

# Frequency of Neurologic Manifestations in COVID-19

## A Systematic Review and Meta-analysis

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## Abstract

### Background and objectives

One year after the onset of the coronavirus disease 2019 (COVID-19) pandemic, we aimed to summarize the frequency of neurologic manifestations reported in patients with COVID-19 and to investigate the association of these manifestations with disease severity and mortality.

### Methods

We searched PubMed, Medline, Cochrane library, ClinicalTrials.gov, and EMBASE for studies from December 31, 2019, to December 15, 2020, enrolling consecutive patients with COVID-19 presenting with neurologic manifestations. Risk of bias was examined with the Joanna Briggs Institute scale. A random-effects meta-analysis was performed, and pooled prevalence and 95% confidence intervals (CIs) were calculated for neurologic manifestations. Odds ratio (ORs) and 95% CIs were calculated to determine the association of neurologic manifestations with disease severity and mortality. Presence of heterogeneity was assessed with  $I^2$ , meta-regression, and subgroup analyses. Statistical analyses were conducted in R version 3.6.2.

### Results

Of 2,455 citations, 350 studies were included in this review, providing data on 145,721 patients with COVID-19, 89% of whom were hospitalized. Forty-one neurologic manifestations (24 symptoms and 17 diagnoses) were identified. Pooled prevalence of the most common neurologic symptoms included fatigue (32%), myalgia (20%), taste impairment (21%), smell impairment (19%), and headache (13%). A low risk of bias was observed in 85% of studies; studies with higher risk of bias yielded higher prevalence estimates. Stroke was the most common neurologic diagnosis (pooled prevalence 2%). In patients with COVID-19  $\geq 60$  years of age, the pooled prevalence of acute confusion/delirium was 34%, and the presence of any neurologic manifestations in this age group was associated with mortality (OR 1.80, 95% CI 1.11–2.91).

### Discussion

Up to one-third of patients with COVID-19 analyzed in this review experienced at least 1 neurologic manifestation. One in 50 patients experienced stroke. In those  $>60$  years of age, more than one-third had acute confusion/delirium; the presence of neurologic manifestations in this group was associated with nearly a doubling of mortality. Results must be interpreted with the limitations of observational studies and associated bias in mind.

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From the Department of Neurology (S.M., D.R., A.K., A.D., A.K.S., A.A.), All India Institute of Medical Sciences, New Delhi, India; Brain Health Unit (K.K., T.D.), World Health Organization, Geneva, Switzerland; Department of Clinical Research and Epidemiology (M.P.), Institute of Liver and Biliary Sciences, New Delhi, India; Columbia University Irving Medical Center—New York Presbyterian Hospital (K.T.T.), NY; Institute of Infection, Veterinary and Ecological Sciences (T.S., B.D.M., G.K.W.), University of Liverpool; Department of Neurology (T.S., B.D.M.), Walton Centre NHS Foundation Trust; NIHR Health Protection Research Unit for Emerging and Zoonotic Infection (B.D.M.), Liverpool, UK; Center for Global Health (A.S.W.), Department of Neurology, Technical University of Munich, Germany; Centre for Global Health (A.S.W.), Institute of Health and Society, University of Oslo, Norway; Istituto di Ricerche Farmacologiche Mario Negri IRCCS (E.B.), Milan, Italy; Moscow Research and Clinical Center for Neuropsychiatry and Pirogov Russian National Research Medical University (A.G.), Russia; Departments of Neurology and Pathology (C.A.P.), Johns Hopkins University School of Medicine, Baltimore, MD; University of Pittsburgh School of Medicine (S.H.-Y.C.); Department of Critical Care Medicine (E.L.F.), UPMC Children's Hospital of Pittsburgh, PA; Department of Neurology (E.S.), Medical University Innsbruck, Austria; Departments of Neurology and Otolaryngology—Head & Neck Surgery (A.K.), The Johns Hopkins Hospital, Baltimore, MD; Department of Neurology (F.K.H.), Faculty of Medicine and Health Sciences, University Putra Malaysia, Seri Kembangan; and Rajendra Institute of Medical Sciences (K.P.), Ranchi, Jharkhand, India.

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## Glossary

CI = confidence interval; COVID-19 = coronavirus disease 2019; OR = odds ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

## Systematic Review Registration

PROSPERO CRD42020181867.

One year into the coronavirus disease 2019 (COVID-19) pandemic, the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has left nearly no place on Earth untouched, with >202 million confirmed cases and 4.28 million deaths across 220 countries and territories up to August 9, 2021.<sup>1</sup> The disease spectrum has ranged from asymptomatic cases with or without mild respiratory symptoms to severe cases with respiratory failure and multiorgan dysfunction.<sup>2-4</sup> Over the past year, reports of neurologic manifestations associated with COVID-19 have increased rapidly, with the CNS, peripheral nervous system, and musculoskeletal system affected.<sup>5-7</sup> The World Health Organization (WHO) has recognized the clinical relevance of neurologic manifestations of COVID-19.<sup>8,9</sup>

Prior systematic reviews have highlighted the frequency of common neurologic symptoms observed in COVID-19, including fatigue, myalgia, impaired sense of smell or taste, and headaches.<sup>10-12</sup> Additional neurologic manifestations reported include dizziness, acute confusion/delirium, agitation, stroke, hypoxic ischemic injury, seizures, coma, and encephalitis, among others.<sup>11,12</sup> In some cases, neurologic manifestations have been reported even without respiratory symptoms.<sup>13-15</sup> However, considerable variations in the frequency of neurologic manifestations have been reported with respect to different ethnic populations, age, and hospitalization status of included patients, and severity of disease.<sup>12</sup> Reports of neurologic manifestations in patients with COVID-19 are accumulating rapidly, and this warrants updated meta-analyses with pooled prevalence estimates. In addition, questions remain as to whether the presence of neurologic manifestations is associated with increased mortality, as initial reports have suggested.<sup>16</sup>

We conducted a systematic review and meta-analysis to obtain pooled prevalence estimates and to understand the variations in the reported frequencies of various neurologic manifestations (including symptoms and diagnoses) in patients with COVID-19 across different age groups. This review updates the findings of the previously published systematic reviews on neurologic symptoms, explores the reasons for heterogeneity of published studies, and gives novel insights into the pooled prevalence of neurologic diagnoses in patients with COVID-19. Our review further investigates the association of neurologic manifestations with COVID-19 severity and mortality.

## Methods

### Literature Search

Our intention was to cover a 1-year period to reflect on the cumulative knowledge about neurologic manifestations seen in COVID-19. A comprehensive literature search was carried out by 5 authors (S.M., D.R., K.T.T., A.K., and A.D.) for the period of December 31, 2019, to December 15, 2020, in PubMed, EMBASE, MEDLINE, Google Scholar, Cochrane Library and ClinicalTrials.gov. The detailed search strategy is provided in eAppendix 1 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)).

### Population

The target population for this review includes patients clinically suspected to have COVID-19 confirmed by real-time reverse-transcription PCR detection, high-throughput sequencing, SARS-CoV-2 viral culture in throat swab specimens, or SARS-CoV-2 antibody detection in blood samples. Studies had to report  $\geq 1$  new-onset neurologic manifestation(s) in a proportion of the included patients temporally associated with SARS-CoV-2 infection and not explained by an alternate etiology. We also included studies reporting probable cases of COVID-19, according to WHO case definitions,<sup>17</sup> based on clinical presentation when diagnostic testing was not available.

### Intervention

None.

### Comparator

The main objective of this review (describing the frequency of neurologic manifestations) did not merit a comparator group; however, for the secondary objectives of determining whether neurologic manifestations were associated with severity or mortality, the events were compared between patients with severe and nonsevere COVID-19 and between those with and without neurologic manifestations.

### Outcomes

The primary outcome was the frequency of neurologic manifestations in patients with COVID-19. Considering the lack of uniformity and reporting regarding classifications, definitions, and diagnostic criteria of neurologic manifestations across studies, we decided to accept study definitions as reported. For calculating pooled prevalence, both the numerator (number with neurologic manifestations) and denominator (total number of patients with COVID-19 attending the facility) were required.

Studies without the denominator were not included in the meta-analysis and are listed in eTables 1 and 2 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)). Secondary outcomes included age-specific variations in neurologic manifestations and association of neurologic manifestations with severity of and mortality in COVID-19.

### Inclusion and Exclusion Criteria

Our systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol 2015 guidelines<sup>18</sup> (checklist provided in supplemental material) and included observational studies on humans that (1) included individuals with probable or confirmed COVID-19 defined as above, (2) reported neurologic manifestations, (3) had full texts available, and (4) were published in indexed journals. There were no restrictions on language.

Studies meeting the above inclusion criteria were excluded if either of the following applied: they did not specify inclusion of consecutive patients with COVID-19 or they were individual case reports, or reviews, narratives, or editorials. The protocol of this systematic review and meta-analysis was registered in PROSPERO (registration CRD42020181867), and there were no major deviations from the protocol.<sup>19</sup>

### Data Extraction

Two authors (S.M. and D.R.) independently screened titles and abstracts retrieved by the literature search against the eligibility criteria. Duplicate records were excluded. The following information was extracted from each eligible study: first author; year of publication; study design; sample size; mean or median age of participants; comorbid conditions; clinical parameters; severity of COVID-19 infection; neurologic symptoms; and diagnoses. Hospitalization status of patients with COVID-19 was extracted independently by 2 authors. The definitions are given in eAppendix 2 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)), and interrater agreements are shown in eTables 3 and 4. Any disagreement between the reviewers was settled by consensus or by referring to a third author.

### Risk of Bias Assessment

To choose a tool for assessing risk of bias, 5 available tools were critically evaluated for coverage of selection and measurement bias, clarity of wording, suitability for descriptive case series, and ease of use. The Joanna Briggs Institute tool was selected, and risk of bias assessment was conducted by 5 authors (S.M., D.R., K.T.T., A.K., and A.D.) for all studies included in this review.<sup>20</sup>

### Statistical Analysis

Age was represented by mean with SD, whereas sex was represented by number with percentages. Meta-analyses were performed if data on the frequency of a specified neurologic manifestation were available from  $\geq 2$  or studies. Pooled prevalence for each neurologic manifestation, along with its corresponding 95% confidence interval (CI), was calculated with a random-effects model. For pooling, prevalence estimates were transformed with the Freeman-Tukey double arcsine transformation for better approximation to normal distribution as

required by the assumption of conventional meta-analytic model.<sup>21</sup> The associations between neurologic symptoms and both severity of and mortality in COVID-19 were determined with the odds ratio (OR) and 95% CI. Subgroup analyses were also conducted to estimate the pooled prevalence of neurologic symptoms and diagnoses in the elderly and young populations. The false discovery rate was controlled with the Benjamini-Hochberg procedure. The presence of heterogeneity was assessed with  $I^2$ . Funnel plots were used to assess the risk of publication bias. The Egger regression test<sup>22</sup> was used to quantitatively assess the funnel plot asymmetry, with a value of  $p < 0.05$  indicating the possibility of publication bias. The trim-and-fill test of Duval and Tweedie<sup>23</sup> was then used to impute the missing studies into the funnel plots until symmetry was achieved.

A meta-regression analysis was performed to further explore the source of heterogeneity for neurologic symptoms and diagnoses wherein  $\geq 10$  studies were pooled. If risk of bias was found to be significantly associated with prevalence, then a subgroup analysis was conducted to stratify the outcome variables in terms of low, moderate, and high risk of bias. Values of  $p < 0.05$  were considered to be statistically significant. Statistical analyses were conducted in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).<sup>24</sup>

### Data Availability

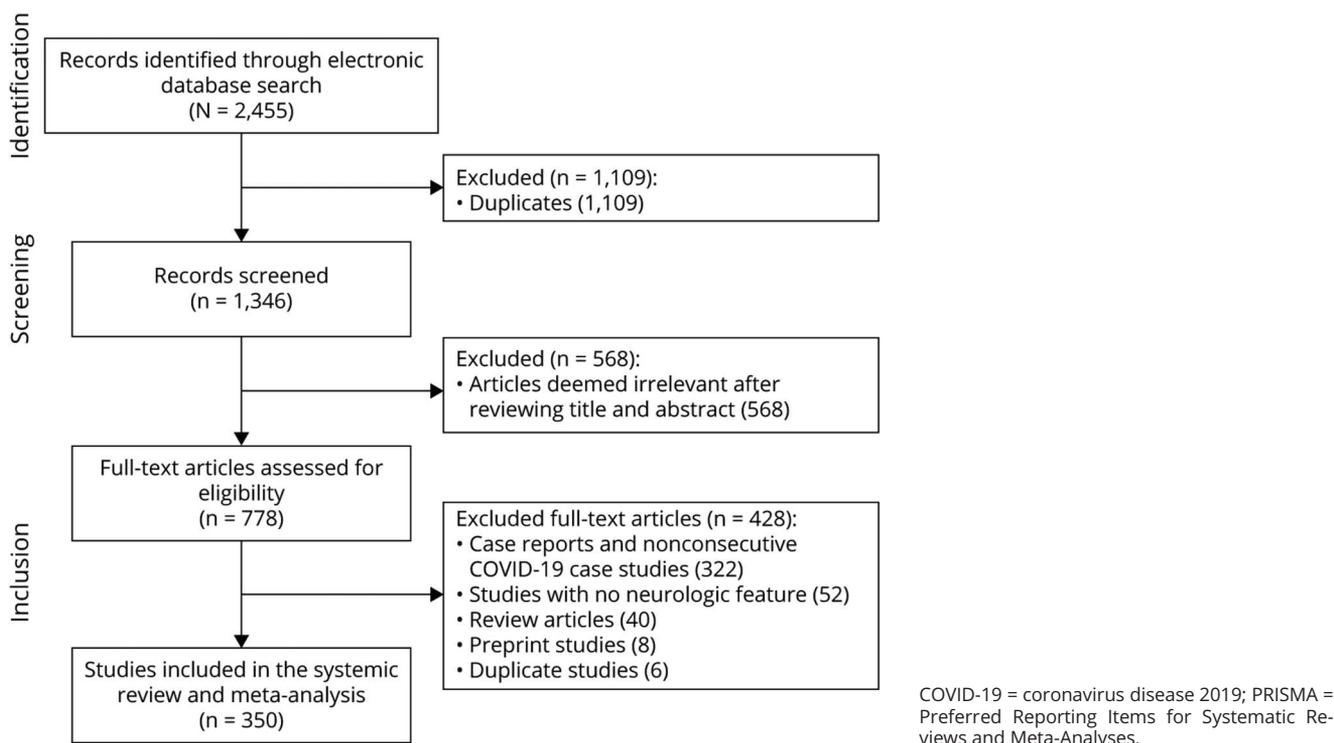
The full dataset and statistical codes will be available on reasonable request from any qualified investigator.

## Results

Our search yielded 2,455 articles, of which 778 were screened by full text; 350 met the inclusion criteria and were included in our systematic review and meta-analysis (Figure 1). Of the 350 studies, 15 were included from non-English languages, for which the online English versions were retrieved. Twenty studies included only young patients with COVID-19 (age  $< 18$  years), while 14 studies included only elderly patients (age  $\geq 60$  years). The studies included data from 55 countries. Baseline characteristics of all the studies included in this systematic review and meta-analysis are provided in eTables 5 and 6 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)) (including countries classified by World Bank Income Category and WHO regions). The pictorial representation of the coverage of studies from different parts of the world included in our systematic review and meta-analysis is given in eFigure 1. The included studies were published between January 2020 and December 2020.

A total of 145,721 cases with COVID-19 (mean 416.34, median 120, IQR 62–299, range 8–15,111) were analyzed in our systematic review, including 51% males. Hospitalization was reported for 129,786 cases (89%); 9,188 cases (6%) were not hospitalized, and hospitalization status was not reported for 6,747 (5%). Preexisting medical comorbid conditions were reported for hypertension (26%, 95% CI 24%–28%); diabetes (14%, 95% CI 13%–15%); cardiovascular/

**Figure 1** PRISMA Flow Diagram for the Systematic Review and Meta-analysis



cerebrovascular disease (aggregated reporting) (18%, 95% CI 12%–23%); cardiovascular disease (10%, 95% CI 9%–11%); chronic obstructive pulmonary disease (5%, 95% CI 4%–6%); chronic kidney disease (5%, 95% CI 4%–5%); cerebrovascular disease (4%, 95% CI 3%–4%); malignancy (4%, 95% CI 3%–4%); and chronic liver disease (3%, 95% CI 3%–4%).

Individual case reports and case series including neurologic manifestations in nonconsecutive cases of COVID-19 or a specific subgroup of cases of COVID-19 were present in an additional 322 studies detailed in eTables 1 and 2 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)).

### Risk of Bias Assessment

Risk of bias scores assessed with the Joanna Briggs Institute tool were categorized into low (13–16), moderate (7–12), and high (0–6). Overall, 296 studies (84.6%) had a low risk of bias, 49 studies (14%) had a moderate risk, and 5 studies (1.4%) had a high risk. eTable 7 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)) represents the risk of bias assessment done for studies included in our systematic review and meta-analysis.

### Neurologic Manifestations in Patients With COVID-19

Twenty-four neurologic symptoms from 305 articles are included in our systematic review and meta-analysis. Pooled prevalences (95% CI, number of studies) of the most common neurologic symptoms include the following: fatigue 32% (95% CI 30%–35%, 169 studies); myalgia 20% (95% CI

18%–23%, 207 studies); myalgia or fatigue 31% (95% CI 25%–37%, 22 studies); headache 13% (95% CI 12%–15%, 202 studies); dizziness 7% (95% CI 5%–8%, 46 studies); headache and dizziness together 12% (95% CI 8%–17%, 9 studies); smell impairment 19% (95% CI 13%–25%, 51 studies); taste impairment 21% (95% CI 15%–29%, 38 studies); smell or taste impairment 18% (95% CI 10%–28%, 14 studies); acute confusion/delirium 11% (95% CI 7%–16%, 19 studies); disturbance of consciousness 7% (95% CI 5%–10%, 25 studies); and agitation 45% (95% CI 3%–93%, 3 studies). Pooled prevalences of neurologic symptoms included in the meta-analysis are given in Table 1, including the individual prevalence of neurologic symptoms for which meta-analyses were not possible.

Seventeen different neurologic diagnoses in patients with COVID-19 were observed in 33 studies. The highest number of studies ( $n = 29$ ) were pooled for stroke with a pooled prevalence of 2% (95% CI 1%–2%) (Figure 2). Acute cerebrovascular events were categorized into ischemic stroke or TIA in 1% (95% CI 1%–2%, 29 studies), hemorrhagic stroke in 0.31% (95% CI 0.15%–0.50%, 21 studies), and cerebral venous thrombosis in 0.12% (95% CI 0%–2%, 2 studies). The pooled prevalence of neuropsychiatric disorders was 24% (95% CI 2%–61%, 3 studies) and that of skeletal muscle injury was 5% (95% CI 1%–12%, 4 studies). Pooled prevalences of neurologic diagnoses included in the meta-analysis are given in Table 2, including the individual prevalence of various neurologic diagnoses for which meta-analyses were not possible.

**Table 1** Prevalence of Various Neurologic Symptoms Included in the Systematic Review and Meta-analysis

Study	Variables	Studies, n	Pooled events, n	Pooled sample size, n	Pooled prevalence (95% CI), %	I <sup>2</sup> value, %
1	Myalgia	207	12,183	59,821	20 (18–23)	97
2	Fatigue	169	14,121	45,766	32 (30–35)	97
3	Myalgia or fatigue <sup>a</sup>	22	619	2,246	31 (25–37)	89
4	Headache	202	8,609	51,969	13 (12–15)	98
5	Dizziness	46	809	13,473	7 (5–8)	91
6	Headache and dizziness <sup>a</sup>	9	676	3,520	12 (8–17)	88
7	Smell impairment	51	4,647	30,925	19 (13–25)	99
8	Taste impairment	38	2,934	12,631	21 (15–29)	99
9	Smell or taste impairment <sup>a</sup>	14	518	3,100	18 (10–28)	97
10	Acute confusion/delirium	19	2,318	23,921	11 (7–16)	99
11	Disturbance of consciousness	25	693	15,129	7 (5–10)	97
12	Seizure	15	127	15,467	1 (0–2)	90
13	Ataxia	5	25	2,266	1 (0–2)	89
14	Vision impairment	10	126	2,904	4 (1–9)	95
15	Hearing impairment	6	20	819	3 (1–5)	54
16	Sensory impairment	4	23	1,082	2 (1–5)	81
17	Cognitive impairment	3	22	1,131	2 (0–5)	83
18	Neuralgia	7	41	3,183	1 (0–3)	90
19	Tinnitus	5	30	884	5 (1–10)	88
20	Agitation	3	145	468	45 (3–93)	99
21	CN palsy	3	7	463	2 (0–8)	75
22	Hemiplegia/hemiparesis	2	5	467	2 (0–10)	88
23	Corticospinal tract signs	2	128	198	65 (58–71)	0
24	Language impairment	1	6	38	16 (6–31)	—

Abbreviations: CI = confidence interval; CN = cranial nerve.

<sup>a</sup> These studies did not separate myalgia from fatigue, headache from dizziness, and smell from taste impairment.

## Neurologic Manifestations and Severity of COVID-19

Forty-eight studies consisting of 2,829 severe cases (classified as either severe or critical) and 7,493 nonsevere cases (classified as either mild or moderate) were analyzed to determine the association between neurologic manifestations and severity of COVID-19. Skeletal muscle injury/damage in 2 studies (OR 3.29, 95% CI 2.15–5.04), disturbance of consciousness (OR 5.68, 95% CI 2.08–15.50) in 4 studies, and fatigue in 33 studies (OR 1.27, 95% CI 1.06–1.51) were significantly associated with severe COVID-19.

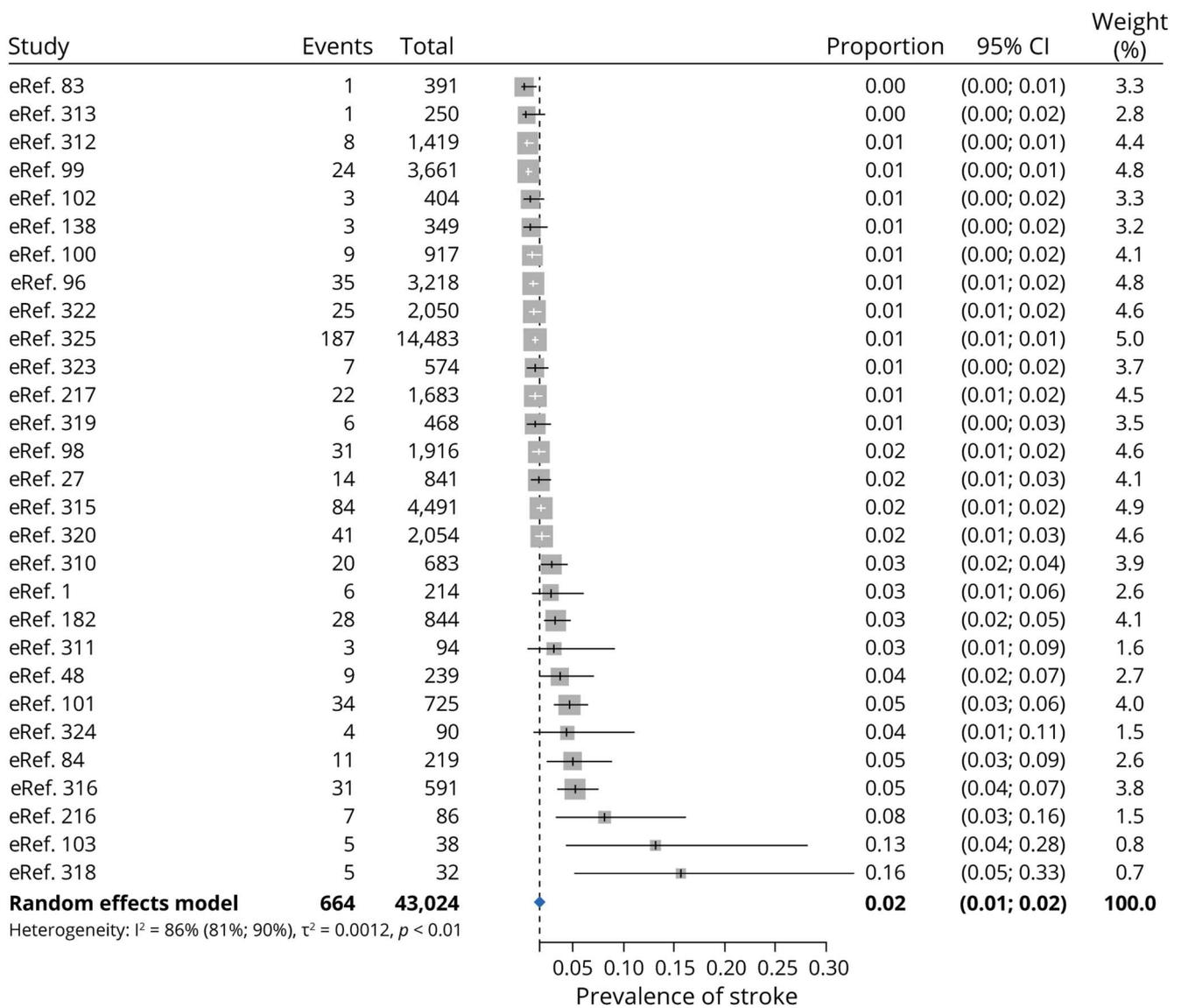
Patients with severe COVID-19 were less likely than those with mild disease to have alterations in smell (OR 0.44, 95% CI 0.28–0.68) in 8 studies and taste (OR 0.62, 95% CI 0.42–0.91) in 5 studies. No significant association was found

between other neurologic manifestations with the severity of COVID-19. Table 3 represents the pooled association of various neurologic manifestations with severity of COVID-19, including the individual association of various neurologic diagnoses with severity of COVID-19 for which meta-analyses were not possible. No significant deviation was observed after controlling the false discovery rate (eTable 8, [links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)).

## Publication Bias

The risk of bias was assessed for neurologic manifestations for which  $\geq 10$  studies were pooled. The asymmetry of funnel plot was apparent, and the Egger test was significant for dizziness ( $p = 0.003$ ), disturbance of consciousness ( $p = 0.006$ ), and stroke ( $p = 0.002$ ). Twenty Egger tests were conducted, of which 3 were significant ( $p < 0.05$ ) and underwent trim-and-

**Figure 2** Forest Plot Depicting the Pooled Prevalence of Stroke



CI = confidence interval.

fill analysis. For these 3 manifestations, we used the Duval and Tweedie trim-and-fill procedure and observed that studies with a lower prevalence were missing in dizziness, disturbance of consciousness, and total stroke. The shape of the funnel plots was symmetric for the rest of the neurologic manifestations assessed for the presence of publication bias.

While assessing the association between neurologic manifestations and severity of COVID-19, we did not find the presence of significant publication bias for any manifestations assessed using the shape of the funnel plots and the Egger regression test. The funnel plots and their respective  $p$  values are depicted in eFigure 2 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)).

### Meta-regression and Subgroup Analysis

In an assessment of the prevalence of neurologic manifestations in COVID-19, risk of bias was significantly associated with pooled prevalence for acute confusion/delirium ( $p = 0.001$ ,  $R^2 = 3.49\%$ ) and myalgia or fatigue ( $p = 0.0001$ ,  $R^2 = 41.09\%$ ), where  $R^2$  is the degree of heterogeneity accounted for. A subgroup analysis by risk of bias for acute confusion/delirium demonstrated that 2 studies with moderate risk of bias had a pooled prevalence of 42% (95% CI 7%–83%), while the pooled prevalence dropped to 11% (95% CI 7%–16%) for 17 studies having a low risk of bias. A similar trend was observed while conducting the subgroup analysis for myalgia or fatigue. On stratification, a single study with a high risk of bias had a high prevalence of 68% (95% CI 48%–85%), followed by 6 studies with moderate risk of bias 43% (95% CI

**Table 2** Prevalence of Various Neurologic Diagnoses Included in the Systematic Review and Meta-analysis

Study	Variables	Studies, n	Pooled events, n	Pooled sample size, n	Pooled prevalence (95% CI), %	I <sup>2</sup> value, %
1	Stroke	29	664	43,024	2 (1–2)	86
	Ischemic stroke/TIA	29	527	43,024	1 (1–2)	83
	Hemorrhagic stroke	21	133	36,972	0.31 (0.15–0.50)	73
	Cerebral venous thrombosis	2	4	14,573	0.12 (0–2)	78
2	Neuropsychiatric disorders	3	243	1,293	24 (2–61)	99
3	Encephalopathy	4	463	5,668	7 (1–17)	98
4	Skeletal muscle injury <sup>a</sup>	4	111	1,545	5 (1–12)	95
5	Myopathy <sup>b</sup>	3	55	5,736	2 (0–4)	95
6	Movement disorder	5	48	6,581	1 (0–1)	37
7	CIN/polyneuropathy	5	48	7,251	1 (0–2)	90
8	Status epilepticus	2	2	282	1 (0–5)	53
9	Encephalitis	4	8	4,658	0.30 (0–1)	80
10	Guillain-Barre syndrome	4	22	7,403	0.28 (0–1)	0
11	Parainfectious radiculitis	2	2	858	0.23 (0–1)	0
12	PRES	3	6	4,311	0.12 (0.02–0.27)	12
13	Dysexecutive syndrome	1	14	39	36 (21–53)	—
14	Dysautonomia	1	21	841	2 (2–4)	—
15	Restless leg syndrome	1	4	239	2 (0–4)	—
16	Rhabdomyolysis	1	2	509	0.39 (0.05–1)	—
17	Miller-Fisher syndrome	1	1	2,054	0.05 (0–0.27)	—

Abbreviations: CI = confidence interval; CIN = critical illness neuropathy; PRES = *posterior reversible encephalopathy syndrome*.

<sup>a</sup> Includes significant creatinine kinase elevation.

<sup>b</sup> Includes critical illness myopathy.

33%–53%), while the lowest pooled prevalence was observed for 15 studies having a low risk of bias 24% (95% CI 19%–29%). This subgroup analysis is presented in eTables 9 and 10 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)). Another subgroup analysis by last month of data extraction showed that pooled prevalence of headache was higher from April to September 2020 (16%–22%) compared to the initial 3 months (8%–14% in January–March 2020) (eTable 11).

### Neurologic Symptoms in COVID-19 in the Elderly and Young Subpopulations

Subgroup analyses were conducted on studies that included or disaggregated data on patients with COVID-19 who were ≥60 years and those <18 years of age presenting with neurologic symptoms. For the elderly, we found 13 studies reporting solely on older patients and 2 studies with disaggregated data, representing 3,176 hospitalized patients presenting with 10 neurologic symptoms, with the most prevalent (95% CI, number of studies) as follows: acute confusion/delirium 34% (95% CI 23%–46%, 5 studies), fatigue 20% (95% CI 11%–31%, 9 studies), myalgia 11%

(95% CI 7%–15%, 10 studies), dizziness 5% (95% CI 2%–9%, 3 studies), and headache 5% (95% CI 2%–8%, 10 studies). eTable 12 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)) presents the pooled prevalence of neurologic symptoms in the elderly COVID-19 subpopulation, including the individual prevalence of neurologic symptoms for which meta-analyses were not possible.

For patients with COVID-19 who were <18 years of age, we found 20 studies with 3,051 hospitalized patients presenting with 10 neurologic symptoms, with the most prevalent (95% CI, number of studies) as follows: fatigue or myalgia 17% (95% CI 9%–26%, 2 studies); smell or taste impairment 13% (95% CI 6%–22%, 2 studies); headache 10% (95% CI 5%–15%, 13 studies); fatigue 9% (95% CI 3%–18%, 9 studies); myalgia 7% (95% CI 2%–15%, 5 studies); seizure 4% (95% CI 2%–6%, 2 studies); and smell impairment 3% (95% CI 1%–5%, 5 studies). eTable 13 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)) presents the pooled prevalence of neurologic symptoms in the young COVID-19 subpopulation, including the individual prevalence of

**Table 3** Results From Systematic Review and Meta-analysis of Patients With COVID-19 (Severe and Nonsevere) Developing Neurologic Manifestations (Symptoms and Diagnosis)

Study	Variables	Studies, n	Severe COVID-19 (event/total), n	Nonsevere COVID-19 (event/total), n	OR (95% CI)	p Value
1	Skeletal muscle injury	2	69/417	36/638	3.29 (2.15–5.04)	<0.0001
2	Smell impairment <sup>a</sup>	8	27/670	130/1,355	0.44 (0.28–0.68)	0.0003
3	Disturbance of consciousness	4	95/450	21/652	5.68 (2.08–15.50)	0.0007
4	Fatigue	33	916/1,968	2067/5,358	1.27 (1.06–1.51)	0.009
5	Taste impairment <sup>a</sup>	5	38/617	138/1,221	0.62 (0.42–0.91)	0.01
6	Acute confusion/delirium	4	103/1,031	84/1,418	3.21 (0.82–12.59)	0.09
7	Stroke	3	14/426	9/644	2.03 (0.83–4.96)	0.12
8	Seizure	3	6/426	3/644	2.40 (0.63–9.19)	0.20
9	Headache and dizziness <sup>b</sup>	3	24/131	64/454	1.29 (0.76–2.18)	0.34
10	Myalgia	31	477/2,146	1,229/5,859	1.08 (0.90–1.30)	0.40
11	Movement disorder	2	2/463	2/887	2.02 (0.29–13.82)	0.47
12	Myalgia or fatigue <sup>b</sup>	4	52/102	82/262	1.51 (0.32–7.11)	0.60
13	Vision impairment	2	2/417	2/638	1.55 (0.23–10.70)	0.65
14	Headache	32	293/2,262	799/5,998	1.05 (0.84–1.32)	0.67
15	Dizziness	11	90/1,084	185/2,024	0.98 (0.65–1.47)	0.92
16	Neuropsychiatric disorder	2	75/338	95/518	1.00 (0.30–3.31)	0.99
17	Myopathy	1	22/329	4/512	9.10 (3.11–26.66)	<0.0001
18	Neuralgia	1	4/88	1/126	5.95 (0.65–54.19)	0.11
19	Dysautonomia	1	6/329	15/512	0.62 (0.24–1.60)	0.32
20	Encephalopathy	1	1/134	8/375	0.34 (0.04–2.78)	0.32
21	Rhabdomyolysis	1	1/134	1/375	2.81 (0.17–45.28)	0.46
22	Encephalitis	1	2/9	1/6	1.42 (0.10–20.44)	0.79

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019.

<sup>a</sup> When patients with severe COVID-19 reached hospital, they probably were not in a position to give a history for smell and taste impairment. However, for completeness of data, we noted that the recorded number of patients with smell and taste impairment was higher in the nonsevere group than in the severe group.

<sup>b</sup> These studies did not separate myalgia from fatigue and headache from dizziness.

neurologic symptoms for which meta-analyses were not possible.

### Neurologic Symptoms in COVID-19 Cases Analyzed by Hospitalization Status

We included 129,786 hospitalized and 9,188 non-hospitalized cases of COVID-19. The data for neurologic symptoms in nonhospitalized cases of COVID-19 could be extracted from only 13 studies. Smell impairment (50%), taste impairment (44%), headache (31%), and myalgia (31%) were found to be more common in nonhospitalized cases, whereas fatigue (31%) and myalgia or fatigue (30%) were found to be more common in hospitalized cases. A full comparison is available in eTable 14 ([links.lww.com/WNL/B607](https://links.lww.com/WNL/B607)).

### Mortality in Patients With COVID-19 With and Without Neurologic Manifestations

Mortality in patients with COVID-19 having  $\geq 1$  neurologic manifestations was assessed in 21 studies included in the systematic review and meta-analysis. A total of 770 patients died of 2,982 experiencing neurologic manifestations. The pooled prevalence of mortality in patients with COVID-19 with  $\geq 1$  neurologic manifestations was 27% (95% CI 19%–35%).

The association between mortality and neurologic manifestations was assessed in 13 studies consisting of 2,706 and 10,808 patients with COVID-19 with and without neurologic manifestations, respectively. There was a nonsignificant trend toward higher odds of mortality in patients with neurologic manifestations compared to those without them (OR 1.39,

95% CI 0.92–2.11). For patients ≥60 years of age, the presence of neurologic manifestations was significantly associated with increased mortality (OR 1.80, 95% CI 1.11–2.91) (Figure 3).

## Discussion

It is increasingly apparent that SARS-CoV-2 can have many effects on the CNS and peripheral nervous system. In this review, we report all acute neurologic manifestations reported in COVID-19, comorbid conditions associated with COVID-19 infection, the association with acute neurologic manifestations and severity or mortality, and subgroup analyses of neurologic manifestations by age group. Our pooled prevalence estimates indicate that up to one-third of patients with COVID-19 analyzed in our review experienced at least 1 neurologic manifestation and that 1 in 50 people developed a stroke.

Our review shows that preexisting neurologic conditions are a common comorbidity associated with COVID-19. After hypertension and diabetes, the combined comorbidity of cardiovascular/cerebrovascular disease was the third most commonly reported comorbidity associated with COVID-19. Disaggregated data released from national and international COVID-19 registries similarly indicate a high prevalence of preexisting neurologic conditions and an association with severe disease.<sup>25-27</sup>

This review identified 41 neurologic manifestations (24 symptoms and 17 diagnoses). The following neurologic symptoms were found to be common in a large number of studies: fatigue, myalgia, smell and taste impairment, headaches, and agitation. Neuropsychiatric disorders were found to affect 1 in 4 hospitalized patients, although data were available from only 3 studies. Critically, the pooled prevalence in our review for the diagnosis of

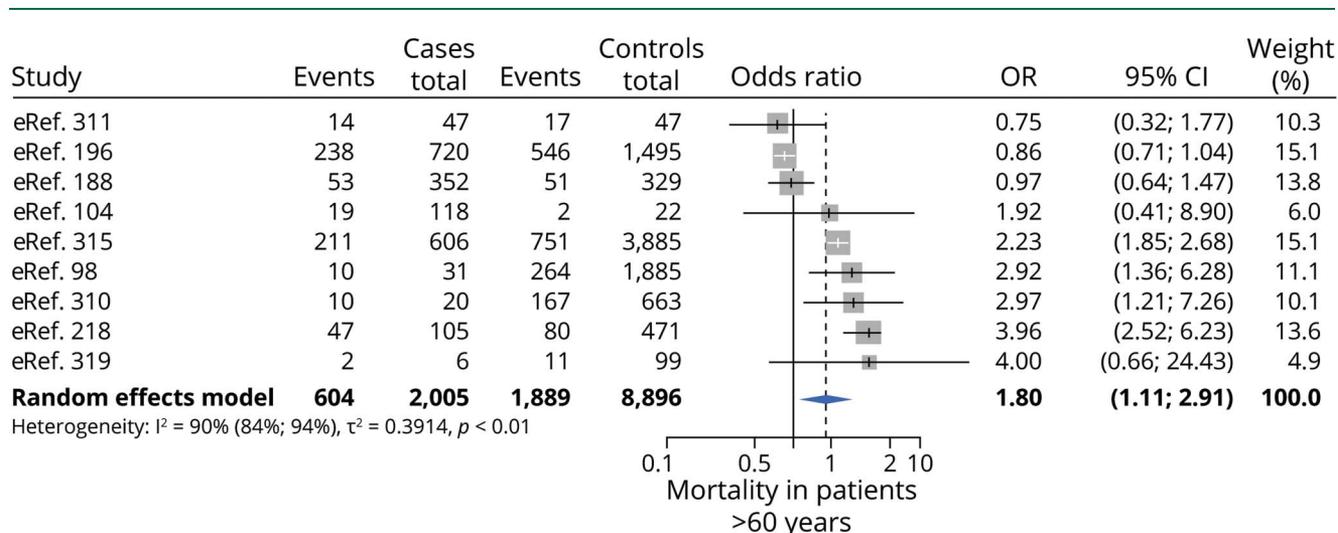
stroke was 2%, with data extracted from 29 studies; the majority of studies reported a prevalence between 1% and 3%. The pooled prevalence for stroke reported in our review in patients with COVID-19 indicates an alarming, enduring neurologic morbidity associated with the pandemic. In addition, we note that this pooled prevalence is far higher than has previously been reported for patients with influenza. One recent study<sup>28</sup> compared the risk of stroke in COVID-19 and influenza and found the prevalence of stroke to be 0.2% in influenza vs 1.2% in COVID-19.

Acute confusion/delirium is significantly more common in older people who have COVID-19, with data from 5 studies demonstrating that 1 in 3 hospitalized older patients with COVID-19 are affected (pooled prevalence 34%) compared with 5% in young adults and 12% for all ages. This bears implications for both cognitive outcomes and mortality. Delirium in older hospitalized patients has previously been demonstrated to be an independent risk factor for mortality 1 year after hospitalization, increasing the risk of death by >2-fold.<sup>29</sup> Moreover, delirium in older adults is a risk factor for developing dementia, increasing the risk nearly 9-fold over 10 years of follow-up for adults ≥85 years of age.<sup>30</sup>

For adults with COVID-19 who are >60 years of age, the presence of any neurologic manifestation was associated with increased mortality (OR 1.80, 95% CI 1.11–2.91). We also note that the relationship between COVID-19 severity and neurologic manifestations may be bidirectional; critically ill patients are more likely to experience multiorgan system dysfunction.

Therefore, our analysis shows age and severity as predictors of neurologic findings. However, analysis of other potential and independent predictors was neither feasible from the published data nor within the scope of this review.

**Figure 3** Forest Plot Depicting the Association Between Presence of Neurologic Manifestations and Mortality of Patients With COVID-19 ≥60 Years of Age



CI = confidence interval; COVID-19 = coronavirus disease 2019; OR = odds ratio.

It has been posited that there may be pathophysiologic basis for the association between smell and taste impairment and mild COVID-19; inflammation in mucosal membranes may play a role in preventing migration of the virus elsewhere in the body.<sup>31</sup> Moreover, patients with severe COVID-19 may not have been able to provide a clear history regarding smell or taste impairment, and we note that the majority of the data we have analyzed come from hospitalized patients.<sup>32</sup>

Multiple, potentially interacting, mechanisms have been proposed for the neurologic manifestations, including hypoxia, severe cytokine storm during infection and postinfectious autoimmune responses, hypercoagulability, endotheliopathy, multiple organ failure (e.g., liver failure leading to metabolic derangement), and possibly direct neuro-invasion. The neuro-invasive and neurotropic potential of SARS-CoV-2 is controversial but may be explained by the expression of angiotensin-converting enzyme-2 receptor in the brain.<sup>33</sup>

There are several important limitations to this review. First, there are few data from prospective studies; most data came from retrospective cohorts or case series. Second, standardized classifications, definitions, and diagnostic criteria for neurologic manifestations were not uniformly used or reported. Moreover, studies relating to many manifestations were not suitable for pooling. Third, because the vast majority (89%) of data analyzed came from hospitalized cases, our pooled prevalence estimates of neurologic manifestations, especially those of severe manifestations such as stroke, may not represent community prevalence. Therefore, we cannot draw conclusions about the prevalence of neurologic manifestations among patients with COVID-19 in the community. In addition, interpretation of data on preexisting neurologic conditions and COVID-19 diagnoses is limited due to the proportion of hospitalized cases studied. Fourth, 14 studies in our review used positive serology as one of the diagnostic criteria. However, they included hospitalized patients, and none of these studies relied on positive serology alone and used either PCR testing or clinical suspicion as a criterion. It is possible, however, that some of the patients included in these studies may have been experiencing neurologic symptoms from parainfectious/postinfectious syndromes or secondary autoimmune diseases due to COVID-19.

Meta-analyses for most outcomes in this review had high heterogeneity, which could be explained only partly by meta-regression and subgroup analyses. It is expected that the patient populations in the included studies were clinically diverse, having presented to centers with varied referral pathways, and this may have contributed to the heterogeneity observed. For almost all symptoms, studies with a higher risk of bias yielded higher pooled prevalence, indicating overestimation from bias in selection or measurement. Bias is known to exaggerate effect estimates in studies.<sup>34</sup> Studies were varying in terms of biases in selection, measurement, and reporting. Confounding bias limited severity and mortality analyses in this review in that given estimates were not adjusted for potential confounders such as comorbid conditions.

The timing of symptom onset is not reported in most studies, which has implications for understanding causality, and we are unable to distinguish acute neurologic manifestations caused by COVID-19 from the incidence of similar symptoms and diagnoses in the general population. In addition, this review has focused mainly on new-onset neurologic symptoms. We have not analyzed worsening of underlying or preexisting neurologic disorders, for which data are emerging in relation to COVID-19 and dementia, Parkinson disease, epilepsy,<sup>35</sup> myasthenia gravis,<sup>36</sup> and multiple sclerosis.<sup>37</sup> We also did not analyze the temporal trends in the prevalence of neurologic symptoms because doing so was beyond the scope of this review.

In addition, we have included fatigue, a nonspecific neurologic symptom, which can be comorbid with conditions involving multiple organ systems. Central fatigue (specifically mental/cognitive fatigue, as opposed to purely physical weakness) in many conditions, including serious viral infections, is thought to be due at least partially to neuroinflammatory processes or cascades precipitated by peripheral cytokines.<sup>38</sup> We recognize that purely physical weakness is not necessarily CNS mediated. Unfortunately, none of the studies we analyzed included the granularity of data to distinguish between mental/cognitive and physical fatigue.

It is important to note that the majority of the data analyzed in this review are from high- and middle-income countries. There are few data from low-income countries on neurologic manifestations available in published studies to date.

We hope that the data provided in this review might aid clinical practice and future research. Pooled prevalence estimates reported here may be used to design or validate clinical checklists for detecting neurologic manifestations that may otherwise be missed. In addition, neurologic manifestations may be factored into risk stratification, especially for older persons with COVID-19, given the association with higher mortality for any neurologic manifestation in this subpopulation.

Several questions remain as to the characteristics, timing, and severity of neurologic manifestations of COVID-19. Well-designed cohort, case-control, and population-based studies are required to understand risk factors and to suggest underlying mechanisms, which should be confirmed by neuropathologic studies. The timing of risk for acute, subacute, and long-term neurologic manifestations remains unclear, and this is particularly relevant for stroke and cognitive impairment. It is vital to have data on neurologic manifestations from geographically and resource diverse settings. Furthermore, as future studies are conducted, neurologic manifestations of COVID-19 can be considered for each variant of concern whenever it would be feasible to conduct the necessary testing. It is indeed possible that certain variants may be more virulent and have worse or previously unseen impacts on the nervous system. One year into the pandemic, it is critical to have robust, harmonized standards for methodology and

reporting to minimize the risk of bias and to enhance confidence in our understanding of the true neurologic implications of this illness.

## Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

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Continued

## Appendix (continued)

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## Appendix (continued)

Name	Location	Contribution
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## Frequency of Neurologic Manifestations in COVID-19: A Systematic Review and Meta-analysis

Shubham Misra, Kavitha Kolappa, Manya Prasad, et al.

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