depression, obsessive–compulsive disorder, psychosis, Parkinson’s disease and Alzheimer’s disease [218]. An experimental animal study has also shown that coronavirus can persist in the central nervous system of its host [219]. The study results of Helms et al. showed that 36% of severe COVID-19 survivors developed Dysfunction Syndrome [220], and some studies also reported that patients with severe dysfunction after the acute phase had significant recovery after active neurological rehabilitation [221]. 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 [213]. 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 [214].

**Advantages and disadvantages of this study**
Our meta-analysis included 168 articles (n = 292,693) detailing the various neurologic symptoms common in COVID-19 patients and providing a comprehensive view of the neurologic symptoms of COVID-19. The results were comprehensive. We started the discussion of 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 literature was 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 will be 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 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, to reduce mortality, reduce disease severity, control disease progression and prevent possible long-term nervous system complications.

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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. HU finished the quality evaluation. All authors read and approved the final manuscript.

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