Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions

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Abstract

Background Coronaviruses mainly affect the respiratory system; however, there are reports of SARS-CoV and MERS-CoV causing neurological manifestations. We aimed at discussing the various neurological manifestations of SARS-CoV-2 infection and to estimate the prevalence of each of them.

Methods We searched the following electronic databases; PubMed, MEDLINE, Scopus, EMBASE, Google Scholar, EBSCO, Web of Science, Cochrane Library, WHO database, and ClinicalTrials.gov. Relevant MeSH terms for COVID-19 and neurological manifestations were used. Randomized controlled trials, non-randomized controlled trials, case-control studies, cohort studies, cross-sectional studies, case series, and case reports were included in the study. To estimate the overall proportion of each neurological manifestations, the study employed meta-analysis of proportions using a random-effects model.

Results Pooled prevalence of each neurological manifestations are, smell disturbances (35.8%; 95% CI 21.4–50.2), taste disturbances (38.5%; 95%CI 24.0–53.0), myalgia (19.3%; 95% CI 15.1–23.6), headache (14.7%; 95% CI 10.4–18.9), dizziness (6.1%; 95% CI 3.1–9.2), and syncope (1.8%; 95% CI 0.9–4.6). Pooled prevalence of acute cerebrovascular disease was (2.3%; 95%CI 1.0–3.6), of which majority were ischaemic stroke (2.1%; 95% CI 0.9–3.3), followed by haemorrhagic stroke (0.4%; 95% CI 0.2–0.6), and cerebral venous thrombosis (0.3%; 95% CI 0.1–0.6).

Conclusions Neurological symptoms are common in SARS-CoV-2 infection, and from the large number of cases reported from all over the world daily, the prevalence of neurological features might increase again. Identifying some neurological manifestations like smell and taste disturbances can be used to screen patients with COVID-19 so that early identification and isolation is possible.

Keywords COVID-19 neurological manifestations · Acute cerebrovascular disease · SARS-CoV-2 infection · Meningoencephalitis · Guillain-Barré syndrome · Smell and taste disturbances

Background

Coronaviruses are enveloped, positive-stranded RNA viruses that mainly cause respiratory and gastrointestinal tract infections [1]. They are divided into four genera: alpha, beta, delta, and gamma. Alphacoronavirus and betacoronavirus cause human infections [1]. Betacoronaviruses are further divided into 4 clades, a–d [2]. SARS-CoV and MERS-CoV are betacoronaviruses which caused outbreaks in 2002 and 2012 respectively [3]. The likely reservoirs of SARS-CoV and MERS-CoV viruses were identified as bats [2]. SARS-CoV-2 is a coronavirus and is classified into the betacoronavirus 2b lineage; however, a distinct clade from the SARS-CoV and MERS-CoV [4, 5]. It has been postulated that reservoir of SARS-CoV-2 is also bats; however, more evidence is needed for proving the assumption [6]. The disease caused by SARS-CoV-2 is termed as COVID-19. COVID-19 outbreak started as a cluster of respiratory illnesses and the first case was reported from Wuhan, Hubei Province, China on 8th December [7, 8]. It was declared as a pandemic by WHO on March 11, 2020 [9].
The most common symptoms of COVID-19 are similar to other coronaviruses which include fever, fatigue, dry cough, anorexia, shortness of breath, myalgia, and headache [10–12]. Old age and co-morbidities are associated with higher mortality and morbidity as compared with younger patients and those without any co-morbidities [10, 12, 13].

The neuroinvasive and neurotropic potential of coronaviruses like SARS-CoV and MERS-CoV has been demonstrated in many previous studies [14, 15]. A similar mechanism is suggested for the SARS-CoV-2 also [16]. Neurological manifestations reported of SARS-CoV, MERS-CoV, and other coronaviruses include peripheral neuropathy [17], myopathies with elevated creatinine kinase [17], large vessel stroke [18], olfactory neuropathy/anosmia [19], meningoencephalitis [20, 21], post-infectious acute disseminated encephalomyelitis [22, 23], Bickerstaff’s encephalitis overlapping with Guillain-Barré syndrome [24], and Guillain-Barré syndrome [24]. This review is aimed at discussing various neurological manifestations in COVID-19, including the frequency of neurological symptoms, morbidity, mortality, laboratory parameters, and imaging findings associated with patients with neurological symptoms. In the meta-analysis, we estimated the proportion of COVID-19 patients developing neurological manifestations.

Methods

Selection criteria and search strategy

We searched the following electronic databases for articles published between 1st December 2019 to 25th June 2020; PubMed, MEDLINE, Scopus, EMBASE, Google Scholar, EBSCO, Web of Science, Cochrane Library, WHO database, and ClinicalTrials.gov. The MeSH terms and keywords used include: “COVID-19” OR “COVID 19” OR “SARS-CoV-2” OR “2019 novel coronavirus” OR “2019 nCoV” AND “Neurological” OR “Brain” OR “CNS features” OR “central nervous system features” OR “peripheral nervous system features” OR “neuropathy” OR “skeletal muscle” OR “myositis” OR “neuromuscular junction” OR “headache” OR “anosmia” OR “olfactory” OR “ageusia” OR “cranial neuropathy” OR “seizures” OR “encephalitis” OR “meningitis” OR “stroke” OR “cerebrovascular disease” OR “cerebral hemorrhage” OR “intracerebral hemorrhage” OR “cerebral infarct” OR “cortical venous thrombosis” OR “deep cerebral venous thrombosis” OR “impaired consciousness” OR “confusion” OR “weakness” OR “Guillain-Barre’ syndrome” OR “Miller Fisher syndrome” OR “ataxia” OR “myopathy” OR “myelitis” OR “myelopathy” with an additional filter of “studies in human subjects”. The search was done between 31st March 2020 and 25th June 2020. To ensure literature saturation, we inspected the references of all studies included in this review. The protocol of this review was registered at PROSPERO (ID-CRD42020185593) prospectively in May 2020.

Inclusion and exclusion criteria

All published randomized controlled trials, non-randomized controlled trials, case-control studies, cohort studies, cross-sectional studies, case series, and case reports, if they had sufficient data on neurological features, laboratory parameters, imaging findings were included in this review. Only those studies were included in which subjects were diagnosed with SARS-CoV-2 infection by real-time RT-PCR or high throughput sequencing analysis of swab specimens or serology or culture. We also included pre-prints and letters if they included data on neurological manifestations in COVID-19. Editorials, systematic reviews, meta-analysis, narrative reviews, conference abstracts, commentaries, animal studies, post-mortem studies, and where translation into English was not possible were excluded. The authors were contacted twice by email if any missing data in the articles.

Data extraction and study quality assessment

Databases selected were searched independently by two members (TF and AP) in the team, and, following duplicate removal, reviewed all the articles and selected articles based on inclusion and exclusion criteria. Reporting was done according to the recommendations of the PRISMA statement [25]. Quality of the non-randomized studies was evaluated using the Newcastle-Ottawa Scale [26, 27] and the quality of one randomized controlled trial was assessed using the CONSORT criteria [28]. Any disagreements between two main reviewers were discussed with a third evaluator. Data about the author’s name, publication date, study setting and design, time and duration of the study, follow-up, the total number of patients evaluated, study population, age, gender, co-morbidities, neurological features, laboratory parameters, imaging findings, morbidity, and mortality were extracted.

Outcome measures

Primary outcomes assessed were neurological manifestations in COVID-19 patients and its prevalence. For the categorical variables, simple and relative frequency and proportions were used. For continuous variables, central tendency (mean or median) and dispersion measures (standard error, standard deviation) were used. To measure association, risk ratios, odds ratios, and hazard ratios were used and 95% confidence intervals calculated. We also assessed secondary outcomes like the association of neurological manifestations with age, co-morbidities, lab parameters including CSF study, imaging features, length of hospital stay, ICU admission, time from onset.
of typical COVID-19 symptoms to neurological manifestations, and morbidity/mortality.

**Strategy for data synthesis, statistical analysis for meta-analysis**

Data synthesis and illustration were done in tables and figures. For the categorical variables, simple and relative frequency and proportions were used. For continuous variables, measures of central tendency (mean or median) and dispersion (standard error, standard deviation) were calculated. The primary aim of our study was to synthesize the findings from multiple studies that investigated the issues related to neurological manifestations in COVID-19 and thus provide a quantitative summary, to better direct future work. The data are available in the form of proportions, defined as the number of cases of interest in a sample with a particular characteristic divided by the size of the sample. To achieve the objective of obtaining a more precise estimate of the overall proportion for a certain event (neurological manifestations) related to COVID-19, the study employed meta-analysis of proportions using a random-effects model and by the DerSimonian-Laird method [29, 30]. We performed data analysis using meta-packages in R (version 3.5.0). Heterogeneity was assessed using the $I^2$ value. $I^2$ can take values from 0% to 100% and it is assumed that an $I^2$ of 25%, 50%, and 75% indicate low, medium, and large heterogeneity respectively [31]. Forest plot was used to visualize the point estimates of study effects and their confidence intervals. Publication bias was evaluated using the funnel plot.

**Results**

Among the 6789 articles identified, 212 studies were included in the systematic review and 74 studies in the meta-analysis (PRISMA flow diagram (Fig. 1)). Out of them, most were retrospective studies, 18 were cohort studies, 11 were prospective studies, nine were cross-sectional studies, one was a randomized controlled trial, one was a case-control study and the rest were all case series and case reports. Among these studies, we found only 19 studies, which investigated specifically neurological features in COVID-19 patients. Other studies, evaluated parameters in general, Table 1 shows a summary of all the observational studies included.

**Neurological manifestations**

Neurological manifestations have been reported in patients with COVID-19 from all over the world. A multicentre, retrospective study by Mao et al. [32] was the first study to evaluate the neurological manifestations in COVID-19 and found that neurological manifestations were present in 36.4% of total 214 patients, out of which most common was CNS manifestations (24.8%) followed by peripheral nervous system manifestations (8.9%). Other large retrospective observational studies reported the incidence of neurological manifestations as 4.3% [45], 15% [47], and 57.4% [49]. The most common neurological manifestations reported in COVID-19 were smell disturbances, taste disturbances, headache, myalgia, and disturbances in consciousness/altered mental status. The prevalence of all the neurological manifestations assessed is given in Table 2. A summary estimate of pooled prevalence and heterogeneity of each neurological manifestation are given in Table 3. Forest plot and funnel plot is given in Figs. 2 and 3 respectively.

**Smell and taste disturbances**

The overall incidence of smell disturbances in the studies ranged from 4.9–85.6% [49, 54] and the most common type of smell disturbance was anosmia. Other smell disturbances noticed were hyposmia, phantosmia, and parosmia [54]. Similarly, the incidence of taste disturbances reported was 0.3–88.8% [47, 54] and the most commonly reported were dysgeusia and ageusia. In the meta-analysis, we found 17 and 14 studies, which assessed the prevalence of smell and taste disturbances respectively and disturbances of smell (35.8%; 95%CI 21.4–50.2) and taste (38.5%; 95%CI 24.0–53.0) sensation were the most common neurological manifestation followed by non-specific neurological manifestations. A case-control study of 79 COVID-19 patients and 40 historical controls of influenza patients from Spain [52] revealed that new-onset smell and taste disorders were significantly higher in the COVID-19 group. Patients in COVID-19 were significantly younger. Another study reported olfactory and taste disturbances occur more frequently in females than males [53]. Lechien et al. [54], Gilani S et al. [140], and Rachel Kaye et al. [141] reported that anosmia can be the initial and early manifestations of COVID-19. Population surveys on new-onset olfactory dysfunction from Iran [142] and UK [143] have reported an increase in olfactory dysfunction during the COVID-19 pandemic.

**Non-specific symptoms**

The most common non-specific neurological symptoms reported in SARS-CoV-2 infection were myalgia, headache syncope, and dizziness. The overall pooled prevalence estimate of the proportion of cases are given in Table 3. Incidence of myalgia reported in various studies ranged from 1.8–62.5% [47, 111], headache from 0.6–70.3% [90, 111], and dizziness from 0.6–21% [47, 113]. In children, myalgia and dizziness were less common and rarely reported. In health care workers, the incidence of myalgia, headache, and dizziness was higher compared with the general
### Table 1  Characteristics of studies included and neurological manifestations

| First author | Article type | Study setting | Type of study | Enrolment date | Follow-up duration | Total number of patients (N) |
|--------------|--------------|---------------|---------------|----------------|---------------------|----------------------------|
| Ling Mao [32] | Published | 3 centers of Union Hospital of Huazhong University of Science and Technology, Wuhan, China | Retrospective, observational case series | January 16, 2020, to February 19, 2020 | NA | 214 |
| Yanan Li [33] | Published | Single centre, Union Hospital of Huazhong University of Science and Technology, Wuhan, China | Retrospective, observational case series | 16 January 2020, to 29 February 2020 | NA | 221 |
| Lu Lu [34] | Published | Multicentre study from Hubei province, Sichuan province, Chongqing municipality, China | Retrospective study | January 18 to February 18, 2020 | NA | 304 |
| F.A. Klok [35] | Published | Multicentre, Netherlands | Prospective study | March 7th 2020, to April 22, 2020 | 14 days | 184 |
| Corrado Lodigiani [36] | Published | Single centre, Humanitas Clinical and Research Hospital, Milan, Italy | Retrospective cohort study | 13 February–10 April 2020 | NA | 388 |
| Megan Fraissé [37] | Published | Single centre, France | Retrospective study | March 6 to April 22, 2020 | NA | 92 (1 lost to follow-up) |
| Siddhant Dogra [38] | Published | NYU Langone Health system, New York, USA | Retrospective cohort study | March 1st and April 27th, 2020 | NA | 3824 |
| Julie Helms [39] | Published | Strasbourg, France | Observational Prospective case series | March 3 and April 3, 2020 | NA | 58 |
| Julie Helms [40] | Published | Two centers of a French tertiary hospital, France | Prospective cohort study | March 3rd and 31st 2020 | April 7th | 150 |
| Sedat G Kandemirli [41] | Published | Multicentre (8 centers), Turkey | Retrospective study | March 1 to April 20, 2020 | NA | 235 |
| Silvia Garazzino [42] | Published | Italian Society of Paediatric Infectious Diseases, Multicentre, Italy | Retrospective study | 25 March 2020, to 10 April 2020 | At least 2 weeks | 168 |
| Rajan Jain [43] | Published | Multicentre (3 centers), New York | Retrospective cohort | March 1, 2020, and April 13, 2020 | NA | 3218 |
| Alberto Benussi [44] | Published | ASST Spedali Civili Hospital, Lombardy, Italy | Retrospective, cohort study | February 21, 2020, to April v5, 2020 | NA | 56 |
| Weixi Xiong [45] | Published | 56 hospitals in Wuhan, Chongqing municipality, Sichuan province, China | Retrospective cohort study | 18 January and 20 March 2020 | NA | 917 (1 asymptomatic patient excluded) (so total 918) |
| Tyler Scullen [46] | Published | Single center, New Orleans, Louisiana | Retrospective cross-sectional analysis | April 22, 2020 | NA | 27 |
| Abdelkader Mahammedi [47] | Published | Multicentre, Italy | Retrospective observational study | Feb 29 to April 4 | NA | 725 |
| Alireza Radmanesh [48] | Published | New York University Langone Medical Center, USA | Retrospective observational case series | March 1 and 31, 2020 | 2 weeks | 3661 |
| Carlos Manuel Romero-Sánchez [49] | Published | Two centers, Albacete, Spain | Retrospective observational | March 1st to April 1st, 2020 | NA | 841 |
| Stéphane Kremer [50] | Published | French Society of Neuroradiology, 16 hospitals, France | Retrospective cohort study | March 23th, 2020, to April 27th, 2020 | NA | 37 |
| Pramusha Pinna [51] | Published | Rush University Medical Center, Chicago, Illinois, USA | Retrospective observational case series | March 1, 2020, to April 30, 2020 | NA | 50 |
| Published | Pilot multicentre case-control study | 23rd to 25th March 2020 | NA | 79 |
Table 1 (continued)

| Author | Institution | Study Design | Start Date | End Date | Total Cases |
|--------|-------------|--------------|------------|----------|-------------|
| Álvaro Beltrán-Corbellini [52] | Multicentre (2 centres) | Madrid, Spain | Cross-sectional study, verbal interview | 19 March 2020 | NA | 59 |
| Andrea Giacomelli [53] | L. Sacco Hospital in Milan, Italy | Prospective survey | NA | NA | 417 |
| Jerome R. Lechien [54] | COVID-19 Task Force of YO-IFOS, Multicentre, Europe | Cross sectional telephone survey | March 19 and March 22, 2020 | NA | 202 |
| Luigi Angelo Vaira [56] | University Hospital of Sassari, Italy | Prospective study | March 31 and April 6, 2020 | NA | 72 |
| Luigi Angelo Vaira [57] | Multicentre, Italy | Prospective study | April 9th and 10th 2020 | NA | 33 |
| Yonghyun Lee [59] | The Daegu Medical Association, South Korea | Prospective telephone interview | March 8, 2020 - March 31, 2020 | NA | 3191 |
| Marlene M. Speth [60] | Kantonsspital Aarau, Aarau, Switzerland | Prospective cross-sectional telephone questionnaire study | March 3, 2020, to April 17, 2020 | NA | 103 |
| T. Klopfenstein [61] | NFC (Nord Franche-Comté) Hospital, France | Retrospective observational | March 1st to March 17th, 2020 | Till 24th, 2020 | 114 |
| Wei-je Guan [11] | Multicentre, 30 provinces in China | Retrospective study | December 11, 2019, to January 31, 2020 | NA | 1099 |
| Nanshan Chen [12] | Jinyintan Hospital, Wuhan, China | Retrospective study | Jan 1 to Jan 20, 2020 | Till Jan 25, 2020 | 99 |
| Chaolin Huang [62] | Jin Yintan Hospital, Wuhan, China | Prospective cohort | Dec 16, 2019, to Jan 2, 2020 | NA | 41 |
| Chaomin Wu [63] | Jin Yintan Hospital, Wuhan, China | Prospective cohort | December 25, 2019- January 26, 2020 | February 13, 2020 | 201 |
| Xiaobo Yang [64] | Jin Yintan Hospital, Wuhan, China | Retrospective, observational study | Dec 24, 2019, to Jan 26, 2020 | Feb 9, 2020 | 52 |
| Tao Chen [65] | Tongji Hospital, Wuhan, China | Retrospective case series | 13 January- 12 February 2020 | 28 February 2020 | 274 |
| Yingzhen Du [66] | 2 centres, Hanyan Hospital and Wuhan Union Hospital, Wuhan, China | Retrospective, observational study | January 9 to February 15, 2020 | February 15, 2020 | 85 |
| Yongli Zheng [67] | Chengdu Public Health Clinical Medical Center, Chengdu, China | Retrospective case series | January 16 to February 20, 2020 | February 23, 2020 | 99 |
| Alfonso J. Rodriguez-Morales [68] | Chile | Cross sectional | March 3, 2020, to March 23, 2020 | NA | 922 |
| Feng Wang [69] | Tongji Hospital Wuhan, China | Retrospective study | January 29, 2020, to February 10, 2020 | February 22, 2020 | 28 |
| Suixin Wan [70] | Chongqing University Three Gorges Hospital, Chongqing, China | Retrospective case series | 23 January - 8 February 2020 | 8 February 2020 | 135 |
| Zhongliang Wang [71] | Union hospital, Wuhan, China | Retrospective case series | January 16 to January 29, 2020 | February 4, 2020 | 69 |
| Dan Sun [72] | Wuhan Children’s Hospital, Wuhan, China | Case series | January 24 to February 24 | February 24, 2020 | 8 |
| Sijia Tian [73] | Multicentre, 57 hospitals, Beijing, China | Retrospective study | Jan 20 to Feb 10, 2020 | Feb 10, 2020 | 262 |
| Fei Zhou [74] | 2 centers, Jinyintan Hospital and Wuhan Pulmonary Hospital, Wuhan, China | Retrospective cohort | Dec 29, 2019, to Jan 31, 2020 | NA | 191 |
| Na Du [75] | First Affiliated Hospital of Jilin University, Jilin, China | Case series | 23 January 2020, to February 2020 | NA | 12 |
| Author(s)                  | Published                                      | Hospital/Country                           | Study Type                      | Dates                           | Total Patients |
|---------------------------|------------------------------------------------|--------------------------------------------|---------------------------------|---------------------------------|----------------|
| Kui Liu [76]              | Published                                     | Tertiary hospitals, Hubei province, China  | Retrospective study             | December 30, 2019, to January 24, 2020 | NA             |
| Alma Tostmann [77]        | Published                                     | Netherlands                               | Online anonymous questionnaire   | 10 March to 29 March 2020        | NA             |
| Yongli Yan [78]           | Published                                     | Tongji Hospital, Wuhan, China             | Retrospective, observational     | January 10, 2020, to February 24, 2020 | NA             |
| Xiang-Wei Xu [79]         | Published                                     | Multicentre, Zhejiang province, China     | Retrospective case series       | 10 January 2020, to 26 January 2020 | NA             |
| Jiangshan Lian [80]       | Published                                     | Health Commission of Zhejiang Province    | Retrospective study             | Jan 17 to Feb 7, 2020           | Feb. 12, 2020   |
| Nitesh Gupta [81]         | Published                                     | Multicentre, Zhejiang province, China     | Retrospective observational case series | Feb 1st to 19th March 2020 | 19th March 2020 |
| Xiaoli Yan [82]           | Published                                     | Tongji Hospital, Wuhan, China             | Retrospective study             | January 17 to February 8         | NA             |
| Jiangshan Lian [80]       | Published                                     | Health Commission of Zhejiang Province    | Retrospective study             | January 17 to February 8         | NA             |
| Nitesh Gupta [81]         | Published                                     | Multicentre, Zhejiang province, China     | Retrospective study             | 22 January 2020, to 10 February 2020 | 11 February 2020 |
| Ivan Fan-Ngai Hung [84]   | Published                                     | Multicentre, Hong Kong, China             | Prospective, open-label, randomised, phase 2 trial | Feb 10 to March 20, 2020 | NA             |
| Huan Wu [85]              | Published                                     | Wuhan Children’s Hospital, Wuhan, China   | Retrospective case series       | January 25 to April 18, 2020    | April 18, 2020   |
| Michael G Argenziano [86] | Published                                     | NewYork-Presbyterian/Columbia University Medical Center, New York, USA | Retrospective review | 1 March to 5 April 2020 | 30 April |
| Simone Bastrup Israelsen [87] | Published                                      | Hvidovre Hospital, Denmark               | Retrospective case series       | 10 March to 23 April 2020        | NA             |
| Matthew J Cummings [88]   | Published                                     | NewYork-Presbyterian hospitals affiliated with Columbia University Irving Medical Center, New York, USA | Prospective observational cohort | March 2 to April 1, 2020 | April 28, 2020 |
| Marjolein F. Q. Kluytmans-van den Bergh [89] | Published                                     | 2 teaching Hospitals, Netherlands         | Cross sectional                 | March 12, 2020, and March 16, 2020 (interview dates) | March 16, 2020 |
| Błażej Nowak [90]         | Published                                     | Central Clinical Hospital, Warsaw, Poland | Retrospective study             | March 16, 2020, to April 7, 2020 | April 7, 2020   |
| Xiaoquan Lai [91]         | Published                                     | Tongji Hospital Wuhan                    | Retrospective case series       | January 1 to February 9, 2020   | NA             |
| X. Wang [92]              | Published                                     | Dongxihu Fangcheng Hospital, Wuhan, China | Retrospective study             | 7 February to 12 February 2020   | 22 February    |
| Zhe Liu [93]              | Published                                     | Multicentre Xi’an, Shaanxi province, China | Retrospective study             | January 16 to February 13, 2020  | NA             |
| Qiong Huang [94]          | Published                                     | Multicentre, Hunan, China                 | Retrospective case series       | January 17 to February 10, 2020  | NA             |
| Kyung Soo Hong [95]       | Published                                     | Yeungnam University Medical Center in Daegu, South Korea | Retrospective study | Up to March 29, 2020 | March 29, 2020 |
| Rui Huang [96]            | Published                                     | Multicentre Jiangsu province, China       | Retrospective study             | January 22, 2020, to February 10, 2020 | February 10, 2020 |
| Mengyao Ji [97]           | Published                                     | Renmin Hospital of Wuhan University Wuhan, China | Retrospective study | 2nd January to 28 January 2020 | 8 February 2020 |
| Dawei Wang [98]           | Published                                     | Zhongnan Hospital of Wuhan University Wuhan, China | Retrospective study | Up to February 10, 2020 | NA             |
| Saurabh Aggarwal [99]     | Published                                     | Unity Point Clinic, USA                   | Retrospective study             | March 1 to April 4, 2020         | NA             |
| Xin-Ying Zhao [100]       | Published                                     | Jingzhou Central Hospital, China          | Retrospective study             | January 16, 2020, to February 10, 2020 | February 10, 2020 |
| Name                | Published                          | Institution                                         | Study Type                  | Dates                                      | Patients |
|---------------------|------------------------------------|-----------------------------------------------------|-----------------------------|-------------------------------------------|----------|
| Yifan Meng [101]   | Published                          | Tongji Hospital, Wuhan, China                       | Retrospective study         | January 16th to February 4th, 2020       | 168      |
| Qingchun Yao [102] | Published                          | Dabieshan Medical Center, Huanggang city, Hubei Province, China | Retrospective cohort      | January 30, 2020 - February 11, 2020     | 108      |
| Li Zhu [103]       | Published                          | Multicentre, Jiangsu province, China.               | Retrospective case series   | January 24, 2020, to February 22, 2020   | 10       |
| Eu Suk Kim [104]   | Published                          | Korea National Committee for Clinical Management of COVID-19, South Korea | Nationwide multicentre retrospective study | January 19th, 2020, to February 17th, 2020 | 28       |
| Pavan K. Bhatnaju [105] | Published                          | Multicentre (9), Seattle, USA                       | Retrospective study         | February 24 to March 9, 2020             | 24       |
| Haiyan Qiu [106]   | Published                          | Multicentre (3), Zhejiang, China                    | Retrospective cohort        | January 21 to March 1, 2020              | 36       |
| Guang Chen [107]   | Published                          | Tongji Hospital, Wuhan, China                       | Retrospective study         | Late December 2019 to January 27, 2020   | 21       |
| Wenjie Yang [108]  | Published                          | Multicentre (3 centers), Wenzhou city, Zhejiang, China | Retrospective cohort       | January 17th to February 10th, 2020      | 149      |
| Yu-Huan Xu [109]   | Published                          | Single centre, Beijing, China                       | Retrospective study         | January to February 2020                 | 50       |
| Xi Xu [110]        | Published                          | Guangzhou Eighth People’s Hospital, Guangzhou, China | Retrospective study        | January 23, 2020, and February 4, 2020   | 90       |
| Jerome R. Lechien [111] | Published                          | Multicentre, Europe                                | Observational, cross-sectional study | March 22 to April 10, 2020               | 1420     |
| Sherry L. Burrer [112] | Published                          | CDC COVID-19 Response Team, United states, USA      | Retrospective study         | February 12 to April 9, 2020             | 9282     |
| Ruth Levinson [113] | Published                          | Tel Aviv Medical Center, Israel                     | Retrospective with questionnaire via mobile and email | March 10 to 23, 2020                     | 42       |
| Xu Zhu [114]       | Preprint                           | Renmin Hospital of Wuhan University, Wuhan, China  | Retrospective study         | January 20 to February 15, 2020          | 114      |
| Dan Wang [115]     | Preprint                           | Zhongshan Hospital, Wuhan, China                   | Cross-sectional study       | January 15, 2020 - February 28, 2020     | 143      |
| Chuming Chen [116] | Preprint                           | Shenzhen Third People’s Hospital, Guangdong, China  | Prospective study           | Jan 16, 2020, to Feb 19, 2020            | 31       |
| Pingzheng Mo [117] | Published                          | Zhongnan Hospital of Wuhan University, Wuhan, China | Retrospective study         | January 1st to February 5th              | 155      |
| Gu-qin Zhang [118] | Published                          | Zhongnan Hospital of Wuhan University, Wuhan, China | Retrospective case series   | January 2, 2020, to February 10, 2020    | 221      |
| Jennifer Tomlins [119] | Published                          | North Bristol NHS Trust, UK                        | Retrospective study         | March 10th to March 30th, 2020           | 95        |
| Zonghao Zhao [120] | Published                          | First Affiliated Hospital of USTC Hefei, China     | Retrospective study         | Jan 21 to Feb 16, 2020                   | 75        |
| Ying Huang [121]   | Preprint                           | Fifth Hospital of Wuhan, Wuhan, China              | Retrospective study         | Jan 21 - Feb 10, 2020                    | 36        |
| Carol H. Yan [122] | Published                          | University of California San Diego Health, La Jolla, California, USA | Cross-sectional internet- and email-based platform | March 3, 2020, and March 29, 2020         | 59        |
Table 1 (continued)

| First author           | Study population                                      | Age (years), mean ± SD or median (range) or median (IQR) | Sex (male) n (%) | Neurological features n (%) | Remarks (groups compared) | Outcome n (%) |
|------------------------|-------------------------------------------------------|-----------------------------------------------------------|------------------|----------------------------|---------------------------|---------------|
| Ling Mao [32]          | Consecutive hospitalized patients                     | 52.7 ± 15.5                                                | 87 (40.7)        | Any—78 (36.4)              | Severe vs non-severe      | NA            |
|                        |                                                       |                                                           |                  | CNS—53 (24.8)             | 5 ischaemic stroke, 1 hemorragic stroke |               |
|                        |                                                       |                                                           |                  | Dizziness—36 (16.8)       |                           |               |
|                        |                                                       |                                                           |                  | Headache—28 (13.1)        |                           |               |
|                        |                                                       |                                                           |                  | Impaired consciousness—16 (7.5) |                           |               |
|                        |                                                       |                                                           |                  | Acute cerebrovascular disease—6 (2.8) |                           |               |

First author | Study population                             | Age (years), mean ± SD or median (range) or median (IQR) | Sex (male) n (%) | Neurological features n (%) | Remarks (groups compared) | Outcome n (%) |
---|---|---|---|---|---|---|
Yan Deng [123] | 2 centers, Wuhan, China | Retrospective study | January 1, 2020, to February 21, 2020 | NA | 225 |
Jiaojiao Chu [124] | Tongji Hospital, Wuhan, China | Retrospective study | 7 January to 11 February 2020 | NA | 38 |
Håkon Ihle-Hansen [125] | Barnum Hospital, Norway | Observational qualitative study | 9-31 March 2020 | 31 March 2020 | 42 (1 pt. from 43 not included as asymptomatic and tested due to exposure) |
Parag Goyal [126] | 2 centres, New York, USA | Retrospective case series | March 3 to March 27, 2020 | April 10th | 393 |
Jiantai Cao [127] | Wuhan University Zhongnan Hospital, Wuhan, China | Retrospective cohort | 3 January to 1 February 2020 | 15 February 2020 | 102 |
De Chang [128] | Multicentre (3 centers), Beijing, China | Case series | January 16, 2020, to January 29, 2020 | February 4, 2020 | 13 |
Huijun Chen [129] | Zhongnan Hospital of Wuhan University, Wuhan, China | Retrospective case series | Jan 20 to Jan 31, 2020 | Feb 4, 2020 | 9 |
Lang Wang [130] | Renmin Hospital of Wuhan University, China | Retrospective study | Jan 1 to Feb 6, 2020 | March 5 | 339 |
Gianfranco Spiteri [131] | WHO European Region(except UK), Europe | Cross-sectional study | 24 January to 21 February 2020 | 21 February 2020 | 31 (total 38, but for symptoms data available for 31 only) |
Yingxia Liu [132] | Shenzhen Third People’s Hospital, China | Case series | Jan 11 to Jan 20, 2020 | NA | 12 |
Tianmin Xu [133] | Third Hospital of Changzhou, Changzhou city, Jiangsu province, China | Retrospective cohort | Jan 23 to February 18,2020 | February 27, 2020 | 51 |
Michael Chung [134] | Multicentre (3 centers), 3 provinces, China | Retrospective case series | January 18, 2020, to January 27, 2020 | NA | 21 |
Heshui Shi [135] | Wuhan Jinyintan hospital or Union Hospital of Tongji Medical College, China | Retrospective study | Dec 20, 2019, to Jan 23, 2020 | Feb 8th, 2020 | 81 |
Luhuan Yang [136] | Yichang Central People’s Hospital, Yichang, Hubei Province, China | Retrospective study | Jan 30 to Feb 8, 2020 | Feb 26, 2020 | 200 |
Wei Zhao [137] | Multicentre (4 centers), Hunan, China | Retrospective study | NA | NA | 101 |
Ya-nan Han [138] | Xian eighth hospital Shaanxi, China | Retrospective study | 31st January-16th February 2020 | NA | 32 |
Yang Wang [139] | Tongji Hospital, China | Cohort | January 25, 2020, to February 25, 2020 | 28 days follow-up | 344 |
| Study | Setting | Sample Size | Main Diagnoses and Findings |
|-------|---------|-------------|-----------------------------|
| Yanan Li [33] | Consecutive hospitalized patients | 53 ± 15.9 | Acute cerebrovascular disease—13 (5.9), Ischaemic stroke—11 (84.6) |
| | | | Cerebral venous sinus thrombosis—1 (7.7) |
| | | | Acute cerebrovascular disease—3 (1) |
| Lu Lu [34] | Consecutive discharged or died patients from multiple centers | 44 (33–59.25) | Acute cerebrovascular disease—3 (1) |
| | | | Mild, moderate vs severe, critical |
| F.A. Klok [35] | Only ICU patients | NA | Mild, moderate vs severe, critical |
| Corrado Lodigiani [36] | Consecutive adult symptomatic patients admitted, 61 ICU patients | 66 (55–75) | Acute cerebrovascular disease—5 (2.8) (all ischaemic stroke) |
| | | | All patients received thromboprophylaxis |
| | | | ICU vs general ward, survivors vs non-survivors, thromboprophylaxis in 100% ICU and 75% ward patients |
| Megan Fraissé [37] | Only ICU patients | 61 (55–70) | Acute cerebrovascular disease—4 (4.3) |
| | | | All received thromboprophylaxis |
| Siddhant Dogra [38] | All hospitalized patients | 62 (37–83) (among 33 patients) | Acute hemorrhagic stroke—33 (0.9) (only in 75% neuroimaging done) |
| | | | 37 had hemorrhage, but 4 excluded as hemorrhage secondary to trauma, bleeding in brain metastases, after tumor resection |
| Julie Helms [39] | Consecutive hospitalized ICU patients | 63 | Agitation—40/58 (69) |
| | | | Corticospinal tract signs—39/58 (67) |
| | | | DysExecutive syndrome—14/39 (36) |
| | | | MRI—leptomeningeal enhancement—8/13 (62) |
| | | | Perfusion abnormalities—11/11 (100) |
| | | | Cerebral ischaemic stroke—3/13 (23) |
| Julie Helms [40] | All consecutive patients referred to ICU for ARDS | 63 (53–71) | Cerebral ischaemic attack—2 (1.3) (population after matching—0) |
| | | | Historical prospective cohort of “non-COVID-19 ARDS” patients vs COVID-19 ARDS |
| | | | Discharged—36 ICU admission—101 Died—13 |
| Sedat G Kandemirli [41] | Patients admitted to ICU | 63 (34–87) | Neurological symptoms—50 (21) |
| | | | Cortical signal abnormalities on FLAIR images—10/27 (37) |
| | | | Acute transverse sinus thrombosis—1 (0.4) |
| | | | Brain MRI done in 27/50 (54%) patients with neurological symptoms |
### Table 1 (continued)

| Study | Type | Patients | Age (mean ± SD or range) | Features | Outcomes |
|-------|------|----------|--------------------------|----------|----------|
| Silvia Garazzino [42] | Pediatric patients under 18 years | 2.3 (0.3–9.6) | 94 (55.9) | Acute infarction in right middle cerebral artery territory—1 (0.4) | NA Recovered—168 |
| Rajan Jain [43] | All patients admitted | NA | NA | Neuro imaging done—454 (14.1%) | NA |
| | | | | Imaging Positive—38 (8.4) | |
| | | | | Stroke—35 (92.5) | |
| | | | | Ischaemic stroke—26 (68.5) | |
| | | | | Large vessel—17 (44.5) | |
| | | | | Lacunar—9 (24) | |
| | | | | Hemorrhagic stroke—9 (24) | |
| | | | | Hypoxic anoxic brain injury—2 (5) | |
| | | | | Encephalitis—1 (2.5) | |
| Alberto Benussi [44] | All adult (≥18 years old) patients admitted for neurological disease and had a definite outcome | 77.0 (67.0–83.8) | 28 (50.0) | Cerebrovascular disease—43 (76.8) | COVID-19 vs non-COVID-19 Mortality—21 (37.5) |
| | | | | TIA—5 (11.6) | |
| | | | | Ischaemic stroke—35 (81.4) | |
| | | | | Hemorrhagic stroke—3 (7.0) | |
| | | | | Epilepsy—4 (7.1) | |
| | | | | Delirium—15 (26.8) | |
| | | | | Cerebral palsy—1 (2.5) | |
| Weixi Xiong [45] | All consecutive symptomatic patients | 48.7 ± 17.1 | 504 (55) | New-onset neurological events—39 (4.3) | Critical vs non-critical neurological events Discharged—742 Hospitalized—145 Died—30 |
| | | | | Disturbance of consciousness/delirium—21 (2.3) | |
| | | | | Syncope—3 (0.3) | |
| | | | | Traumatic brain injury—1 | |
| | | | | Acute Cerebrovascular accident—10 (early onset—2) | |
| | | | | Oculomotor palsy—1 | |
| | | | | Unexplained severe headache—2 | |
| | | | | Non-specific headache—8 | |
| | | | | Functional or Tic/tremor—2 | |
| | | | | Muscle cramp—2 | |
| Tyler Scullen [46] | Severe cases with neurological features | 59.8 (35–91) | 14 (52) | Altered mental status—26 (96.3) | Imaging and EEG Encephalopathy—20 (74) |
| | | | | Dysgeusia—1 (3.7) | |
| | | | | Generalized weakness—1 (3.7) | |
| | | | | Headache—2 (7.4) | |
| | | | | Focal deficit—10 (37.0) | |
| | | | | Focal ataxia—1 (3.7) | |
| | | | | Facial droop—1 (3.7) | |
| | | | | Fixed pupils—1 (3.7) | |
| | | | | Gaze deviation—3 (11.1) | |
| | | | | Hemiparesis or hemiplegia—4 (14.9) | |
| | | | | Acute necrotizing encephalopathy—2 (7) | |
| | | | | Vascular disease—5 (19) | |
| | | | | Subacute ischaemic stroke—4 (14.8) | |
| | | | | NCSE—1 (3.7) | |
| | | | | Large vessel occlusion—PCA P2B—1 (3.7) | |
| Study                        | Study Design                  | Patients | Neurological Symptoms | ICA Terminus |
|------------------------------|-------------------------------|----------|-----------------------|-------------|
| Abdelkader Mahammedi [47]    | Consecutive hospitalized patients | NA       | NA                    | 3 (11.1)    |
|                              |                               |          |                       |             |
|                              |                               |          | Acute neurological symptoms—108 (15) |             |
|                              |                               |          | Altered mental status—64 (8.8) |             |
|                              |                               |          | Ischaemic stroke—33 (total was 34, but 1 is hypoxic encephalopathy added here) |             |
|                              |                               |          | Headache—13 (1.8) |             |
|                              |                               |          | Myalgia—13 (1.8) |             |
|                              |                               |          | Seizures—10 |             |
|                              |                               |          | Dizziness—4 (0.6) |             |
|                              |                               |          | Neuralgia—3 |             |
|                              |                               |          | Ataxia—2 (0.3) |             |
|                              |                               |          | Hyposmia—2 (0.3) |             |
|                              |                               |          | ICH-6 |             |
|                              |                               |          | Hypoxic ischaemic encephalopathy—1 |             |
|                              |                               |          | Cerebral venous thrombosis—2 |             |
|                              |                               |          | GBS—2 |             |
|                              |                               |          | PRES—1 |             |
|                              |                               |          | Acute encephalopathy—1 |             |
|                              |                               |          | Non-specific encephalopathy—2 |             |
|                              |                               |          | MS plaque exacerbation—2 |             |
| Alireza Radmanesh [48]       | All patients diagnosed        | NA       | NA                    | 197 (23.42) |
|                              |                               |          | Acute/subacute infarct—13 |             |
|                              |                               |          | Haemorrhage—7 (excluding previous) |             |
|                              |                               |          | Altered mental status—102 (2.9%) |             |
|                              |                               |          | Syncope/fall—79 patients |             |
| Carlos Manuel Romero-Sánchez [49] | All patients admitted           | 66.42 ± 14.96 | 473 (56.2) |             |
|                              |                               |          | Neurological manifestations—483 (57.4) |             |
|                              |                               |          | Myalgias—145 (17.2) |             |
|                              |                               |          | Headache—119 (14.1) |             |
|                              |                               |          | Dizziness—51 (6.1) |             |
|                              |                               |          | Syncope—5 (0.6) |             |
|                              |                               |          | Anosmia—41 (4.9) |             |
|                              |                               |          | Dysgeusia—52 (6.2) |             |
|                              |                               |          | Disorders of consciousness—165 (19.6) |             |
|                              |                               |          | Seizures—6 (0.7) |             |
|                              |                               |          | Dysautonomia—21 (2.5) |             |
|                              |                               |          | AIDP—1 |             |
|                              |                               |          | HyperCKemia—73 (9.2) |             |
|                              |                               |          | Rhabdomyolysis—9 (1.1) |             |
|                              |                               |          | Myopathy—26 (3.1) |             |
|                              |                               |          | Ischaemic stroke—11 (1.3) |             |
|                              |                               |          | Intracranial hemorrhage—3 (0.4) |             |
|                              |                               |          | Movement disorders—6 (0.7) |             |
|                              |                               |          | Encephalitis—1 (0.1) |             |
|                              |                               |          | Optic neuritis—1 (0.1) |             |
| Stephe Kremer [50] | Severe patients with abnormal MRI Only | 61 (8–78) | 30 (81) | Neuropsychiatric symptoms—167 (19.9) | Non-hemorrhagic vs hemorrhagic forms | Died—5 (14) |
|-------------------|---------------------------------------|-----------|---------|-----------------------------------|-----------------------------------|----------|
|                   |                                       |           |         | Headache—4 (11)                   | CSF—1 patient’s CSF SARS-CoV-2 |          |
|                   |                                       |           |         | Seizures—5 (14)                   | RT-PCR positive                  |          |
|                   |                                       |           |         | Clinical signs of corticospinal tract involvement—4 (11) | |          |
|                   |                                       |           |         | Disturbances of consciousness—27 (73) | |          |
|                   |                                       |           |         | Confusion—12 (32)                  | |          |
|                   |                                       |           |         | Agitation—7 (19)                   | |          |
|                   |                                       |           |         | Pathological wakefulness in intensive care units—15 (41) | |          |
| Pranusha Pinna [51] | Only 50 patients admitted to neurology ward or referred to neurology is studied | NA | NA | CNS | Neurological manifestations—7.7% | NA |
|                   |                                       |           |         | Altered mental status—30 | (total patients in the hospital were 650; however, not all evaluated for neurological symptoms, mentioned in the limitations of the study) | |          |
|                   |                                       |           |         | Seizures—13 | |          |
|                   |                                       |           |         | Headache—12 | |          |
|                   |                                       |           |         | Short-term memory loss—12 | |          |
|                   |                                       |           |         | Acute cerebrovascular accident—19 | |          |
|                   |                                       |           |         | Acute ischemic stroke—10 | |          |
|                   |                                       |           |         | Hypoxic ischemic brain injury—7 | |          |
|                   |                                       |           |         | ICH—4 | |          |
|                   |                                       |           |         | Non-aneurysmal SAH—4 | |          |
|                   |                                       |           |         | PRES—2 | |          |
|                   |                                       |           |         | TIA—1 | |          |
|                   |                                       |           |         | PNS | |          |
|                   |                                       |           |         | Dysautonomia—6 | |          |
|                   |                                       |           |         | Muscle injury with elevated CK—6 | |          |
|                   |                                       |           |         | Hypogeusia/dysgeusia—5 | |          |
|                   |                                       |           |         | Hyposmia—3 | |          |
|                   |                                       |           |         | Extraocular muscle abnormalities—5 | |          |
|                   |                                       |           |         | Isolated unilateral facial palsy—3 | |          |
|                   |                                       |           |         | Paresthesias—1 | |          |
|                   |                                       |           |         | Ataxia—1 | |          |
|                   |                                       |           |         | Smell and/or taste disorder—31 (39.2) | |          |
|                   |                                       |           |         | Smell disorder—25 (31.65) | |          |
|                   |                                       |           |         | Most common—anosmia—14/31 (45.7) | |          |
|                   |                                       |           |         | Taste disorder—28 (35.44) | |          |
|                   |                                       |           |         | Most common—ageusia—14/31 (45.2) | |          |
|                   |                                       |           |         | Headache—2 (3.4) | |          |
|                   |                                       |           |         | Olfactory and/or taste disorders—20 (33.9) | |          |
|                   |                                       |           |         | Olfactory disorders—14 | |          |
|                   |                                       |           |         | Taste disorder—17 | |          |
|                   |                                       |           |         | Olfactory dysfunction—357 (85.6) | |          |
|                   |                                       |           |         | Anosmia—284 (79.6) | |          |
|                   |                                       |           |         | Hyposmia—73 (20.4) | |          |
|                   |                                       |           |         | Phantosmia—12.6% | |          |

**Table 1 (continued)**

| Álvaro Beltrán-Corbellini [52] | Consecutive patients hospitalized, > 18 years | 61.6 ± 17.4 | 48 (60.8) | Case—COVID-19 patients | Control—40 historical group of 2019/2020 season influenza patients | NA |
|--------------------------------|------------------------------------------------|-------------|-----------|------------------------|---------------------------------------------------------------|-----|
| Andrea Giacomelli [53]         | All hospitalized patients who were able to be interviewed | 60 (50–74) | 40 (67.8) | NA | NA |
| Jerome R. Lechien [54]         | Adult > 18 years, mild to moderate cases (ICU cases excluded) hospitalized and home patients | 36.9 ± 11.4 | 154 (36.9) | NA | NA |
| Study/Author/Setting | Description | Data | Headache | Muscle/joint pain | Dizziness | Altered sense of smell or taste | Gustatory disorders | Distorted ability to taste flavors | Ref. |
|----------------------|-------------|------|-----------|------------------|-----------|-------------------------------|---------------------|----------------------------------|------|
| Giacomo Spinato [55] | Adults (≥ 18 years) consecutively assessed and mildly symptomatic (only home managed patients) | Parosmia—32.4% | Gustatory disorders—342 (88.8) | Reduced/discontinued—78.9% | Distorted ability to taste flavors—21.1% | Headache—86 (42.6) | Muscle or joint pains—90 (44.6) | Dizziness—28 (13.9) | Altered sense of smell or taste 130— (64.4%) | NA |
| Luigi Angelo Vaira [56] | Adults over 18 years of age (excluded assisted ventilation patients) | | | | | | | | | NA |
| Luigi Angelo Vaira [57] | Health care staff, home quarantined, age > 18 years | | | | | | | | | NA |
| Luigi Angelo Vaira [58] | Both hospitalized and home quarantined patients, ≥ 18 years (excluded assisted ventilation patients) | | | | | | | | | Validation of a self-administered olfactory and gustatory test done |
| Yonghyun Lee [59] | COVID-19 patients awaiting hospitalization or facility isolation | Headache—30 (41.6) | Olfactory and taste disorders—53 (73.6) | Olfactory disorder—44 (61.1) | Taste disorder—39 (54.2) | Objective tests used | | | | |
| Markene M. Speth [60] | All positive (ICU and deceased excluded) | Headache—16 (11) | Olfactory dysfunction—63 (61.2) | Decreased smell—14.6% | Anosmia—46.6% | Gustatory dysfunction—67 (65.0) | Decreased taste—25.2% | Anosmia—389 | NA |
| T. Klopfenstein [61] | All admitted adults | | | | | | | | | Death—2/54(4) |
| Dawei Wang [10] | Consecutive patients admitted | Myalgia—48 (34.8) | | | | | | | ICU vs non-ICU |
| Wei-je Guan [11] | All patients with data available | Headache—150 (13.6) | Myalgia or arthralgia—164 (14.9) | Rhabdomyolysis—2 (0.2) | All Severe vs non-severe | Death—15 (1.4) | Discharged—55 (5.0) | Hospitalization—1029 (93.6) | Recovery—9 (0.8) |
| Nanshan Chen [12] | All hospitalized patients | Muscle ache—11 (11) | Headache—8 (8) | Confusion—9 (9) | NA | | | | |
| Chaolin Huang [62] | Hospitalized | Myalgia or fatigue—18 (44) | Headache—3/38 (8) | ICU vs non-ICU | | | | | |
| Source                  | Patient Description                                      | Total Patients | Fatigue or myalgia (Number of Cases and Percentage) | Headache (Number of Cases and Percentage) | ARDS vs non-ARDS | Survivors vs non-survivors | Deaths vs recovered | Hospitalized | Discharged | Discharged | Death | Died |
|------------------------|----------------------------------------------------------|----------------|------------------------------------------------------|------------------------------------------|------------------|----------------------------|---------------------|--------------|------------|------------|-------|-------|
| Chaomin Wu [63]        | All hospitalized patients                                | 51 (43–60)     | 128 (63.7)                                           |                                          |                  |                            |                     |              |            |            | 6 (15) | 44 (21.9) |
| Xiao Wang Yang [64]    | Only critically ill patient admitted in ICU             | 59.7 (13-3)    | 35 (67)                                              | Myalgia—6 (11.5) Headache—3 (6)          |                  |                            |                     |              |            |            | 32 (61.5) | 8 |
| Tao Chen [65]          | 113 died and 161 fully recovered and discharged patients | 62.0 (44.0–70.0)| 171 (62)                                             | Myalgia—60 (22) Headache—31 (11)        |                  |                            |                     |              |            |            | 12     |
| Yingzhen Du [66]       | Consecutive severe patients                              | 65.8 ± 14.2    | 62 (72.9)                                            | Myalgia—14 (16.5) Headache—4 (7.7)      |                  |                            |                     |              |            |            | 85     |
| Yongli Zheng [67]      | Consecutively hospitalized All ages                     | 49.40 ± 18.45  | 51 (52)                                              | Muscle ache and headache—12 (12)        |                  |                            |                     |              |            |            | NA     |
| Alfonso J. Rodriguez-Morales [68] | First notified cases of COVID-19                | NA            | NA                                                   | Headache—597 (64.8) Myalgia—32 (3.5)  |                  |                            |                     |              |            |            | NA     |
| Feng Wang [69]         | Diabetic, hospitalized patients                         | 68.6 ± 9.0     | 21 (75)                                              | Headache—3 (10.7)                       |                  |                            |                     |              |            |            | 1 (0.7) |       |
| Suxin Wan [70]         | Hospitalized patients                                   | 47 (36–55)     | 72 (53.3)                                            | Myalgia or fatigue—44 (32.5) Headache—24 (17.7) |                  |                            |                     |              |            |            | 12     |
| Zhongliang Wang [71]   | Hospitalized patients                                   | 42.0(35.0–62.0)| 32(46)                                               | Myalgia—21 (30) Headache—10 (14)        |                  |                            |                     |              |            |            | 44 (65.7) | 18 (26.9) |
| Dan Sun [72]           | Pediatric ICU (severe and critically ill only)         | 47.5 (1–94)    | 127 (48.5)                                           | Headache—17 (6.5)                       |                  |                            |                     |              |            |            | 5 (7.5) | 3 |
| Sijia Tian [73]        | Hospitalized, all age groups                            | 64.6 ± 9.0     | 21 (75)                                              | Headache—3 (10.7)                       |                  |                            |                     |              |            |            | 1 (0.7) | 54 |
| Fei Zhou [74]          | All adult ≥ 18 hospitalized and either dead or discharged patients | 56.0 (46.0–67.0)| 119 (62)                                             | Myalgia—29 (15)                         |                  |                            |                     |              |            |            | 2 (0.7) | 99 |
| Na Du [75]             | Consecutive hospitalized patients                       | 45.25(23–79)   | 7(54.3)                                              | Headache—3 (20)                         |                  |                            |                     |              |            |            | 44 (32.1) | 77 |
| Kui Liu [76]           | Hospitalized patients                                   | 45.25(23–79)   | 7(54.3)                                              | Headache—3 (20)                         |                  |                            |                     |              |            |            | 44 (32.1) | 77 |
| Alma Tostmann [77]     | Only health care workers                                | 45.25(23–79)   | 7(54.3)                                              | Headache—3 (20)                         |                  |                            |                     |              |            |            | 44 (32.1) | 77 (56.2) |
| Yongli Yan [78]        | Adults over 18 years, hospitalized, severe (all hospitalized admitted there included) | 64 (49–73)    | 114 (59.1)                                           | Myalgia or fatigue—44(32.1) Headache—13(9.5) |                  |                            |                     |              |            |            | 48 (32.1) | 48 |
| Xiao-Wei Xu [79]       | Adult hospitalized patients                             | 41 (32–52)     | 35 (56)                                              | Myalgia or fatigue—32 (52) Headache—21 (34) |                  |                            |                     |              |            |            | 2 (0.7) |       |

Note: NA indicates data not available.

*Death* refers to deaths among patients who were admitted to hospitals.

*Discharged* refers to patients who were discharged from hospitals.

*Hospitalized* refers to patients who were hospitalized.

*Mortality* refers to deaths among patients who were admitted to hospitals.
| Study | Population | Median age (IQR) | Median days of illness (IQR) | Symptoms |
|-------|------------|-----------------|-----------------------------|----------|
| Jiang-shan Lian [80] | All confirmed cases | NA | 407 (51.65) | Muscle ache—91 (11.54) Headache—75 (9.52) |
| Nitesh Gupta [81] | First 21 hospitalized patients in the centre | 40.3 (16–73) | 14 (66.7) | Headache—3 (13.6) |
| XiaoLi Zhang [82] | All hospitalized patients | NA | 328 (50.85) | Muscle ache—71 (11.01) Headache—67 (10.39) |
| Jie Li [83] | All hospitalized patients | 45.1 ± 12.8 | 9 (52.9) | Myalgia—4 (23.5) |
| Ivan Fan-Ngai Hung [84] | Adult at least 18 years, admitted | NA | 68 (53.54) | Headache—6 (4.72) |
| Huan Wu [85] | Pediatric mild and moderate cases only | 84 (18–123) | 60 (40.5) | Headache—5 (3.4) |
| Michael G Argenziano [86] | First 1000 consecutive patients presented to centre | 63.0 (50.0–75.0) | 596 (59.6) | Myalgia—268 (26.8) Headache—101 (10.1) |
| Simone Bastrup Israelsen [87] | Consecutive patients, adult ≥ 18, hospitalized | 71 (55–81) | 85 (48.6) | Myalgia—46 (26.3) Headache—32 (18.3) |
| Matthew J Cummings [88] | Only critically ill adults aged ≥18 years | 62 (51–72) | 171 (67) | Myalgia—67 (26) Headache—10 (4) |
| Marjolein F. Q. Kluytmans-van den Bergh [89] | Only health care workers infected | 49 (22–66) | 15 (17) | Severe myalgia—54 (63) Headache—49 (57) |
| Blażej Nowak [90] | Consecutive patients hospitalized | 63.7 ± 19.6 | 87 (51.5) | Headache—1 | Anosmia and ageusia—3 (1.7) |
| Xiaoquan Lai [91] | Only health care workers | 36.5 (30.0–47.0) | 31 (28.2) | Myalgia or fatigue—66 (60.0) |
| X. Wang [92] | Only non-critically ill (however, all patients admitted in that hospital included) | 50 (39–58) | 524 (51.8) | Muscle ache—50 (45.5) Headache—33 (30.0) |
| Zhe Liu [93] | All hospitalized | 46.2 ± 15.9 | 39 (54.2) | Muscle soreness—7 (9.7) Headache—4 (5.6) |
| Qiong Huang [94] | All hospitalized patients | 41 (31–51) | 28 (51.9) | Muscle soreness—9 (16.7) Headache—3 (5.6) |
| Kyung Soo Hong [95] | Consecutive hospitalized patients | 55.4 ± 17.1 | 38 (38.8) | Myalgia—37 (37.8) |

**Notes:**
- With Wuhan exposure vs without
- Normal imaging vs abnormal imaging
- Discharged vs non-discharged
- Combination triple antiviral drug vs control group (lopinavir–ritonavir)
- Emergency vs ward vs ICU
- Survivors vs non-survivors
- Uncomplicated vs mild vs severe
- ICU vs non-ICU

**Additional Data:**
- Discharged—32 (15.3)
- Discharged—699
- Discharged—109 (62.3)
- Discharged alive—58 (23)
- Discharged—101 (39)
- Discharged—98 (38)
- Discharged—58 (23)
- Discharged—46 (26.3)
- Hospital admission—2 (2)
- Died—1 (0.9)
- Died—9 (9.2)
- Died—46 (26.3)
- Died—57 (58.2)
- Died—32
- Died—46 (26.3)
- Died—0
- Died—40
| Study | Description | Mean Age ± SD | Headache Count | Headache Severity | Death Count | Hospitalization Count | Cured Count | Others |
|-------|-------------|---------------|----------------|-------------------|-------------|-----------------------|-------------|--------|
| Rui Huang [96] | All hospitalised | 44.0 (33.0–54.0) | 116 (57.4) | Muscle ache—21 (10.4) Headache—12 (5.9) | Severe vs non-severe | Transferred—6 (6.1) Remained in hospital—165 (81.7) Hospital discharge—37 (18.3) Death—0 (0) | | |
| Mengyao Ji [97] | Random selection of confirmed patients | 51.0 (37.0–61.0) | 48 (48) | Myalgia—16 (16) Vertigo—4 (4) Headache—6 (6) | | | | |
| Dawei Wang [98] | All the discharged (alive at home and dead) patients with confirmed COVID-19 | 51.0 (36.0–65.0) | 57 (53.3) | Myalgia—33 (30.8) Headache—7 (6.5) Dizziness—7 (6.5) | | | | |
| Saurabh Aggarwal [99] | All admitted patients | 67 (38–95) | 12 (75) | Lightheadedness—3 (19) Headache—4 (25) | | | ICU, shock, death vs no Died—3 (19) Discharged—11 Admitted—2 | |
| Xin-Ying Zhao [100] | All hospitalized patients | 46.00 | 49 (53.8) | Myalgia—16 (16.5) | | | Severe vs mild Remained in hospital—75 (82.4) Discharged—14 (15.4) Died—2 (2.2) Died—17 (8.9) Discharge—136 Hospital—15 | |
| Yifan Meng [101] | All consecutive admitted (all were severe or critically ill patients) | 56.7 ± 15.1 | 86 | Myalgia—48 (28.6) Headache—22(13.1) Dizziness—7(4.2) | | | | |
| Qingchun Yao [102] | Consecutive adult patients admitted | 52 (37–58) | 43 (39.8) | Myalgia or fatigue—28 (25.9) Headache—2 (20.0) | | | Non-severe vs severe alive vs severe dead Died—12 Discharged—96 Discharged—5 (50.0) Hospitalized—5 (50.0) Died—10 Hospitalized—18 Died—12 (50) Discharged—5 (21) Hospitalized—7 (30) | |
| Li Zhu [103] | 1–18 years, children | NA | 5 (50.0) | | | | | |
| Eu Suk Kim [104] | First 28 patients in Republic of Korea, hospitalized | 42.6 ± 13.4 | 15 (53.6) | Myalgia—7 (25.0) Headache—7 (25.0) | | | | |
| Pavan K. Bhatnaju [105] | Only critically ill ICU patients | 64 ± 18 (23–97) | 15 (63) | Headache—2 (8) | | | | |
| Haiyan Qiu [106] | All pediatric 0–16 years | 8.3 ± 3.5 | 23 (64) | Muscle pain—5 (3.36%) Headache—13 (8.72%) | | | | |
| Guang Chen [107] | All hospitalized patients | 56.0 (50.0–65.0) | 17 (81.0) | | | | | |
| Wenjie Yang [108] | Consecutive hospitalized patients | 45.11 ± 13.35 | 81 | | | | | |
| Yu-Huan Xu [109] | All hospitalized patients | 43.9 ± 16.8 | 29 (58) | Headache—5 (10) Muscle ache—8 (16) | | | | |
| Xi Xu [110] | All hospitalized patients | 50 (18–86) | 39 (43) | Myalgia—25 (28) Headache—4 (4) | | | | |
| Jerome R. Lechien [111] | Mild to moderate (but all reported) | 39.17 ± 12.09 | 458 (32.3) | Headache—998 (70.3) Loss of smell—997 (70.2) Reduction of smell—201 (14.2) Myalgia—887 (62.5) | | | Based on age | |

Table 1 (continued)
| Author                        | Study Type                              | Cases Reported (Range) | New Disease Symptoms Reported (Range) | Hospitalization Status | Not Hospitalized (90%) | Hospitalized (10%) | Death (0.1%) | Recovery Status |
|-------------------------------|-----------------------------------------|------------------------|---------------------------------------|------------------------|-------------------------|---------------------|--------------|-----------------|
| Sherry L. Burrer [112]        | Cases reported to CDC, only health care personal | 42 (32–54)            | 2464(27)                              |                         | NA                      | 6760 (90%)          | 723 (8–10%) | 27 (0.3–0.6%)   |
| Ruth Levinson [113]           | Hospitalized adults and adolescents (age ≥ 15 years), and mild symptoms (all admitted were mild) | 34 (15–82)            | 23                                     | Myalgia or arthralgia—24 (57) | NA                      |                      |              |                 |
| Xu Zhu [114]                  | Only elderly (>70) patients             | 76 (72–82)            | 67 (58.8)                             | Myalgia—4 (3.5)         | Severe vs non-severe    | 87 (76.3)           | 27 (23.7)   |                 |
| Dan Wang [115]                | All consecutive admitted patients       | 58(39–67)             | 73(51.0)                              | Myalgia—49(34.3)        | Mild/moderate vs severe/critical |                    |              |                 |
| Chuming Chen [116]            | Only pediatric, <18 years, hospitalized patients | 7.33 ± 4.35          | 13 (41.9)                             | Headache—1 (3.2)        | NA                      | 184 (2–5%)          |              |                 |
| Pingzheng Mo [117]            | All Consecutive admitted patients       | 54 (42–66)            | 86 (55.5)                             | Myalgia or arthralgia—50 (61.0) | General vs refractory   |                    |              |                 |
| Gu-qin Zhang [118]            | All hospitalized patients               | 55.0 (39.0–66.5)      | 108(48.9)                             | Headache—17(7.7)        | Severe vs non-severe    | 168 (76.0)          |              |                 |
| Jennifer Tomlins [119]        | All sequential hospitalized patients    | 75 (59–82)            | 60 (63)                               | Myalgia—13 (14)         | NA                      | 107 (27.2)          |              |                 |
| Zonghao Zhao [120]            | All positive cases                     | 47 (34–55)            | 42 (56)                               | Muscle soreness—9 (12.00) | NA                      |                    |              |                 |
| Ying Huang [121]              | Non survivors only                     | 69.22 (9.64)          | 25 (69.44)                            | Myalgia—1 (2.78)        | NA                      |                    |              |                 |
| Carol H. Yan [122]            | All positive COVID-19 who completed survey (most are mild cases) | NA                   | 29 (49.2)                             | Headache—39 (66.1)      | With subjective olfaction score |                    |              |                 |
| Yan Deng [123]                | Only dead and recovered patients admitted | 124                  | Myalgia or fatigue—57               | Headache—13 (11.5)      | NA                      |                    |              |                 |
| Jiaojiao Chu [124]            | Only medical staff(54 tested, but only 38 positive for nucleic acid tests) | 39 (26–66)            | 24 (63.2)                             | Muscle ache—2 (5.3)     | Common vs severe, positive RT-PCR vs negative |                    |              |                 |
| Håkon Ihle-Hansen [125]       | All consecutive admitted               | 72.5 (30–95)          | 28 (67)                               | New-onset confusion—5 (19) | Severe vs critical     |                    |              |                 |
| Parag Goyal [126]             | First consecutive patients hospitalized, adults ≥ 18 years | 62.2 (48.6–73.7)      | 238 (60.6)                            | Myalgia—107 (27.2)      | invasive mechanical ventilation vs no invasive mechanical ventilation |                    |              |                 |
| Study | Group Description | Age Range | No. | Male (%) | Symptom(s) | Outcome | Notes |
|-------|-------------------|-----------|-----|----------|------------|---------|-------|
| Cao [127] | All patients admitted | 37–67 | 54 | 37 (69.6) | Muscle ache | 35 (64.8) | Non survivors vs survivors | Discharge 85 (83.3), Died 17 (16.7) |
| De Chang [128] | All hospitalized patients | 34–48 | 10 | 77 (77) | Myalgia | 3 (30) | NA | All recovered 12 (still quarantined) |
| Chen [129] | Only pregnant patients | 26–40 years | NA | 100 | Myalgia | 3 (30) | NA | All nine live birth |
| Wang [130] | Consecutive cases over 60 years | 65–76 | 166 (49) | Myalgia | 16 (4.7) | NA | Survival vs dead | Discharged 91 (26.8), Died 65 (19.2) |
| Spiteri [131] | First cases in the WHO European region except UK | 2–81 | 42 | 25 | Myalgia | 1 (3.22) | Infected in Europe vs China | Died 1 |
| Liu [132] | Patients admitted | 10–72 years | 8 | 100 | Myalgia | 4 (50) | NA | NA |
| Xu [133] | Patients admitted | NA | 25 | 100 | Myalgia | 8 (32) | NA | NA |
| Chang [134] | Admitted patients who underwent chest CT | 17–75 | 51 | 13 (62) | Headache | 3 (14) | NA | Infected in Europe vs China |
| Shi [135] | Admitted and had CT chest done | 49.5 ± 11 | 42 | 100 | Headache | 5 (6) | NA | NA |
| Yang [136] | All admitted patients | 55 ± 17.1 | 98 | 100 | Myalgia or malaise | 44 (44.9) | ICU vs non-ICU | Hospitalization 143 (71.5), Died 42 (21), Death 15 (7.5) |
| Zhao [137] | Consecutive laboratory confirmed COVID-19 who underwent CT | 44.4 (17–75) | 56 | 100 | Headache | 27 (48) | NA | Emergency vs non-emergency group |
| Han [138] | All admitted patients | NA | 16 | 100 | Myalgia or fatigue | 13 (81.3) | Emergency vs non-emergency group | Discharged 32 |
| Wang [139] | Severely and critically ill (ICU) | 52–72 | 179 | 52 (97.7) | Rhabdomyolysis | 17 (9.5) | Survivors vs non-survivors | Died 133 (38.7), Discharged 185 (87.7), Hospitalized 26 |
population. Syncope was reported in three studies with incidence of 0.3% [45], 0.6% [49], and 4.8% [86]. Few studies showed an increase in creatine kinase, LDH, and myoglobin in COVID-19 patients [12, 62, 66].

**Acute cerebrovascular disease**

Acute cerebrovascular disease (CVD) was reported in 0.5–5.9% [33, 48] of COVID-19 patients. Out of them, the most common type was acute ischaemic stroke and severe COVID-19 patients were more at risk of developing the acute CVD [33]. From these studies, the incidence of acute CVD in severe/ICU patients reported were 0.8–9.8% [33, 41]. The incidence of ischaemic stroke, hemorrhagic stroke, and cerebral venous thrombosis reported from various studies ranged from 0.4–4.9% [33, 48], 0.2–0.9% [38, 48], and 0.3–0.5% [33, 47] respectively. A study by Mao et al. [32] reported that two patients presented with hemiplegia without any typical COVID-19 symptoms. The median time to onset of cerebrovascular disease was 9 days. Another study by Li Y et.al [33] showed that acute CVD was more likely to be present with severe COVID-19; however, they were older, and had cardiovascular risk factors. These findings were similar to the above study by Mao et al. [32]. In both these studies, the laboratory parameters in patients with CNS symptoms were different from the other COVID-19
patients, with a higher white cell and neutrophil counts, reduced lymphocyte and platelet counts, elevated CRP and D-dimer levels [32, 33].

We found two studies that specifically studied the thrombotic complications in COVID-19 patients and found acute ischaemic stroke in COVID-19 patients receiving thromboprophylaxis [35, 36]. A retrospective observational case series in COVID-19 patients from Italy [144] reported six cases of stroke, four were ischaemic and two were hemorrhagic. Five of them had pre-existing vascular risk factors. Three patients with ischaemic stroke and one patient with hemorrhagic stroke showed hypercoagulable blood parameters [144]. Two studies reported six cases of stroke in young(< 50 years) COVID-19 patients, out of which three patients did not have any risk factors [145, 146].

Also there are multiple case reports and case series of ischemic stroke including large artery [147], aneurysmal [148, 149] and non-aneurysmal SAH [51], deep cerebral venous thrombosis [150–157], hemorrhagic stroke [38, 158, 159] and CNS vasculitis [160] from all over the world in COVID-19 patients [38, 51, 147–173].

**Meningoencephalitis, encephalopathy, disturbances in consciousness**

Several cases of meningoencephalitis and encephalopathy were reported in COVID-19 patients [39, 43, 49, 174–183]. The incidence of encephalitis reported in two retrospective studies was 0.03% [43] and 0.1% [49]. Only in four of the 15 reported cases of encephalitis, CSF RT-PCR test was positive.

| Table 3 | Meta-analysis, summary estimate of pooled prevalence and heterogeneity of each neurological manifestations |
|---------|-------------------------------------------------------------------------------------------------|
| Studies (N) | Sample size (N) | Cases (n) | Prevalence (95% CI) | 95% CI | 5 |
| Smell disturbances | 17 | 7919 | 2488 | 31.4% (30.4–32.4) | 99.87 |
| Taste disturbances | 14 | 7033 | 1979 | 28.1% (27.1–29.2) | 99.65 |
| Headache | 54 | 13,623 | 2751 | 20.2% (19.5–20.9) | 99.09 |
| Myalgia | 38 | 11,169 | 2288 | 20.5% (19.7–21.2) | 98.98 |
| Disturbances in consciousness/altered mental status | 9 | 6687 | 408 | 6.1% (5.5–6.7) | 98.26 |
| Syncope | 3 | 1000 | 56 | 5.6% (4.3–7.2) | 99.93 |
| Dizziness | 12 | 2595 | 137 | 5.3% (4.5–6.2) | 93.44 |
| Acute cerebrovascular disease | 8 | 10,186 | 148 | 1.4% (1.2–1.7) | 96.61 |
| Ischaemic stroke | 7 | 9268 | 108 | 1.2% (1.0–1.4) | 96.67 |
| Hemorrhagic stroke | 7 | 12,704 | 60 | 0.5% (0.4–0.6) | 98.75 |
| Cerebral venous thrombosis | 2 | 946 | 3 | 0.3% (0.1–0.9) | 99.98 |
| Seizures | 5 | 2043 | 23 | 1.1% (0.7–1.7) | 96.61 |
| Ataxia | 2 | 939 | 3 | 0.3% (0.1–0.9) | 99.98 |
Among them had negative nasopharyngeal swab [50, 50], positive for SARS-CoV-2 RNA, and surprisingly two cases any respiratory involvement has also been reported [175, 185]. COVID-19 patient [184]. Isolated meningoencephalitis without subdural hematoma was positive for SARS-CoV-2 RT-PCR in a [177, 181]. Interestingly, fluid from the surgical evacuation of hemorrhagic encephalopathy [191, 197], hypoxic brain injury among infected patients.

Table 1. Proportion of different neurological symptoms in COVID-19 patients.

| Symptom           | Proportion | 95% CI       |
|-------------------|------------|--------------|
| Headache          | 7.36%      | [6.92%, 7.80%]|
| Fatigue           | 11.22%     | [10.57%, 11.87%]|
| Myalgia           | 13.89%     | [13.08%, 14.70%]|
| Asthenia          | 14.70%     | [13.91%, 15.49%]|
| Myocardial infarction | 11.97%     | [11.26%, 12.68%]|
| Ischemic stroke   | 12.50%     | [11.79%, 13.21%]|
| Hemorrhagic stroke| 12.70%     | [11.98%, 13.42%]|
| Seizure           | 12.90%     | [12.19%, 13.61%]|
| Tetraparesis      | 13.00%     | [12.29%, 13.71%]|
| Tissue necrosis   | 13.10%     | [12.39%, 13.82%]|
| Accidental death  | 13.20%     | [12.49%, 13.92%]|
| Myocardial infarction | 13.30%     | [12.59%, 13.93%]|
| Acute myocardial infarction | 13.40%     | [12.69%, 14.13%]|
| Ischemic stroke   | 13.50%     | [12.79%, 14.21%]|
| Hemorrhagic stroke| 13.60%     | [12.89%, 14.32%]|
| Seizure           | 13.70%     | [12.99%, 14.51%]|
| Tetraparesis      | 13.80%     | [13.09%, 14.52%]|
| Tissue necrosis   | 13.90%     | [13.19%, 14.61%]|
| Accidental death  | 14.00%     | [13.29%, 14.72%]|
| Myocardial infarction | 14.10%     | [13.39%, 14.83%]|
| Acute myocardial infarction | 14.20%     | [13.49%, 15.02%]|
| Ischemic stroke   | 14.30%     | [13.59%, 15.12%]|
| Hemorrhagic stroke| 14.40%     | [13.69%, 15.22%]|
| Seizure           | 14.50%     | [13.79%, 15.31%]|
| Tetraparesis      | 14.60%     | [13.89%, 15.51%]|
| Tissue necrosis   | 14.70%     | [13.99%, 15.61%]|
| Accidental death  | 14.80%     | [14.09%, 15.72%]|
| Myocardial infarction | 14.90%     | [14.19%, 15.83%]|
| Acute myocardial infarction | 15.00%     | [14.29%, 15.92%]|
| Ischemic stroke   | 15.10%     | [14.39%, 16.01%]|
| Hemorrhagic stroke| 15.20%     | [14.49%, 16.12%]|
| Seizure           | 15.30%     | [14.59%, 16.21%]|
| Tetraparesis      | 15.40%     | [14.69%, 16.31%]|
| Tissue necrosis   | 15.50%     | [14.79%, 16.41%]|
| Accidental death  | 15.60%     | [14.89%, 16.52%]|
| Myocardial infarction | 15.70%     | [14.99%, 16.62%]|
| Acute myocardial infarction | 15.80%     | [15.09%, 16.72%]|
| Ischemic stroke   | 15.90%     | [15.19%, 16.81%]|
| Hemorrhagic stroke| 16.00%     | [15.29%, 16.91%]|
| Seizure           | 16.10%     | [15.39%, 17.01%]|
| Tetraparesis      | 16.20%     | [15.49%, 17.12%]|
| Tissue necrosis   | 16.30%     | [15.59%, 17.23%]|
| Accidental death  | 16.40%     | [15.69%, 17.34%]|
| Myocardial infarction | 16.50%     | [15.79%, 17.45%]|
| Acute myocardial infarction | 16.60%     | [15.89%, 17.56%]|
| Ischemic stroke   | 16.70%     | [15.99%, 17.67%]|
| Hemorrhagic stroke| 16.80%     | [16.09%, 17.78%]|
| Seizure           | 16.90%     | [16.19%, 17.89%]|
| Tetraparesis      | 17.00%     | [16.29%, 18.00%]|
| Tissue necrosis   | 17.10%     | [16.39%, 18.11%]|
| Accidental death  | 17.20%     | [16.49%, 18.22%]|
| Myocardial infarction | 17.30%     | [16.59%, 18.33%]|
| Acute myocardial infarction | 17.40%     | [16.79%, 18.44%]|
| Ischemic stroke   | 17.50%     | [16.79%, 18.55%]|
| Hemorrhagic stroke| 17.60%     | [16.99%, 18.66%]|
| Seizure           | 17.70%     | [17.00%, 18.77%]|
| Tetraparesis      | 17.80%     | [17.20%, 18.88%]|
| Tissue necrosis   | 17.90%     | [17.40%, 19.00%]|
| Accidental death  | 18.00%     | [17.60%, 19.20%]|

Fig. 2 Forest plot of each neurological manifestations

positive for SARS-CoV-2 RNA, and surprisingly two cases among them had negative nasopharyngeal swab [50, 174–176]. Two reports showed elevated levels of cytokines like IL-6, IL-8, TNF-α, β2-microglobulin, IP-10, MCP-1 in CSF [177, 181]. Interestingly, fluid from the surgical evacuation of subdural hematoma was positive for SARS-CoV-2 RT-PCR in a COVID-19 patient [184]. Isolated meningoencephalitis without any respiratory involvement has also been reported [175, 185]. Another case of rhombencephalitis as a rare complication of COVID-19 patient has been reported [186]. Few retrospective studies [32, 47, 49] reported seizures with the incidence ranging from 0.5–1.4% [32, 47]. Cases of all types of seizures like febrile seizures [42], focal seizures [180, 187–189], generalized tonic-clonic seizures [183, 190–192], myoclonic status epilepticus [193], status epilepticus [188, 194] and non-convulsive status epilepticus [46] were reported in COVID-19 patients.

Generally, the SARS-CoV-2 virus causes mild disease in children. However, a study from Italy showed a total five patients with seizures, and out of them, two had febrile seizures (three children had a known history of epilepsy, one child had a history of febrile seizures, one child had a first episode of febrile seizures) [42]. Also, a case of a 6-week-old infant with SARS-CoV-2 in addition to rhinovirus, presenting with brief 10–15 s episodes of upward gaze and bilateral leg stiffening was reported with normal EEG and MRI brain [195]. Another case of an 11-year-old child with COVID-19 viral encephalitis has been reported, with CSF showing viral encephalitis picture [194].

PRES syndrome has also been reported in studies [47, 51]. Transient cortical blindness like presentation of PRES syndrome with MRI brain at admission revealing bilateral T2/FLAIR hyperintensities, especially left occipital, frontal cortical white matter and splenium of the corpus callosum and diffusion restriction in DWI revealing vasogenic edema has been reported [196]. Repeat MRI after 2 weeks showed a complete resolution of findings. Cases of acute necrotizing hemorrhagic encephalopathy [191, 197], hypoxic brain injury with encephalopathy [43, 47, 51, 65], delayed post-hypoxic leukoencephalopathy [198], mild encephalitis/encephalopathy with a reversible splenial lesion(MERS) [199], ADEM in elderly females [200, 201], MS plaque exacerbation [47] and CIS [176] were reported in SARS-CoV-2 infected patients.
Incidence of disturbances of consciousness/delirium ranged from 3.3–19.6% [49, 100] in retrospective studies. S.R. Beach, et al. [202] reported four cases of elderly COVID-19 patients, who presented to the hospital with altered mental status without any respiratory complaints, and only one among them developed respiratory complaints during the hospital stay. Similar cases have been reported in elderly patients from Saudi Arabia [203], Norway [204] and China [205]. An observational case series from France [39] in 58 COVID-19 patients with ARDS admitted in ICU reported agitation in 40(69%) patients, confusion in 26 of 40 patients, diffuse corticospinal tract signs in 39 patients (67%) and out of the 45 patients discharged, 15(33%) had a dysexecutive syndrome. MRI Brain showed enhancement of leptomeningeal spaces in eight patients, bilateral frontotemporal hyperperfusion in 11 patients who underwent perfusion imaging, two asymptomatic patients with small acute ischaemic stroke and one patient with subacute ischaemic stroke.

**Guillain-Barré syndrome**

There are multiple reports of GBS in patients with confirmed COVID-19. GBS has also been reported to be a presenting feature in one case report by Zhao H et al. [206] where the patient, later on, developed fever and other symptoms of COVID-19. All the variants of GBS like AIDP, AMAN, AMSAN has been reported in COVID-19 patients [47, 206–219] including both para [206–212, 220–223] and post-infectious pattern [210, 211, 214–219, 224–226]. Toscano et al. [227] reported a series of five patients of COVID-19 with GBS, with the interval between the onset of fever, cough and symptoms of GBS ranging from 5 to 10 days. Cases of MFS were also reported [47, 226, 228, 229]. One case of MFS was associated with a positive serum GD1b-IgG antibody [228]. Other rare variants reported were GBS/MF overlap syndrome [219], AMSAN variants with severe autonomic neuropathy [219], facial diplegia [222, 227] and post-infectious pattern of the demyelinating type of GBS with brainstem and cervical leptomeningeal enhancement [225]. Cranial neuropathies with abnormal perineural or cranial nerve findings [230], multiple cranial neuropathies [211, 219], peripheral motor neuropathy [231] and ataxia [32, 43, 51] are all reported as presentations of COVID-19.

**Other neurological manifestations**

The incidence of rhabdomyolysis has been reported between 0.2–2.6% in different studies [11, 49, 139]. A report illustrates a 38 year-old COVID-19 patient presenting with fever, dyspnea, and severe myalgia, with high creatine kinase (>42,670 U/L) and LDH (4301 U/La) and was diagnosed as viral myositis [232]. Another two cases of adult COVID-19 patients with lower extremity pain and weakness with rhabdomyolysis with high creatine kinase and LDH were reported [233, 234]. First case developed rhabdomyolysis on the 9th day of admission [233] and 2nd case presented to the hospital with rhabdomyolysis [234]. An isolated case of post-infectious myelitis has been reported from Germany in a COVID-19 patient [235].

Three cases of generalized brainstem type of myoclonus were reported from Spain, with normal CSF study in one patient (others not done) and normal imaging findings. However, nasopharyngeal RT-PCR for SARS-CoV-2 was positive in only one patient. In all these patients, EEG was showing mild diffuse slowing without any epileptic activity [236]. Paresthesias [51] and cutaneous hyperaesthesia [237] were reported as a presentation in COVID-19 patients. A case of COVID-19 patient with oropharyngeal dysphagia followed by aspiration pneumonia, taste impairment, impaired pharyngolaryngeal sensation, and nasopharyngeal contractile dysfunction with absent gag reflex was reported from Japan [238]. Visual symptoms were also reported in a few studies. Mao L et al. [32] reported visual impairment in 1.4% of the COVID-19 patients. Cases of optic neuritis [49], isolated central retinal artery occlusion [239], non-arteritic type of posterior ischaemic optic neuropathy (PION) [240] as a COVID-19...
manifestation were also reported. The summary of all the neurological manifestations reported in COVID-19 is given in Table 4.

**Heterogeneity**

The heterogeneity was high in most of the neurological manifestations studied except for hemorrhagic stroke (medium), cerebral venous thrombosis (low), seizure (low), and ataxia (low). The funnel plots were symmetric in hemorrhagic stroke, ataxia, seizures, cerebral venous thrombosis and myalgia, which is pointing towards no bias in the selection of publications that are included in the study. However, the funnel plots were asymmetric in other neurological manifestations studied, which pointed towards the heterogeneity in the studies undertaken or bias in the selection of publications included in the study.

**Discussion**

In this systematic review and meta-analysis, we assessed the neurological manifestations, risk factors, mortality, laboratory parameters, and imaging findings in those patients with neurological features. Involving 30,159 patients, our meta-analysis is the first and most comprehensive study about the neurological manifestations of COVID-19.

The most common neurological manifestations reported were smell and taste disturbances. Another interesting finding is the geographical variations in the frequency of smell and taste disturbances.
taste disturbances. High incidence of smell and taste disturbances were noted in studies from most of the European countries [54] while studies from Asian countries showed a lower incidence [32]. However, most of the studies which reported a higher incidence of smell and taste disturbances evaluated mainly olfactory and taste symptoms only and studied mild to moderate cases and excluded severe/ICU patients compared with studies with lower incidence. This bias might have caused under-reporting of smell and taste disturbances in severe/ICU patients or could also be because of decreased awareness of investigator about these symptoms at the beginning of the pandemic. Supporting our assumption, a study from Spain which evaluated 841 COVID-19 patients with neurological manifestations reported only 4.9% of cases of smell disturbances and 6.2% cases of taste disturbances [49]. Other possibilities for these variations are, the difference in the incidence of SARS-CoV-2 to tissues between populations, differences in the strain of mutated virus circulating in Europe compared with Asian countries. However, more studies are required to confirm these assumptions. Interestingly a study by Wan Y et al. [241] predicted that binding affinity between 2019-nCoV and human ACE2 may be enhanced by a single N501T mutation. Also, ACE2 receptors are highly expressed by sustentacular cells of the olfactory epithelium. Olfactory and taste disorders were more common in younger patients [52, 140] most occurs in the early stages as initial manifestations of the disease and even as the only manifestation of COVID-19. Hence, olfactory and gustatory disorders can be the initial and early manifestations of COVID-19 and early identification of these symptoms might lead to early diagnosis and disease containment.

Non-specific neurological manifestations could be just systemic features of a viral infection Similar to olfactory disturbances, the incidence of myalgia, headache, and dizziness also shows geographical variations with the highest incidence reported from Europe, the USA, and Chile. The incidence of non-specific symptoms was lower in children. We noticed that non-specific symptoms were higher among the studies conducted in health care workers. This may be due to increased knowledge and awareness of the symptoms and disease.

The most common type of acute CVD reported was an ischaemic stroke. Hemorrhagic stroke, deep cerebral venous thrombosis, SAH (both non-aneurysmal and aneurysmal), and TIA were also reported; however, with much lesser prevalence. Severe infection or ICU requirement, older age, cardiovascular risk factors, prior co-morbidities, and hypercoagulable lab parameters were found to be a risk factor for developing acute CVD [32, 33]. The apparent association of COVID-19 and stroke is likely due to the sharing of similar risk factors. The severity of COVID-19 has been proved to be directly related to the presence of co-morbidities like hypertension and DM. An earlier meta-analysis by Yang J et al. [242] comprising [46, 243] COVID-19 patients reported the prevalence of risk factors, hypertension in 21.1%, DM in 9.7%, and cardiovascular diseases in 8.4%. Also, hypercoagulable blood parameters as shown by Li Y et al. [33], can lead to ischaemic stroke and cerebral venous thrombosis. Nervous system involvement in SARS-CoV-2 infection can be due to direct invasion of neural tissues, inflammatory response, or immune dysregulation. The SARS-CoV-2 virus uses the ACE2 and TMPRSS2 for entry to the host cell and it is one of the main determinants of infectivity [241, 244]. Susceptibility to infection correlated with ACE2 expression in previous studies [245].

Very few retrospective studies showed meningoencephalitis as a presentation of COVID-19; however, there are multiple case reports from all over the world. The probable mechanism can again be direct invasion via the hematogenous route or retrograde pathway via peripheral nerve terminals. Two studies even showed higher levels of inflammatory cytokines in the CSF analysis of these patients [177, 181]. SARS-CoV-2 could trigger a seizure in predisposing patients through neurotropic mechanisms as explained earlier [188]. However, more evaluation is required in this field to find a temporal factor. All types of seizures were reported like febrile seizures, focal seizures, generalized tonic-clonic seizures, status epilepticus and myoclonic status epilepticus, NCSE and also brainstem type of myoclonus. Demyelinating disorders like ADEM, exacerbation of MS plaque, and the clinically isolated syndrome were all reported in COVID-19 patients.

Cases of GBS and its variants were also reported in COVID-19. Both post-infectious and pre-infectious pattern of GBS were reported. The most common type of GBS reported was AIDP. Other variants like AMAN, AMSAN, Miller Fisher syndrome, and facial diplegic variant were also reported. Patients presenting as GBS without any other typical symptoms of COVID-19 were also reported. Possible pathogenesis of GBS in COVID-19 includes immune dysregulation secondary to systemic hyper inflammation and cytokines produced as described by McGonagle et al. [246] and Quin et al. [247]. Hence, it is important to suspect and test for COVID-19 in those patients presenting with GBS and MFS. However, more studies are required to conclude that these cases were not just coincidental and COVID-19 itself is a trigger for GBS and MFS. GBS was also reported in other recent important viral infections like MERS-CoV [248] and Zika virus [243].

Change in laboratory parameters was also reported in COVID-19 patients with neurological manifestations like higher white cell and neutrophil counts, reduced lymphocyte and platelet counts, elevated CRP and D-dimer levels, and higher levels of creatine kinase, LDH, and myoglobin [12, 32, 33, 62].

High heterogeneity in our study could be because of differences in the selection of patients and ethnicity, the severity of the disease, co-morbidities, only a few studies evaluated neurological symptoms specifically, variation in the number of patients in different studies, or due to publication bias and differences in the methodology among the studies.
Comparison with previous systematic reviews

Earlier meta-analyses addressing general clinical features in COVID-19 were published. One such study showed myalgia in (28.5%; 95%CI 21.2–36.2), headache (14.0%; 95%CI 9.9–18.6), and dizziness (7.6%; 95%CI 0.0–23.5) [249]. Our results also found similar results for myalgia, headache, and dizziness, i.e. (19.3%; 95%CI 15.1–23.6), (14.7%; 95%CI 10.4–18.9), and (6.1%; 95%CI 3.1–9.2) respectively. Another similar meta-analysis also showed myalgia in (21.9%; 95%CI 17.7–26.4) and headache in (11.3%; 95%CI 8.9–14.0) [250]. One more study reported the prevalence of headache as (8.0%; 95%CI 5.7–10.2) [251]. However, no meta-analyses are published on the specific neurological manifestations till now.

Strengths and limitations

The strength of our study is that we did a comprehensive search in all the electronic databases. Study limitations include high heterogeneity in the estimation of the prevalence of some neurological manifestations, the inclusion of studies with very small sample size, and lack of meta-regression analysis. We excluded studies in languages other than English where translation was not possible. Most of the included studies were of moderate quality. More good-quality prospective cohort studies are required to establish that the neurological manifestations reported in the studies were not just coincidental.

Conclusions

In conclusion, our study showed neurological manifestations are common in COVID-19 and are even present as the only symptom without any other manifestation of the respiratory system involvement. Hence it is important to suspect every COVID-19 patient with neurological manifestations. In this pandemic, a neurologist needs to take necessary precautions while examining the patients presenting to them. Also, some symptoms like smell and taste disturbance can be used as a screening tool for SARS-CoV-2 infection and can help isolate suspected patients earlier to avoid the spread of the disease.

Author contributions TF and AP conceptualized the study and searched and screened the literature. PD and RNC extracted and analysed the data. RNC contributed to figures, tables, and interpretation of images. KC was involved in extraction of data. DJ, VNM, TF, and AP were involved in study design, data interpretation, and data analysis. RM and MP did the statistical analysis. AK drafted the manuscript, data collection, figures. VKS did literature search, drafted the manuscript, and contributed to study design. TF wrote the first draft of the manuscript with input from AP.

Data availability All data available on request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval Not applicable.

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Consent for publication Not applicable.

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