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COVID-19

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].

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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 222,020	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
Stephane Kremer [50]	Published	French Society of Neuroradiology, 16 hospitals, France	Retrospective cohort study	March 23th, 2020, to April 27th, 2020	NA	37
Pranusha 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)

Álvaro Beltrán-Corbellini [52]		Multicentre (2 centres) Madrid, Spain				
Andrea Giacomelli [53]	Published	L. Sacco Hospital in Milan, Italy	Cross-sectional study, verbal in-terview	19 March 2020	NA	59
Jerome R. Lechien [54]	Published	COVID-19 Task Force of YO-IFOS, Multicentre, Europe	Prospective survey observational case series	NA	NA	417
Giacomo Spinato [55]	Published	Treviso Regional Hospital, Italy	Cross sectional telephone survey	March 19 and March 22, 2020	NA	202
Luigi Angelo Vaira [56]	Published	University Hospital of Sassari, Italy	Prospective case series observational	March 31 and April 6, 2020	NA	72
Luigi Angelo Vaira [57]	Published	Multicentre, Italy	Prospective study	April 9th and 10th 2020	NA	33
Luigi Angelo Vaira [58]	Published	Multicentre, Italy	Multicentre prospective cohort study	NA	NA	345
Yonghyun Lee [59]	Published	The Daegu Medical Association, South Korea	Prospective telephone interview	March 8, 2020 - March 31, 2020	NA	3191
Marlene M. Speth [60]	Published	Kantonsspital Aarau, Aarau, Switzerland	Prospective cross-sectional telephone questionnaire study	March 3, 2020, to April 17, 2020	NA	103
T. Klopfenstein [61]	Published	NFC (Nord Franche-Comté) Hospital, France	Retrospective observational	March 1st to March 17th, 2020	March 24th, 2020	114
Dawei Wang [10]	Published	Single centre,Zhongnan Hospital of Wuhan University in Wuhan, China	Retrospective, case series	January 1 to January 28, 2020	Till Feb. 3rd	138
Wei-jie Guan [11]	Published	Multicentre, 30 provinces in China	Retrospective study	December 11, 2019, to January 31, 2020	NA	1099
Nanshan Chen [12]	Published	Jinyintan Hospital, Wuhan, China	Retrospective study	Jan 1 to Jan 20, 2020	Till Jan 25,2020	99
Chaolin Huang [62]	Published	Jin Yintan Hospital, Wuhan, China	Prospective cohort	Dec 16, 2019, to Jan 2, 2020	NA	41
ChaominWu [63]	Published	Jinyintan Hospital Wuhan, China	Retrospective cohort	December 25, 2019- and January 26, 2020	February 13, 2020	201
Xiaobo Yang [64]	Published	Jin Yin-tan Hospital, Wuhan, China	Retrospective, observational study	Dec 24, 2019, to Jan 26, 2020	Feb 9, 2020	52
Tao Chen [65]	Published	Tongji Hospital, Wuhan, China	Retrospective case series	13 January- 12 February 2020	28 February 2020	274
Yingzhen Du [66]	Published	2 centres, Hannan Hospital and Wuhan Union Hospital Wuhan, China	Retrospective, observational study	January 9 to February 15, 2020	February 15, 2020	85
Yongli Zheng [67]	Published	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]	Published	Chile	Cross sectional	March 3, 2020, to March 23, 2020	NA	922
Feng Wang [69]	Published	Tongji Hospital Wuhan, China	Retrospective study	January 29, 2020, to February 10, 2020	February 22, 2020	28
Suxin Wan [70]	Published	Chongqing University Three Gorges Hospital, Chongqing, China	Retrospective case series	23 January - 8 February 2020	8 February 2020	135
Zhongliang Wang [71]	Published	Union hospital, Wuhan, China	Retrospective case series	January 16 to January 29, 2020	February 4, 2020	69
Dan Sun [72]	Published	Wuhan Children's Hospital, Wuhan, China	Case series	January 24 to February 24	February 24, 2020	8
Sijia Tian [73]	Published	Multicentre, 57 hospitals, Beijing, China	Retrospective study	Jan 20 to Feb 10, 2020	Feb 10, 2020	262
Fei Zhou [74]	Published	2 centers, Jinyintan Hospital and Wuhan Pulmonary Hospital, Wuhan, China	Retrospective cohort	Dec 29, 2019, to Jan 31, 2020	NA	191
Na Du [75]	Published	First Affiliated Hospital of Jilin University, Jilin, China	Case series	23 January 2020, to 11 February 2020	NA	12

Table 1 (continued)

Kui Liu [76]	Published	9 tertiary hospitals, Hubei province, China	Retrospective study	December 30, 2019, to January 24, 2020	NA	137
Alma Tostmann [77]	Published	Netherlands	Online anonymous questionnaire	10 March to 29 March 2020	NA	90
Yongli Yan [78]	Published	Tongji Hospital, Wuhan, China	Retrospective, observational	January 10, 2020, to February 24, 2020	NA	193
Xiao-Wei Xu [79]	Published	Multicentre, Zhejiang province, China	Retrospective case series	10 January 2020, to 26 January 2020	NA	62
Jiang-shan Lian [80]	Published	Health Commission of Zhejiang Province Multicentre, Zhejiang province, China	Retrospective study	Jan 17 to Feb 7, 2020	Feb. 12, 2020	788
Nitesh Gupta [81]	Published	Safdarjung Hospital, India	Retrospective observational case series	Feb 1st to 19th march 2020	19th March 2020	21
Xiaoli Zhang [82]	Published	Health Commission of Zhejiang Multicentre, Zhejiang, China	Retrospective study	January 17 to February 8	NA	645
Jie Li [83]	Published	Dazhou Central Hospital, Dazhou, China	Retrospective case series	22 January 2020, to 10 February 2020	11 February 2020	17
Ivan Fan-Ngai Hung [84]	Published	Multicentre, Hong Kong, China	Prospective, open-label, randomised, phase 2 trial	Feb 10 to March 20, 2020	NA	127
Huan Wu [85]	Published	Wuhan Children's Hospital, Wuhan, China	Retrospective case series	January 25 to April 18, 2020	April 18, 2020	148
Michael G Argenziano [86]	Published	NewYork-Presbyterian/Columbia University Irving Medical Center, New York, USA	Retrospective review	1 March to 5 April 2020	30 April	1000
Simone Bastrup Israelsen [87]	Published	Hvidovre Hospital, Denmark	Retrospective case series	10 March to 23 April 2020	NA	175
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	257
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	86
Błażej Nowak [90]	Published	Central Clinical Hospital, Warsaw, Poland	Retrospective study	March 16, 2020, to April 7, 2020	April 7, 2020	169
Xiaoquan Lai [91]	Published	Tongji Hospital Wuhan	Retrospective case series	January 1 to February 9, 2020	NA	110
X. Wang [92]	Published	Dongxihu Fangcang Hospital, Wuhan, China	Retrospective study	7 February to 12 February 2020	22 February	1012
Zhe Liu [93]	Published	Multicentre Xi'an, Shaanxi province, China	Retrospective study	January 16 to February 13, 2020	NA	72
Qiong Huang [94]	Published	Multicentre, Hunan, China	Retrospective case series	January 17 to February 10, 2020	NA	54
Kyung Soo Hong [95]	Published	Yeungnam University Medical Center in Daegu, South Korea	Retrospective study	Up to March 29, 2020	March 29, 2020	98
Rui Huang [96]	Published	Multicentre Jiangsu province, China	Retrospective study	January 22, 2020, to February 10, 2020	February 10, 2020	202
Mengyao Ji [97]	Published	Renmin Hospital of Wuhan University Wuhan, China	Retrospective study	2nd January to 28 January 2020	8 February 2020	101
Dawei Wang [98]	Published	Zhongnan Hospital of Wuhan University in Wuhan and Xishui Hospital, Hubei Province, China	Retrospective study	Up to February 10, 2020	NA	107
Saurabh Aggarwal [99]	Published	Unity Point Clinic, USA	Retrospective study	March 1 to April 4, 2020	NA	16
Xin-Ying Zhao [100]	Published	Jingzhou Central Hospital Jingzhou, China	Retrospective study	January 16, 2020, to February 10, 2020	February 10, 2020	91

Table 1 (continued)

Yifan Meng [101]	Published	Tongji Hospital, Wuhan, China	Retrospective study	January 16th to February 4th, 2020	March 24th, 2020	168
Qingchun Yao [102]	Published	Dabieshan Medical Center, Huanggang city, Hubei Province, China	Retrospective cohort	January 30, 2020 -February 11, 2020	March 3	108 (1 pregnant patient excluded as information incomplete)
Li Zhu [103]	Published	Multicentre, Jiangsu province, China.	Retrospective case series	January 24, 2020, to February 22, 2020	February 25, 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	February 17th, 2020	28
Pavan K. Bhatraju [105]	Published	Multicentre(9), Seattle, USA	Retrospective study	February 24 to March 9, 2020	March 23, 2020	24
Haiyan Qiu [106]	Published	Multicentre (3), Zhejiang, China	Retrospective cohort	Jan 17 to March 1, 2020	Feb 28, 2020	36
Guang Chen [107]	Published	Tongji Hospital, Wuhan, China	Retrospective study	Late December 2019 to January 27, 2020	February 2, 2020	21 (available data of symptoms in 20 only)
Wenjie Yang [108]	Published	Multicentre(3 centers), Wenzhou city, Zhejiang, China	Retrospective cohort	January 17th to February 10th, 2020	Feb 15th, 2020	149
Yu-Huan Xu [109]	Published	Single centre, Beijing, China	Retrospective study	January to February 2020	NA	50
Xi Xu [110]	Published	Guangzhou Eighth People's Hospital, Guangzhou, China	Retrospective study	January 23, 2020, and February 4, 2020	NA	90
Jerome R. Lechien [111]	Published	Multicentre, Europe	Observational, cross-sectional study	March 22 to April 10, 2020	NA	1420
Sherry L. Burrer [112]	Published	CDC COVID-19 Response Team, United states, USA	Retrospective study	February 12 to April 9, 2020	NA	9282 (symptom data for 4707) (age data for 8945) (sex data for 9067)
Ruth Levinson [113]	Published	Tel Aviv Medical Center, Israel	Retrospective with questionnaire via mobile and email	March 10 to 23, 2020	25th of March	42 (total 45 admitted, only 42 completed questionnaire)
Xu Zhu [114]	Preprint	Renmin Hospital of Wuhan University, Wuhan, China	Retrospective study	January 20 to February 15, 2020	February 20, 2020	114
Dan Wang [115]	Preprint	Zhongshan Hospital, Wuhan, China	Cross-sectional study	January 15, 2020-February 28, 2020	NA	143
Chuming Chen [116]	Preprint	Shenzhen Third People's Hospital, Guangdong, China	Prospective study	Jan 16, 2020, to Feb 19, 2020	NA	31
Pingzheng Mo [117]	Published	Zhongnan Hospital of Wuhan University, Wuhan, China	Retrospective study	January 1st to February 5th	NA	155
Gu-qin Zhang [118]	Published	Zhongnan Hospital of Wuhan University, Wuhan, China	Retrospective case series	January 2, 2020, to February 10, 2020	Feb 15, 2020	221
Jennifer Tomlins [119]	Published	North Bristol NHS Trust, UK	Retrospective study	March 10th to March 30th, 2020	April 6th	95
Zonghao Zhao [120]	Preprint	First Affiliated Hospital of USTC Hefei, China	Retrospective study	Jan 21 to Feb 16, 2020	NA	75
Ying Huang [121]	Preprint	Fifth Hospital of Wuhan, Wuhan, China	Retrospective study	Jan 21 - Feb 10, 2020	Feb 14, 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	NA	59

Table 1 (continued)

Yan Deng [123]	Published	2 centers, Wuhan, China	Retrospective study	January 1, 2020, to February 21, 2020	NA	225
Jiaojiao Chu [124]	Published	Tongji Hospital, Wuhan, China	Retrospective study	7 January to 11 February 2020	NA	38
Håkon Ihle-Hansen [125]	Published	Bærum 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]	Published	2 centres, New York, USA	Retrospective case series	March 3 to March 27, 2020	April 10th	393
Jianlei Cao [127]	Published	Wuhan University Zhongnan Hospital, Wuhan, China	Retrospective cohort	3 January to 1 February 2020	15 February 2020	102
De Chang [128]	Published	Multicentre (3 centers), Beijing, China	Case series	January 16, 2020, to January 29, 2020	February 4, 2020	13
Huijun Chen [129]	Published	Zhongnan Hospital of Wuhan University, Wuhan, China	Retrospective case series	Jan 20 to Jan 31, 2020	Feb 4, 2020	9
Lang Wang [130]	Published	Renmin Hospital of Wuhan University, China	Retrospective study	Jan 1 to Feb 6, 2020	March 5	339
Gianfranco Spiteri [131]	Published	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]	Published	Shenzhen Third People's Hospital, China	Case series	Jan 11 to Jan 20, 2020	NA	12
Tianmin Xu [133]	Published	Third Hospital of Changzhou, Changzhou city, Jiangsu province, China	Retrospective cohort	Jan 23 to February 18,2020	February 27, 2020	51
Michael Chung [134]	Published	Multicentre (3 centers), 3 provinces, China	Retrospective case series	January 18, 2020, to January 27, 2020	NA	21
Heshui Shi [135]	Published	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]	Published	Yichang Central People's Hospital, Yichang, Hubei Province, China	Retrospective study	Jan 30 to Feb 8, 2020	Feb 26, 2020	200
Wei Zhao [137]	Published	Multicentre (4 centers),Hunan, China	Retrospective study	NA	NA	101
Ya-nan Han [138]	Published	Xian eighth hospital Shaanxi, China	Retrospective study	31st January-16th February 2020	NA	32
Yang Wang [139]	Published	Tongji Hospital, China	Cohort	January 25, 2020, to February 25, 2020	28 days follow-up	344

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) CNS—53 (24.8) Dizziness—36 (16.8) Headache—28 (13.1) Impaired consciousness—16 (7.5) Acute cerebrovascular disease—6 (2.8)	Severe vs non-severe 5 ischaemic stroke, 1 hemorrhagic stroke	NA

Table 1 (continued)

				Ataxia—1 (0.5) Seizure—1 (0.5) PNS—19 (8.9) Taste disturbances—12 (5.6) Smell disturbances—11 (5.1) Vision impairement—3 (1.4) Nerve pain-5 (2.3) Skeletal muscle injury—23 (10.7)		
Yanan Li [33]	Consecutive hospitalized patients	53·3 ± 15·9	131 (59.3)	Acute cerebrovascular disease—13 (5·9) Ischaemic stroke—11 (84·6) Cerebral venous sinus thrombosis—1 (7·7) Cerebral haemorrhage—1 (7·7)	Severe vs non-severe, with cerebrovascular disease vs without cerebrovascular disease	4 ischaemic stroke and 1 hemorrhagic stroke patients expired
Lu Lu [34]	Consecutive discharged or died patients from multiple centers	44 (33–59.25)	182 (59.9)	Acute cerebrovascular disease–3 (1)	Mild, moderate vs severe, critical	NA
F.A. Klok [35]	Only ICU patients	NA	NA	Acute cerebrovascular disease—5 (2.8) (all ischaemic stroke)	All patients received thrombo prophylaxis	41(22%) died and 78 (43%) discharged alive
Corrado Lodigiani [36]	Consecutive adult symptomatic patients admitted, 61 ICU patients	66 (55–75)	264 (68)	Acute ischaemic stroke—9 (2.5)	ICU vs general ward, survivors vs non-survivors, thromboprophylaxis in 100% ICU and 75% ward patients	2 stroke patients died 4 patients discharged
Megan Fraissé [37]	Only ICU patients	61 (55–70)	73 (79)	Acute cerebrovascular disease—4 (4.3) Ischaemic—2 (2.2) Hemorrhagic—2 (2.2)	All received thromboprophylaxis	NA
Siddhant Dogra [38]	All hospitalized patients	62 (37–83) (among 33 patients)	26/33 (78.8)	Acute hemorrhagic stroke—33 (0.9) (only in 755 neuroimaging done)	37 had hemorrhage, but 4 excluded as hemorrhage secondary to trauma, bleeding in brain metastases, after tumor resection	NA
Julie Helms [39]	Consecutive hospitalized ICU patients	63	NA	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)	NA	NA
Julie Helms [40]	All consecutive patients referred to ICU for ARDS	63 (53–71)	122 (81.3)	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)	21 (78)	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	NA

Table 1 (continued)

				Acute infarction in right middle cerebral artery territory—1 (0.4)		
Silvia Garazzino [42]	Pediatric patients under 18 years	2.3 (0.3–9.6)	94 (55.9)	Non-febrile seizures—3 (1.8) Febrile seizures—2 (1.2)	NA	Recovered—168
Rajan Jain [43]	All patients admitted	NA	NA	Imaging (3218) Acute cerebrovascular disease—35 (1.1) Ischaemic—26 Hemorrhagic—9 Hypoxic anoxic brain injury—2 Encephalitis—1 Clinical (454) Altered mental status or delirium (37.6%) Stroke (17.3%) Syncope (4%) Headache (3.8%) Dizziness (2.8%) Seizure (2.1%) Ataxia (1.4%)	Neuro imaging done—454 (14.1%) 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)	NA
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) TIA—5 (11.6) Ischaemic stroke—35 (81.4) Hemorrhagic stroke—3 (7.0) Epilepsy—4 (7.1) Delirium—15 (26.8)	COVID-19 vs non-COVID-19	Mortality—21 (37.5)
Weixi Xiong [45]	All consecutive symptomatic patients	48.7 ± 17.1	504 (55)	New-onset neurological events—39 (4.3) Disturbance of consciousness/delirium—21 (2.3) Syncope—3 (0.3) Traumatic brain injury—1 Acute Cerebrovascular accident—10 (early onset—2) Occipital neuralgia—1 Unexplained severe headache—2 Non-specific headache—8 Functional or? Tic/tremor—2 Muscle cramp—2	Critical vs non-critical neurological events	Discharged—742 Hospitalized—145 Died—30
Tyler Scullen [46]	Severe cases with neurological features	59.8 (35–91)	14 (52)	Altered mental status—26 (96.3) Dysgeusia—1 (3.7) Generalized weakness—1 (3.7) Headache—2 (7.4) Focal Deficit—10 (37.0) Decerebrate posturing—1 (3.7) Facial droop—1 (3.7) Fixed pupils—1 (3.7) Gaze deviation—3 (11.1) Hemineglect—2 (7.4) Hemiparesis or hemiplegia—4 (14.9)	Imaging and EEG Encephalopathy—20 (74) Acute necrotizing encephalopathy—2 (7) Vasculopathy—5 (19) Subacute ischaemic stroke—4 (14.8) NCSE—1 (3.7) Large vessel occlusion—PCA P2B—1 (3.7)	NA

Table 1 (continued)

				Quadriplegia 1 (3.7)	Focal stenosis ICA terminus—3 (11.1)	
Abdelkader Mahammedi [47]	Consecutive hospitalized patients	NA	NA	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 MFS—1 PRES—1 Acute encephalopathy—1 Non-specific encephalopathy—2 MS plaque exacerbation—2	119 patients had neurological symptoms; however, only 108 received neuroimaging evaluation	NA
Alireza Radmanesh [48]	All patients diagnosed	NA	NA	Acute/subacuteinfarct—13 Haemorrhage—7 (excluding previous) Altered mental status—102 (2.9%) Syncope/fall (79 patients Focal neurologic deficit—30	242 underwent imaging (CT or MRI)	NA
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)	Non-severe vs severe	Mortality—197 (23.42)

Table 1 (continued)

				Neuropsychiatric symptoms—167 (19.9)		
Stephane Kremer [50]	Severe patients with abnormal MRI Only	61 (8–78)	30 (81)	Headache—4 (11) Seizures—5 (14) Clinical signs of corticospinal tract involvement—4(11) Disturbances of consciousn ess—27 (73) Confusion—12 (32) Agitation-7(19) Pathological wakefulness in intensive care units-15(41)	Non-hemorrhagic vs hemorrhagic forms CSF—1 patient's CSF SARS-CoV-2 RT-PCR positive	Died—5 (14)
Pranusha Pinna [51]	Only 50 patients admitted to neurology ward or referred to neurology is studied	NA	NA	CNS Altered mental status—30 Seizures—13 Headache—12 Short-term memory loss—12 Acute cerebrovascular accident—19 Acute ischaemic stroke—10 Hypoxic ischaemic 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	Neurological manifestations—7.7% (total patients in the hospital were 650; however, not all evaluated for neurological symptoms, mentioned in the limitations of the study)	NA
Álvaro Beltrán-Corbellini [52]	Consecutive patients hospitalized, > 18 years	61.6 ± 17.4	48 (60.8)	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—ageusia14/31 (45.2)	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)	Headache—2 (3.4) Olfactory and/or taste disorders—20 (33.9) Olfactory disorders—14 Taste disorder—17	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)	Olfactory dysfunction—357 (85.6) Anosmia—284 (79.6) Hyposmia—73 (20.4) Phantosmia—12.6%		

Table 1 (continued)

				Parosmia—32.4% Gustatory disorders—342 (88.8) Reduced/discontinued—78.9% Distorted ability to taste flavors—21.1%		
Giacomo Spinato [55]	Adults (≥ 18 years) consecutively assessed and mildly symptomatic (only home managed patients)	56 (45–67)	97 (48.0)	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	NA
Luigi Angelo Vaira [56]	Adults over 18 years of age (excluded assisted ventilation patients)	49.2 ± 13.7	27 (37.5)	Headache—30 (41.6) Olfactory and taste disorders—53 (73.6) Olfactory disorder—44 (61.1) Taste disorder—39 (54.2)	Objective tests used	NA
Luigi Angelo Vaira [57]	Health care staff, home quarantined, age > 18 years	47.2 ± 10	11 (33.3)	Olfactory and taste disorders—21 (63.6) Olfactory disorder—17 (51.5) Taste disorder—17(51.5)	Validation of a self-administered olfactory and gustatory test done	NA
Luigi Angelo Vaira [58]	Both hospitalized and home quarantined patients, ≥ 18 years (excluded assisted ventilation patients)	48.5 ± 12.8	146 (42.3)	Olfactory and/or taste disorders-256(74.2) Olfactory disorder-225 Taste disorder-234	Objective assessment done	NA
Yonghyun Lee [59]	COVID-19 patients awaiting hospitalization or facility isolation	44.0(25.0–58.0)	1161(36.4)	Anosmia and/or ageusia—488 (15.3) Anosmia—389 Ageusia—353	Presence vs absence of anosmia or ageusia	NA
Marlene M. Speth [60]	All positive (ICU and deceased excluded)	NA	50 (48.5)	Olfactory dysfunction—63 (61.2) Decreased smell—14.6% Anosmia—46.6% Gustatory dysfunction—67 (65.0) Decreased taste-25.2% Ageusia—39.8%	NA	NA
T. Klopfenstein [61]	All admitted adults	NA	NA	Anosmia—54 (47) Dysgeusia—46/54 (85) Myalgia—40/54 (74) Headache—44/54 (82)	NA	Death—2/54(4)
Dawei Wang [10]	Consecutive patients admitted	56 (42–68)	75 (54.3)	Myalgia—48 (34.8) Dizziness—13 (9.4) Headache—9 (6.5)	ICU vs non-ICU	NA
Wei-jie Guan [11]	All patients with data available	47.0 (35.0–58.0)	637/1096 (58.1)	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	55·5 ± 13·1	67 (68)	Muscle ache—11 (11) Headache—8 (8) Confusion—9 (9)	NA	Remained in . hospital—57 (58) Discharged—31 (31) Died—11 (11)
Chaolin Huang [62]	Hospitalized	49·0 (41·0–58·0)	30 (73)	Myalgia or fatigue—18 (44) Headache—3/38 (8)	ICU vs non-ICU	Hospitalization—7 (17) Discharge—28 (68)

Table 1 (continued)

						Death—6 (15)
ChaominWu [63]	All hospitalized patients	51 (43–60)	128 (63.7)	Fatigue or myalgia—65 (32.3)	ARDS vs non-ARDS	Death—44 (21.9) Discharged—144(71.6)
Xiaobo Yang [64]	Only critically ill patient admitted in ICU	59·7 (13·3)	35 (67)	Myalgia—6 (11·5) Headache—3 (6)	Survivors vs non-survivors	Died—32 (61·5) Discharged—8 Hospitalized—12
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) Dizziness—21 (8) Hypoxic encephalopathy—24 (9)	Deaths vs recovered	113 died,161 fully recovered
Yingzhen Du [66]	Consecutive severe patients	65.8 ± 14.2	62 (72.9)	Myalgia—14 (16.5) Headache—4 (4.7)	NA	Died—85
Yongli Zheng [67]	Consecutively hospitalized All ages	49.40 ± 18.45	51(52)	Muscle ache and headache—12 (12)	Critically ill vs non-critically ill	NA
Alfonso J. Rodriguez-Morales [68]	First notified cases of COVID-19	NA	NA	Headache—597 (64.8) Myalgia—32 (3.5)	NA	NA
Feng Wang [69]	Diabetic, hospitalized patients	68.6 ± 9.0	21(75)	Headache—3 (10.7)	ICU vs non-ICU	Died—12 Discharged—12 Hospitalized—4
Suxin Wan [70]	Hospitalized patients	47 (36–55)	72 (53.3)	Myalgia or fatigue—44 (32.5) Headache—24 (17.7)	Mild vs severe	Hospitalization—120 (88.9) Discharge—15 (42.9) Death—1 (0.7)
Zhongliang Wang [71]	Hospitalized patients	42.0(35.0–62.0)	32(46)	Myalgia-21 (30) Headache-10 (14) Dizziness—5 (7)	Spo2 < 90 vs Spo2_ > 90	Hospitalization—44(65.7) Discharge—18 (26.9) Death—5 (7.5)
Dan Sun [72]	Pediatric ICU (severe and critically ill only)	2 months to 15 years	6	Myalgia or fatigue—1 Headache—1	NA	Hospitalized—3 Discharged—5
Sijia Tian [73]	Hospitalized, all age groups	47.5 (1–94)	127 (48.5)	Headache—17 (6.5)	Severe vs common (mild, asymptomtic, non-pneumonia)	Discharge—45 (17.2) Hospitalization—214 (81.7) Death—3 (0.9)
Fei Zhou [74]	All adult ≥ 18 hospitalized and either dead or discharged patients	56·0 (46·0–67·0)	119 (62)	Myalgia—29 (15)	Non-survivor vs survivor	Discharged—137 Died—54
Na Du [75]	Consecutive hospitalized patients	45.25(23–79)	7(54.3)	Headache—3 (20)	NA	NA
Kui Liu [76]	Hospitalized patients	57 (20–83)	61 (44.5)	Myalgia or fatigue—44(32.1) Headache—13(9.5)	NA	Discharged-—44 (32.1) Hospitalized—77 (56.2) Death—16 (11.7)
Alma Tostmann [77]	Only health care workers	NA	19 (21.1)	Anosmia—37/79 (46.8) Muscle ache—57/90 (63.3) Headache—64/90 (71.1)	Symptomatic health care workers positive vs negative	NA
Yongli Yan [78]	Adults over 18 years, hospitalized, severe (all hospitalized admitted there included)	64 (49–73)	114 (59.1)	Headache—21 (10.9)	48 diabetic vs 148 non-diabetic, survivors vs non-survivors	Mortality—108 (56.0)
Xiao-Wei Xu [79]	Adult hospitalized patients	41 (32–52)	35 (56)	Myalgia or fatigue—32 (52) Headache—21 (34)	Symptom onset > 10 days vs < 10 days	Hospital admission—61 (98) Discharge—1 (2) Death—0

Table 1 (continued)

Jiang-shan Lian [80]	All confirmed cases	NA	407(51.65)	Muscle ache—91(11.54) Headache—75(9.52)	With Wuhan exposure vs without	Discharged—322 (40.86) Death—0
Nitesh Gupta [81]	First 21 hospitalized patients in the centre	40.3 (16–73)	14 (66.7)	Headache—3 (13.6)	NA	Discharged—15
Xiaoli Zhang [82]	All hospitalized patients	NA	328(50.85)	Muscle ache-71(11.01) Headache-67(10.39)	Normal imaging vs abnormal imaging	NA
Jie Li [83]	All hospitalized patients	45.1 ± 12.8 45 (22–65)	9 (52.9)	Myalgia—4 (23.5) Dizziness—2 (11.8)	Discharged vs non-discharged	Discharged—5 Hospitalized—12
Ivan Fan-Ngai Hung [84]	Adult at least 18 years, admitted	NA	68 (53.54)	Myalgia—18 (14.17) Headache—6 (4.72) Anosmia—5 (3.93)	Combination triple antiviral drug vs control group(lopinavir–ritonavir)	Death-0
Huan Wu [85]	Pediatric mild and moderate cases only	84 (18–123)months	60 (40.5)	Headache—5 (3.4)	NA	Discharged—148 (100) Died—0
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) Syncope—48 (4.8)	Emergency vs ward vs ICU	Discharged—699 Died—211 Hospitalized—90
Simone Bastrup Israelsen [87]	Consecutive patients, adult ≥ 18, hospitalized	71 (55–81)	85 (48.6)	Myalgia—46 (26.3) Headache—32 (18.3) Altered sense of taste—5 (2.9)	General Ward vs ICU	On April 20th Hospitalized—23 (13.1) Discharged—109 (62.3) Died—43 (24.6)
Matthew J Cummings [88]	Only critically ill adults aged ≥ 18 years	62 (51–72)	171 (67)	Myalgia- 67 (26) Headache—10 (4)	NA	Discharged alive—58 (23) Died −101 (39) Hospitalized—98 (38)
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) Altered or lost sense of taste- 6 (7)	Interview within 7 d of the onset of Symptoms vs >7d	Recovered—19 (22) Hospital admission—2 (2)
Błażej Nowak [90]	Consecutive patients hospitalized	63.7 ± 19.6	87 (51.5)	Headache—1 Anosmia and ageusia—3 (1.7)	Survivors vs non-survivors	Hospitalized—80(45.7) Discharged home or to isolation areas—46 (26.3) Died—46 (26.3)
Xiaoquan Lai [91]	Only health care workers	36.5 (30.0–47.0)	31 (28.2)	Myalgia or fatigue—66 (60.0) Muscle ache- 50 (45.5) Headache—33 (30.0) Dizziness—24 (21.8)	Hcw with COVID-19 vs without	Died—1 (0.9)
X. Wang [92]	Only non-critically ill (however, all patient admitted in that hospital included)	50 (39–58)	524 (51.8)	Headache—152 (15.0) Myalgia—170 (16.8)	With and without aggravation during follow up	Died—0 Discharge—93 (9.2) Hospitalized or transferred to another hospital—919 (90.8)
Zhe Liu [93]	All hospitalized	46.2 ± 15.9	39 (54.2)	Muscle soreness—7 (9.7) Headache—4 (5.6)	Uncomplicated vs mild vs severe	Discharged—32 Died—0 Hospitalized—40
Qiong Huang [94]	All hospitalized patients	41 (31–51)	28 (51.9)	Muscle soreness—9 (16.7) Headache—3 (5.6) Dizziness—3 (5.6)	Common vs severe	Discharged—54
Kyung Soo Hong [95]	Consecutive hospitalized patients	55.4 ± 17.1	38 (38.8)	Myalgia—37 (37.8)	ICU vs non-ICU	Remains in hospital—57 (58.2) Discharged—30 (30.6) Died—5 (5.1)

Table 1 (continued)

						Transferred—6 (6.1)
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	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)	Medica staff vs non-medical	Death-11 (11) Hospitalization—53 (52) Cured—37 (37)
Dawei Wang [98]	All the discharged (alive at home and dead) patients with confirmed COVID-19(88 patients overlap with Wang D[10])	51.0 (36.0–65.0)	57 (53.3)	Myalgia—33 (30.8) Headache—7 (6.5) Dizziness—7 (6.5)	Survivors vs non-survivors	Died—19 Survived—88
Saurabh Aggarwal [99]	All admitted patients	67 (38–95)	12 (75)	Lightheadedness—3 (19) Headache—4 (25) Anosmia—3 (19) Dysgeusia—3 (19)	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—15 (16.5) Dizziness—3 (3.3) Disturbance of consciousness—3 (3.3)	Severe vs mild	Remained in hospital—75 (82.4) Discharged—14 (15.4) Died—2 (2.2)
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)	Male vs female	Died—17(8.9) Discharge—136 Hospital—15
Qingchun Yao [102]	Consecutive adult patients admitted	52 (37–58)	43 (39.8)	Myalgia or fatigue—28 (25.9) Headache—1 (0.9)	Non-severe vs severe alive vs severe dead	Died—12 Discharged—96
Li Zhu [103]	1–18 years, children	NA	5 (50.0)	Headache—2 (20.0)	NA	Discharged—5 (50.0) Hospitalized—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)	NA	Discharged—10 Hospitalized—18
Pavan K. Bhatraju [105]	Only critically ill ICU patients	64 ± 18 (23–97)	15 (63)	Headache—2 (8)	NA	Died—12 (50) Discharged—5 (21) Hospitalized—7 (30)
Haiyan Qiu [106]	All pediatric 0–16 years	8·3 ± 3·5	23 (64)	Headache- 3 (8)	Mild vs moderate	All cured
Guang Chen [107]	All hospitalized patients	56.0 (50.0–65.0)	17 (81.0)	Myalgia—8/20 (40.0%) Headache—2/20 (10.0%)	Severe vs moderate	Died—4 Recovered—2
Wenjie Yang [108]	Consecutive hospitalized patients	45.11 ± 13.35	81	Muscle pain—5(3.36%) Headache—13(8.72%)	NA	Remained in hospital—76 (51.01) Discharged—73 (48.99) Died—0 (0.0)
Yu-Huan Xu [109]	All hospitalized patients	43.9 ± 16.8	29 (58)	Headache—5 (10) Muscle ache—8 (16)	Mild vs moderate vs severe vs critically severe	NA
Xi Xu [110]	All hospitalized patients	50 (18–86)	39 (43)	Myalgia—25 (28) Headache—4 (4)	NA	NA
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	NA

Table 1 (continued)

				Taste dysfunction—770 (54.2)		
Sherry L. Burrer [112]	Cases reported to CDC, only health care personal	42 (32–54)	2464(27)	Muscle ache—3122(66) Headache—3048(65) Loss of smell or taste—750(16)	NA	Data of 8945 Not hospitalized—6760 (90%) Hospitalized—723 (8–10%) ICU admission—184 (2–5%) Died—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) Headache—20 (48) Anosmia—14 (33) Dysgeusia—15 (36) Dizziness—9 (21)	NA	NA
Xu Zhu [114]	Only elderly(> 70) patients	76 (72–82)	67 (58.8)	Myalgia—4 (3.5)	Severe vs non-severe	Alive—87 (76.3) Dead—27(23.7)
Dan Wang [115]	All consecutive admitted patients	58(39–67)	73(51.0)	Myalgia—49(34.3) Headache—7(4.9)	Mild/moderate vs severe/critical	NA
Chuming Chen [116]	Only pediatric, < 18 years, hospitalized patients	7.33 ± 4.35	13 (41.9)	Headache—1 (3.2)	NA	Died—0
Pingzheng Mo [117]	All Consecutive admitted patients	54 (42–66)	86 (55.5)	Myalgia or arthralgia—50 (61.0) Headache-8 (9.8) Dizziness-2 (2.4)	General vs refractory	NA
Gu-qin Zhang [118]	All hospitalized patients	55.0 (39.0–66.5)	108(48.9)	Headache—17(7.7)	Severe vs non-severe	Hospitalization—168 (76.0) Discharge—42 (19.0) Death—12 (5.4)
Jennifer Tomlins [119]	All sequential hospitalized patients	75 (59–82)	60 (63)	Myalgia—13 (14) Confusion—20 (21) Seizure—1 (1.1) Headache—9 (9.5) Anosmia—3 (3.2)	NA	Died—21 (21) Discharged—44(43) Hospitalized—30 (29)
Zonghao Zhao [120]	All positive cases	47 (34–55)	42 (56)	Muscle soreness—9 (12.00) Headache —5 (6.67)	NA	NA
Ying Huang [121]	Non survivors only	69.22 (9.64)	25 (69.44)	Myalgia—1 (2.78) Disturbance of consciousness—8 (22.22)	NA	Died—36
Carol H. Yan [122]	All positive COVID-19 who completed survey(most are mild cases)	NA	29 (49.2)	Headache—39 (66.1) Myalgia/arthralgia—37 (62.7) Ageusia—42 (71.2) Anosmia- 40 (67.8)	With subjective olfaction score COVID-19 vs non-COVID-19	NA
Yan Deng [123]	Only dead and recovered patients admitted	NA	124	Myalgia or fatigue—57 Headache—13 (11.5)	Death group vs recovered group	Died—109 Recovered—116
Jiaojiao Chu [124]	Only medical staff(54 tested, but only 38positve for nucliec acid tests)	39 (26–66)	24 (63.2)	Muscle ache—2 (5.3)	Common vs severe, positive RT-PCR vs negative	NA
Håkon Ihle-Hansen [125]	All consecutive admitted	72.5 (30–95)	28 (67)	New-onset confusion—8 (19)	Severe vs critical	NA
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	Died—40 (10.2) Discharged—260 (66.2)

Table 1 (continued)

						Outcome data incomplete—93 (23.7)
Jianlei Cao [127]	All patients admitted	54 (37–67)	53	Muscle ache—35(34.3)	Non survivors vs survivors	Discharge—85 (83.3) Died—17(16.7)
De Chang [128]	All hospitalized patients	34 (34–48)	10 (77)	Myalgia—3 (23.1) Headache—3 (23.1)	NA	All recovered (12 still quarantined)
Huijun Chen [129]	Only pregnant patients	26–40 years	NA	Myalgia—3 (33%)	NA	All nine live birth Died—0
Lang Wang [130]	Consecutive cases over 60 years old	69 (65–76)	166(49)	Myalgia—16 (4.7) Dizziness—13 (3.8) Headache—12 (3.5)	Survival vs dead	Discharged—91(26.8) Hospitalized—183(54.0) Died—65(19.2)
Gianfranco Spiteri [131]	First cases in the WHO European region except UK	42(2–81)	25	Headache—6 Myalgia—1 (3.22)	Infected in Europe vs china	Died—1
Yingxia Liu [132]	Patients admitted	10–72 years	8	Myalgia—4(33.3)	NA	NA
Tianmin Xu [133]	Patients admitted	NA	25	Myalgia—8(15.7)	Imported vs secondary vs tertiary (1 patient diagnosed with anal swab)	NA
Michael Chung [134]	Admitted patients who underwent chest CT	51 ± 14	13 (62)	Headache—3 (14) Muscle soreness—3 (14)	NA	NA
Heshui Shi [135]	Admitted and had CT chest done	49·5 ± 11·0	42 (52)	Headache—5 (6) Dizziness—2 (2)	NA	NA
Luhuan Yang [136]	All admitted patients	55 ± 17.1	98 (49.0)	Myalgia or malaise—44 (22.0) Headache 27—(13.5)	ICU vs non-ICU	Hospitalization—143 (71.5) Discharge—42 (21) Death—15 (7.5)
Wei Zhao [137]	Consecutive laboratory confirmed COVID-19 who underwent CT	44.44(17–75)	56 (55.4)	Myalgia or fatigue—17 (16.8)	Emergency vs non-emergency group	NA
Ya-nan Han [138]	All admitted patients	NA	16	Myalgia or fatigue-13(all adults)	Only 30/32 (93.8%) lab confirmed (2 included based on clinical and epidemiological evidence) Paediatrics vs adults	Discharged—32
Yang Wang [139]	Severely and critically ill (ICU)	64 (52–72)	179 (52.0)	Rhabdomyolysis—9 (2.6)	Survivors vs non-survivors	Died—133 (38.7) Discharged—185 (87.7) Hospitalized—26

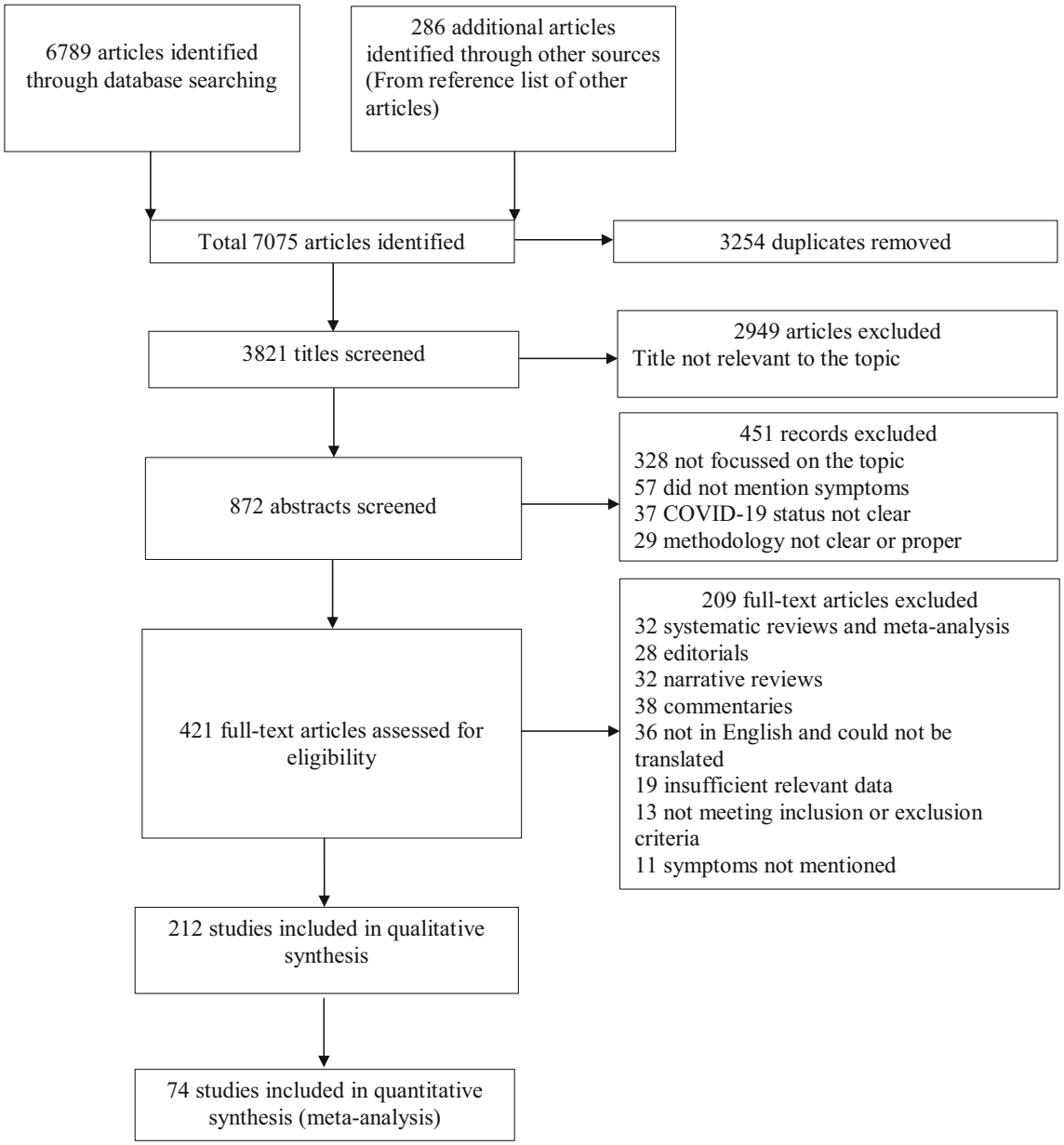

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

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

Table 2 Prevalence of neurological manifestations reported from systematic assessment

	Studies (*N*)	Sample size (*N*)	Cases (n)	Prevalence (95% CI)
Smell disturbances	17	7919	2488	31.4% (30.4–32.4)
Taste disturbances	14	7033	1979	28.1% (27.1–29.2)
Headache	54	13,623	2751	20.2% (19.5–20.9)
Myalgia	38	11,169	2288	20.5% (19.7–21.2)
Disturbances in consciousness/altered mental status	9	6687	408	6.1% (5.5–6.7)
Syncope	3	1000	56	5.6% (4.3–7.2)
Dizziness	12	2595	137	5.3% (4.5–6.2)
Acute cerebrovascular disease	8	10,186	148	1.4% (1.2–1.7)
Ischaemic stroke	7	9268	108	1.2% (1.0–1.4)
Hemorrhagic stroke	7	12,704	60	0.5% (0.4–0.6)
Cerebral venous thrombosis	2	946	3	0.3% (0.1–0.9)
Seizures	5	2043	23	1.1% (0.7–1.7)
Ataxia	2	939	3	0.3% (0.1–0.9)

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 ischaemic 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

Table 3 Meta-analysis, summary estimate of pooled prevalence and heterogeneity of each neurological manifestations

	Number of studies (*N*)	Summary estimate (%)	95% CI	I^2
Smell disturbances	17	35.8	(21.4, 50.2)	99.87
Taste disturbances	14	38.5	(24.0, 53.0)	99.65
Headache	54	14.7	(10.4, 18.9)	99.09
Myalgia	38	19.3	(15.1, 23.6)	98.98
Disturbances in consciousness/altered mental status	9	9.6	(4.9, 14.3)	98.26
Dizziness	12	6.1	(3.1, 9.2)	93.44
Acute cerebrovascular disease	8	2.3	(1.0, 3.6)	96.61
Ischaemic stroke	7	2.1	(0.9, 3.3)	96.67
Hemorrhagic stroke	7	0.4	(0.2, 0.6)	62.36
Cerebral venous thrombosis	2	0.3	(0.1, 0.6)	0.00
Syncope	3	1.8	(0.9, 4.6)	98.48
Ataxia	2	0.3	(0.1, 0.7)	0.00
Seizure	5	0.9	(0.5, 1.3)	9.03

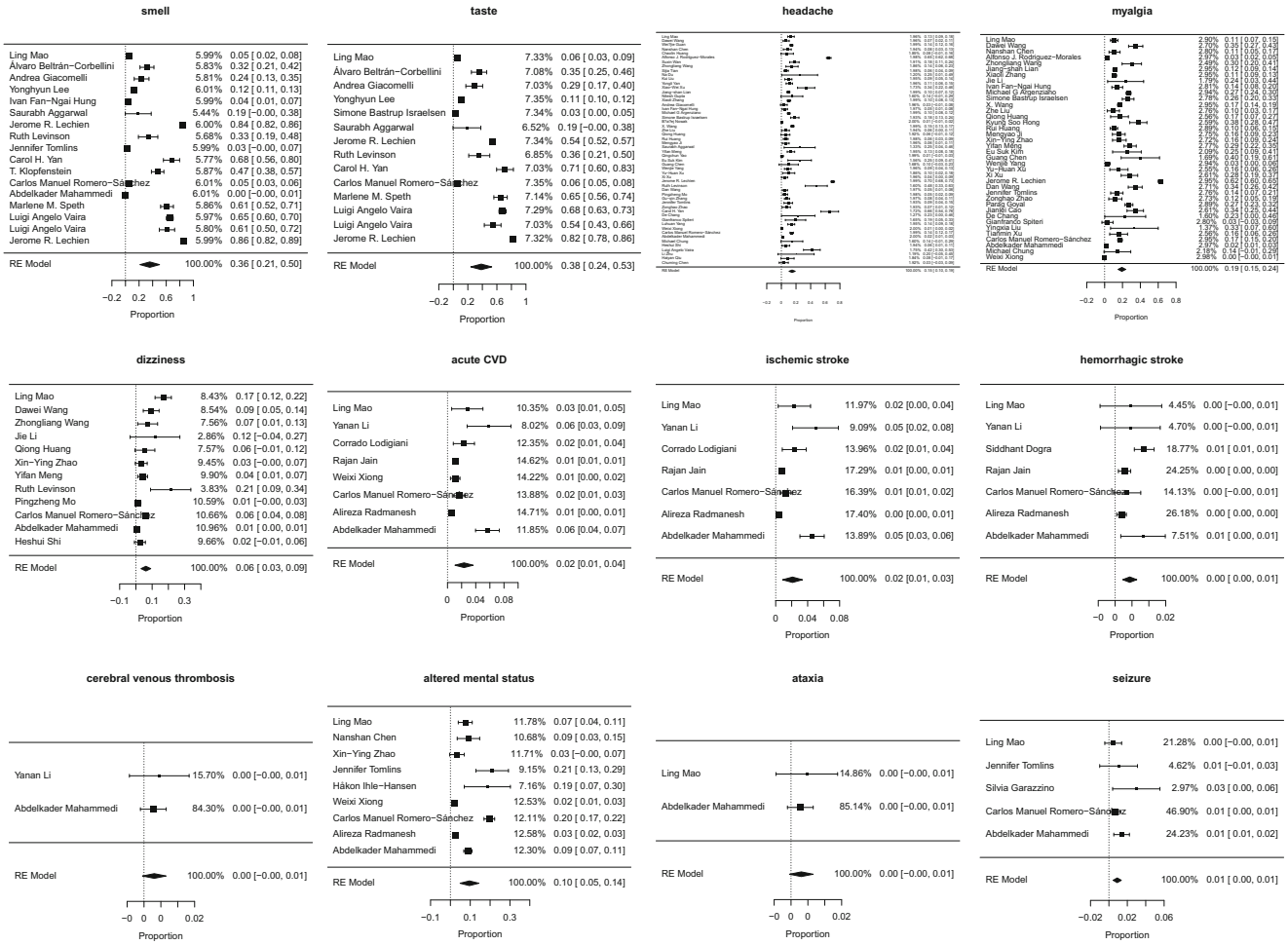

Fig. 2 Forest plot of each neurological manifestations

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.

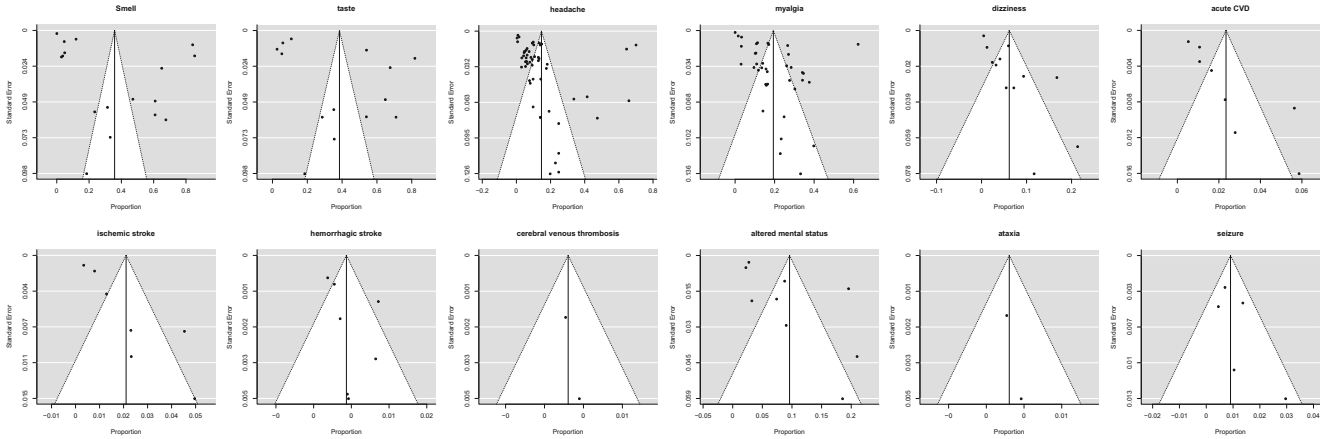

Fig. 3 Funnel plot for assessing publication bias of each neurological manifestations studied

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 hypoperfusion 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

Table 4 Summary of all the neurological manifestations of COVID-19

Non-specific	CNS manifestations	Peripheral nervous system manifestations
Myalgia	Disturbances in consciousness	Taste disturbances (ageusia, reduced taste, distorted taste)
Headache	Agitation	Smell disturbances (anosmia, phantosmia, parosmia)
Dizziness	Pathological wakefulness	Vision impairment
Vertigo	Encephalitis	Nerve pain/neuralgia
Lightheadedness	Encephalopathy	Skeletal muscle injury
	Acute necrotizing hemorrhagic encephalopathy	Rhabdomyolysis
	Post-hypoxic encephalopathy/hypoxic ischaemic brain injury	Myositis
	Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)	Occipital neuralgia
	Rhombencephalitis/myelitis	Dysautonomia
	Seizure (focal, GTCS, NCSE, status epilepticus, febrile seizures)	Extraocular muscle abnormalities
	Acute cerebrovascular disease	Isolated unilateral facial palsy
	Ischaemic stroke/TIA	GBS (AIDP/AMAN/AMSAN)
	Hemorrhagic stroke	DP (facial diplegia) variant of GBS
	SAH (aneurysmal and non-aneurysmal)	Miller Fisher syndrome
	Cerebral venous sinus thrombosis	Cranial neuropathy
	Ataxia	Oropharyngeal dysphagia
	Dysexecutive syndrome	Optic neuritis
	Corticospinal tract signs	Posterior ischaemic optic neuropathy (non-arteritic) (PION)
	Syncope	Central retinal artery occlusion
	Short term memory loss	Cutaneous hyperaesthesia
	Movement disorders	Parasthesias
	Neuropsychiatric symptoms	
	PRES syndrome	
	MS plaque exacerbation	
	Clinically isolated syndrome (CIS)	
	ADEM	
	Post-infectious myelitis	
	Generalized brainstem type of myoclonus	
	CNS vasculitis	

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 affinity of SARS-CoV-2 to tissues between populations, a different 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.

Consent to participate Not applicable.

Consent for publication Not applicable.

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