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Review

# Neurological Manifestations in COVID-19 Patients: A Meta-Analysis

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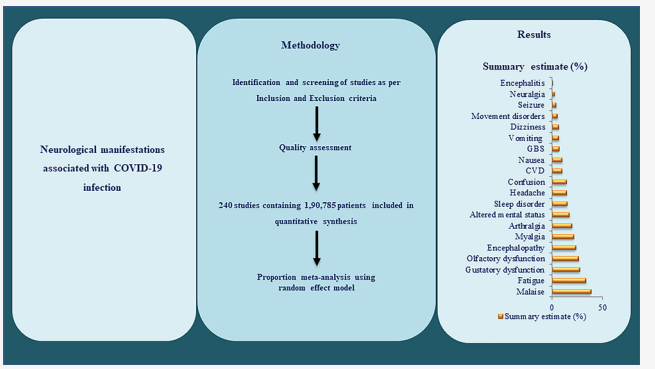
**ABSTRACT:** Common symptoms such as dizziness, headache, olfactory dysfunction, nausea, vomiting, etc. in COVID-19 patients have indicated the involvement of the nervous system. However, the exact association of the nervous system with COVID-19 infection is still unclear. Thus, we have conducted a meta-analysis of clinical studies associated with neurological problems in COVID-19 patients. We have searched for electronic databases with MeSH terms, and the studies for analysis were selected based on inclusion and exclusion criteria and quality assessment. The Stats Direct (version 3) was used for the analysis. The pooled prevalence with 95% confidence interval of various neurological manifestations reported in the COVID-19 patients was found to be headache 14.6% (12.2−17.2), fatigue 33.6% (29.5−37.8), olfactory dysfunction 26.4% (21.8−31.3), gustatory dysfunction 27.2% (22.3−32.3), vomiting 6.7% (5.5−8.0), nausea 9.8% (8.1−11.7), dizziness 6.7% (4.7−9.1), myalgia 21.4% (18.8−24.1), seizure 4.05% (2.5−5.8), cerebrovascular diseases 9.9% (6.8−13.4), sleep disorders 14.9% (1.9−36.8), altered mental status 17.1% (12.3−22.5), neuralgia 2.4% (0.8−4.7), arthralgia 19.9% (15.3−25.0), encephalopathy 23.5% (14.3−34.1), encephalitis 0.6% (0.2−1.3), malaise 38.3% (24.7−52.9), confusion 14.2% (6.9−23.5), movement disorders 5.2% (1.7−10.4), and Guillain−Barre syndrome 6.9% (2.3−13.7). However, the heterogeneity among studies was found to be high. Various neurological manifestations related to the central nervous system (CNS) and peripheral nervous system (PNS) are associated with COVID-19 patients.




**KEYWORDS:** *COVID-19, neurological manifestations, central nervous system, peripheral nervous system, prevalence, meta-analysis*

## 1. INTRODUCTION

In December 2019, Wuhan, the capital city of Hubei province, started reporting to hospitals with severe pneumonia. On etiologic investigation of respiratory samples, on December 31, 2019, China reported the epidemic to the World Health Organization. The infection was named Coronavirus Disease-19 (COVID-19), and it was caused by the SARS CoV-2.[1] As of January 10, 2021, the COVID-19 pandemic had affected 222 countries across the globe with 87M positive cases and 1.9M deaths.[2] COVID-19 patients presented with a varied range of symptoms from asymptomatic to severe respiratory failure. The most common symptoms include fever, cough, fatigue, anorexia, headache, and myalgia.[3] In addition to respiratory illness, several cardiovascular and neurological manifestations were also found to be associated with COVID-19 infection.[4,5]

The COVID-19 related neurological manifestations are hypothesized to be caused by multiple factors such as damage to specific receptors, secondary hypoxia, cytokine-related injury, and retrograde travel along the olfactory nerve and bulb.[6−10] Additionally, global inflammatory markers such as interleukin (IL)-6, IL-12, IL-15, and tumor necrosis factor $\alpha$ (TNF-$\alpha$) can activate glial cells and produce inflammatory responses.[8] These systemic consequences along with lung alveolar damage cause severe hypoxia, which leads to cerebrovascular vasodilation, cerebral edema, and ischemia.[8,9] Since endothelial cells of blood−brain barrier express angiotensin-converting enzyme 2 (ACE2) similar to lung epithelial cells, direct viral entry into the brain is possible.[11,12] The first evidence of direct neuroinvasion of SARS-CoV-2 was reported in a 56-year-old patient; gene sequencing of cerebrospinal fluid (CSF) sample confirmed the presence of SARS-CoV-2 in the brain.[13] However, in another study, RT-PCR assays of CSF samples of 07 COVID-19 patients with neurological problems were found negative.[14] Thus, it is not clear whether SARS-CoV-2 penetrate the brain or not due to difficulty in accessing brain tissue and CSF samples in COVID-19 patients.[15] Few initial systematic reviews reported neurological complications such as headache, myalgia, dizziness, nausea, vomiting, confusion, smell and taste dysfunction, cerebrovascular disorders, and altered mental status in COVID-19 patients.[16,17] However, these articles included

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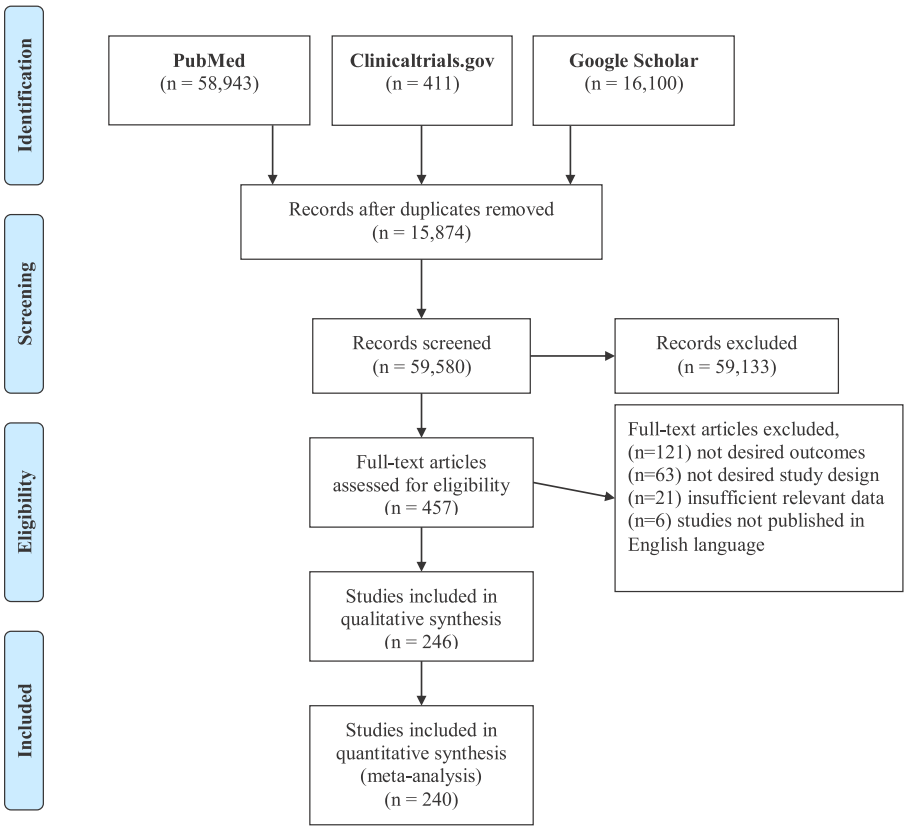


**Figure 1.** Scheme of selection of studies for quantitative analysis.

limited studies. Since the neurological complications in COVID-19 patients are increasingly being reported and the exact association between COVID-19 infection and neurological problems remain unclear; there is a need for pooled analysis of individual studies across the globe to make a better clinical decision. Thus, in the present study, meta-analysis was conducted on pooled data of individual studies reporting neurological manifestations in COVID-19 patients.

## 2. METHODOLOGY

The analysis was conducted as per the preferred reporting items for systematic reviews and meta-analyses (PRISMA guidelines).[18] The protocol of the study was registered with PROSPERO prospectively in January 2021 (registration number CRD42021229115).

**2.1. Search Strategy and Selection Criteria.** We have searched published studies between December 1, 2019, to December 3, 2020, in electronic databases such as PubMed, Google Scholar, and ClinicalTrials.gov. The MeSH terms used for the search were as follows: "Alzheimer's disease" OR "AD" OR "dementia" OR "Parkinson's disease" OR "PD" OR "cognitive impairment" OR "parkinsonism" OR "depression" OR "anxiety" OR "headache" OR "psychosis" OR "confusion" OR "dizziness" OR "anorexia" OR "vomiting" OR "malaise" OR "stroke" OR "epilepsy" OR "seizure" OR "fatigue" OR "myalgia" OR "hyposmia" OR "olfactory dysfunction" OR "nausea" OR "CNS infection" OR "viral encephalitis" AND "COVID-19" OR "SARS CoV-2" OR "novel coronavirus" OR "nCoV-2". Articles were selected based on inclusion and exclusion criteria as mentioned below.

**2.2. Inclusion and Exclusion Criteria.** All published cohort, case-control, cross-sectional studies with relevant data on neurological features in confirmed COVID-19 patients were included. The articles that are available in the English language were only included. The case reports, case series, animal studies, meta-analysis, and systematic reviews were excluded.

**2.3. Data Extraction and Quality Assessment.** Two authors independently searched databases such as PubMed, Google Scholar, and Clinical trials.gov. The duplicates were removed followed by screening as per the inclusion and exclusion criteria. Quality assessments of observational studies and cross-sectional and case-control studies were performed using NIH quality assessment tools. Any disagreements between the two main reviewers were discussed with a third evaluator. Data related to author's name, publication date, study setting, study design, the total number of patients included, age, gender, neurological symptoms, and neurological disorders/complications were extracted out.

**2.4. Data Synthesis and Statistical Analysis.** The primary outcomes measured were neurological problems in COVID-19 patients and their prevalence. For the categorical variables, we used frequencies and proportions. For continuous variables, we have used central tendency (mean or median) and dispersion measures (standard error, standard deviation). An individual patient is considered as the unit of analysis. The proportions were pooled by the random-effects model (DerSimonian−Laird) estimated using the Stuart−Ord (inverse double arcsine square root) method. Forest plots were constructed to visualize the point estimates of the studies and their confidence intervals. Heterogeneity was evaluated using the $I_2$ test with >25%, >50%, and >75% considered as low, moderate, and high degree of heterogeneity, respectively. Publication bias was evaluated quantitatively by Egger's regression tests ($p < 0.05$ considered statistically significant)


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**Table 1. Demographic Characteristics of Included Studies**

| ref | study | sample ($n$) | setting | study design | mean or median age (SD or range) | female/male ratio |
|---|---|---|---|---|---|---|
| 55 | Abrishami et al., 2020 | 142 | Iran | Cross-sectional | 62.6(15) | 1.18:1 |
| 56 | Agarwal et al., 2020 | 115 | New York, USA | Retrospective | NC[a] | 1:2.4 |
| 57 | Aggarwal et al., 2020 | 16 | USA | Retrospective | 67(38−95) | 1:3 |
| 42 | Akhtar et al., 2021 | 833 | Qatar | Prospective | 54.3(13.5) | 1:4.27 |
| 58 | Al Mutair et al., 2020 | 401 | Saudi Arabia | Retrospective | 38.1(13.4) | 1:4 |
| 51 | Almazeedi et al., 2020 | 1096 | Kuwait | Retrospective | 41(0−93) | 1:4.26 |
| 59 | Al-Omari et al., 2020 | 401 | Saudi Arabia | Cross-sectional | NC[a] | 1:4 |
| 60 | Alshami et al., 2020 | 128 | Saudi Arabia | Cross-sectional | 39.6(15.5) | 1.1:1 |
| 61 | Alsofayan et al., 2020 | 1519 | Saudi Arabia | Retrospective | 36(14−66) | 1:1.18 |
| 62 | Azwar et al., 2020 | 44 | Indonesia | Retrospective | NR[a] | 1:1.9 |
| 63 | B. Wang et al., 2020 | 483 | Wuhan, China | Retrospective | 48.4(12.4) | 1.2:1 |
| 64 | B. Wu et al., 2020 | 91 | Hainan, China | Retrospective | 50(14) | 1:1.3 |
| 65 | B. Y. Yang et al., 2020 | 124 | Washington, USA | Retrospective | 75.7(13.2) | 1.13:1 |
| 66 | Barillari et al., 2020 | 294 | Italy | Retrospective | 42.1(12.3) | 1:1 |
| 67 | Beltrán-Corbellini et al., 2020 | $C$ = 40[a]<br>$P$ = 79[a] | Madrid, Spain | Case control | $C$ = 61.1(17.1)<br>$P$ = 61.6(17.4) | NR[a] |
| 39 | Benussi et al., 2020 | 56 | Brescia, Italy | Retrospective | 77(67−83.3) | 1:1 |
| 21 | Berenguer et al., 2020 | 4035 | Spain | Retrospective | 70(56−80) | 1:1.5 |
| 19 | Boscolo-Rizzo et al., 2020 | 202 | Italy | Cross-sectional | 56(20−89) | 1.04:1 |
| 68 | Brendish et al., 2020 | 352 | United kingdom | Retrospective | 68(50−80) | 1:1.3 |
| 69 | Buckner et al., 2020 | 105 | Washington | Retrospective | 69(23−97) | 1:101 |
| 70 | Burrer et al., 2020 | 9282 | USA | Retrospective | 42(32−54) | 2.6:1 |
| 71 | C. Qiu et al., 2020 | 404 | China, Germany, France | Retrospective | 38.8(23−53) | 1:1.3 |
| 72 | C. Yu et al., 2020 | 1464 | Wuhan, China | Retrospective | 64(51−71) | 1:1.01 |
| 73 | Campiglio and Priori, 2020 | 126 | Italy | Retrospective | NR[a] | NR[a] |
| 74 | Carignan et al., 2020 | $C$ = 134<br>$P$ = 134 | Quebec, Canada | Case control | $C$ = 57.2(42.6−64.4)<br>$P$ = 57.1(41.2−64.5) | $C$ = 1.5:1<br>$P$ = 1.09:1 |
| 75 | Chachkhiani et al., 2020 | 250 | Los Angeles, USA | Retrospective | 60(15) | 1.2:1 |
| 76 | Chang et al., 2020 | 13 | Beijing, China | Retrospective | 34(34−48) | 1:3.3 |
| 77 | Chary et al., 2020 | 115 | France | Prospective | 47(20−83) | 2.3:1 |
| 78 | Chen et al., 2020 | 9 | Wuhan, China | Retrospective | 28(26−40) | 1:0 |
| 34 | Chougar et al., 2020 | 73 | France | Cross-sectional | 58.5(15.6) | 1:1.9 |
| 79 | Chu et al., 2020 | 54 | Wuhan, China | Retrospective | 39(26−73) | 1:2 |
| 80 | Cummings et al., 2020 | 257 | New York, USA | Prospective | 62(51−72) | 1:1.9 |
| 81 | D. Liu et al., 2020 | 599 | China | Retrospective | 63(2−93) | 2.2:1 |
| 82 | D. Wang et al., 2020 | 143 | Wuhan, China | Cross-sectional | 58(39−67) | 1:1.04 |
| 83 | de Souza et al., 2020 | 9807 | Brazil | Cross-sectional | 70.2(8.3) | 1.1:1 |
| 84 | Dell'Era et al., 2020 | 355 | Novara, Italy | Cross-sectional | 50(40−59.5) | 1:1.17 |
| 85 | Deng et al., 2020 | 109 | Wuhan, China | Retrospective | 69(62−74) | 1:1.9 |
| 86 | Derespina et al., 2020 | 70 | New York, USA | Retrospective | 15(9−19) | 1:1.59 |
| 87 | Di Domenico et al., 2020 | 310 | Lombardy, Italy | Retrospective | 64(52−76) | 1:1.8 |
| 88 | Du et al., 2020 | 85 | Wuhan, China | Retrospective | 65.8(14.2) | 1:2.6 |
| 89 | El Fakiri et al., 2020 | 74 | Morocco | Retrospective | 7(0.2−17) | NR[a] |
| 90 | Erinoso et al., 2020 | 632 | Lagos, Nigeria | Retrospective | 40.1(13.9) | 1:1.5 |
| 91 | Escalard et al., 2020 | 46 | France | Prospective | 67.6(15.2) | 1:1.7 |
| 92 | F. fang Chen et al., 2020 | 681 | China | Retrospective | 65(54−72) | 1:1.13 |
| 93 | F. Zhou et al., 2020 | 191 | Wuhan, China | Retrospective | 56(46−67) | 1:1.6 |
| 94 | Fasano et al., 2020 | $C$ = 1381<br>$P$ = 105 | Lombardy, Italy | Case control study | $C$ = 73(9.5)<br>$P$ = 70.5(10.1) | $C$ = 1:1.1<br>$P$ = 1:1.1 |
| 95 | Feng et al., 2020 | 114 | Wuhan, China | Prospective | 63.96(13.41) | 1:1.6 |
| 96 | Ferguson et al., 2020 | 72 | California, USA | Retrospective | NR[a] | NR[a] |
| 54 | Filosto et al., 2020 | 30 | Italy | Retrospective | 59(51.5−61.3) | 1:2.75 |
| 97 | Frontera et al., 2020 | 4491 | New York, USA | Prospective | NR[a] | NR[a] |
| 98 | G. Chen et al., 2020 | 21 | Wuhan, China | Retrospective | 56(50−65) | 1:4.25 |
| 99 | Gaborieau et al., 2020 | 157 | Paris, France | Prospective | 0.5(0.1−10) | 1:1.4 |
| 100 | Gao et al., 2020 | 966 | China | Retrospective | 43(40−46.6) | 1.18:1 |
| 101 | Garazzino et al., 2020 | 168 | Italy | Retrospective | 2.3(0.3−9.6) | 1:1.2 |
| 102 | Ghweil et al., 2020 | 66 | Egypt | Retrospective | NC[a] | 1:2.6 |
| 103 | Giacomelli et al., 2020 | 59 | Wuhan, China | Cross-sectional | 60(50−74) | 1:2.1 |
| 104 | Gorzkowski et al., 2020 | 229 | Nancy, France | Retrospective | 39.7(13.7) | 1.7:1 |



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**Table 1. continued**

| ref | study | sample ($n$) | setting | study design | mean or median age (SD or range) | female/male ratio |
|---|---|---|---|---|---|---|
| 105 | H. Zhang et al., 2020 | 194 | Taian, China | Retrospective | 48.3(33−56) | 1:1.23 |
| 106 | H. Zhang et al., 2020 | 88 | China | Retrospective | 55(22−89) | 1:1.04 |
| 107 | Han et al., 2020 | 108 | Wuhan, China | Retrospective | 45(21−90) | 1.8:1 |
| 108 | Hintschich et al., 2020 | 41 | Germany | Prospective | 37 | 2.1:1 |
| 109 | Hong et al., 2020 | 98 | Daegu, South Korea | Retrospective | 55.4(17.1) | 1.5:1 |
| 110 | Huang et al., 2020 | 41 | Wuhan, China | Prospective | 49(41−58) | 1:2.7 |
| 111 | J. C. Shi et al., 2020 | 105 | China | Retrospective | NR[a] | 1:1.18 |
| 112 | J. Chen et al., 2020 | 3309 | Wuhan, China | Retrospective | 62(49−69) | 1.01:1 |
| 113 | J. Chen et al., 2020 | 62 | China | Retrospective | 72(54−88) | 1:1.95 |
| 114 | J. Li et al., 2020 | 164 | Wuhan, China | Retrospective | 41(29−89) | 1:4.8 |
| 116 | J. Lian et al., 2020 | 465 | Zhejiang, China | Retrospective | 45(5−88) | 1:1.09 |
| 117 | J. Liu et al., 2020 | 1190 | Wuhan, China | Retrospective | 57(47−67) | 1:1.14 |
| 118 | J. yeon Lee et al., 2020 | 557 | Daegu, South Korea | Retrospective | 52.10(18.29) | 2.5:1 |
| 44 | Jain et al., 2020 | 3218 | New York, USA | Retrospective | 64(0.1−105) | NR[a] |
| 119 | Jalessi et al., 2020 | 92 | Tehran, Iran | Prospective | 52.94(13.25) | 1:2.06 |
| 120 | Jeong et al., 2020 | 234 | South Korea | Retrospective | 37.78(15.57) | 1.5:1 |
| 121 | Ji et al., 2020 | 101 | Wuhan, China | Retrospective | 51(37−61) | 1.1:1 |
| 122 | Ji Zhou et al., 2020 | 368 | Huanshi, China | Retrospective | 51(22) | 1:1 |
| 123 | Jian Zhou et al., 2020 | 201 | Hunan, China | Retrospective | 45(33.8−59) | 1:1.03 |
| 124 | Jourdes et al., 2020 | 263 | France | Retrospective | 65(54−76) | 1:1.4 |
| 125 | K. Liu et al., 2020 | 137 | Hubei, China | Retrospective | 57(20−83) | 1.2:1 |
| 126 | Kadiane-Oussou et al., 2020 | 114 | France | Retrospective | 56.7(19−97) | 1.3:1 |
| 127 | Karadaş et al., 2020 | 239 | Ankara, Turkey | Prospective | 46.4(15.4) | 1:1.25 |
| 128 | Khan et al., 2020 | 121 | Peshawar, Pakistan | Retrospective | 43.19(17.57) | 1:2.3 |
| 43 | Kihira et al., 2020 | $C$ = 203<br>$P$ = 126 | New York, USA | Case control | $C$ = 67.6(15.9)<br>$P$ = 65.6(13.2) | $C$ = 1:1.39<br>$P$ = 1:1.57 |
| 129 | Killerby et al., 2020 | 527 | Atlanta, Georgia | Retrospective | NC[a] | 1.7:1 |
| 130 | Kim et al., 2020 | 28 | Republic of Korea | Retrospective | 42.6(13.4) | 1:1.15 |
| 131 | Kirenga et al., 2020 | 56 | Uganda | Prospective | 33(25−43) | 1:2.1 |
| 5 | Klironomos et al., 2020 | 185 | Sweden | Retrospective | 62(19−95) | 1:3 |
| 132 | Klopfenstein et al., 2020 | 114 | France | Retrospective | 47(16) | 2:1 |
| 133 | Kluytmans-van den Bergh et al., 2020 | 86 | Netherland | Cross-sectional | 49(22−66) | 4.7:1 |
| 134 | Koh et al., 2020 | 47572 | Singapore | Prospective | 34(1−102) | 1:49 |
| 135 | Kong et al., 2020 | 17 | Wuhan, China | Retrospective | 75(66−82) | 1:3.25 |
| 136 | Korkmaz et al., 2020 | 81 | Turkey | Observational cohort study | 9.5(3.16−15.08) | 1:1.4 |
| 137 | Kosugi et al., 2020 | 145 | Brazil | Prospective | 36(31−44) | 1.13:1 |
| 30 | Kremer et al., 2020 | 37 | France | Retrospective | 61(8−78) | 1:4.2 |
| 25 | Kremer et al., 2020a | 64 | France | Retrospective | 66(20−92) | 1:2.04 |
| 138 | L. Hong et al., 2020 | 67 | Wenzhou, China | Retrospective | 45(15.2) | 1:1.16 |
| 139 | L. Wang et al., 2020 | 339 | Wuhan, China | Retrospective | 69(65−76) | 1.04:1 |
| 140 | L. Yang et al., 2020 | 200 | Hubei, China | Retrospective | 55(17.1) | 1.04:1 |
| 141 | La Torre et al., 2020 | $C$ = 75<br>$P$ = 30 | Italy | Prospective Case control | $C$ = 43.6(12.9)<br>$P$ = 40.7(12.9) | $C$ = 1:2.2<br>$P$ = 1:1.1 |
| 142 | Lan et al., 2020 | 83 | USA | Retrospective | 43.9(12.7) | 2.6:1 |
| 143 | Lapostolle et al., 2020 | 1487 | Paris, France | Prospective | 44(32−57) | 1.07:1 |
| 144 | Le Bon et al., 2020 | 72 | Belgium | Prospective | 38.9(12.4) | 2.1:1 |
| 145 | Lechien et al., 2020 | 417 | Belgium, France, Spain, Italy | Prospective | 36.9(19−77) | 1.7:1 |
| 146 | Lechien et al., 2020b | 1420 | Europe | Retrospective | 39.17(12.09) | 2.1:1 |
| 147 | Lee et al., 2020 | 3191 | Daegu, Korea | Prospective | 44(25−58) | 1.7:1 |
| 148 | Lenka et al., 2020 | 32 | New York, USA | Retrospective | 62.2(11.2) | 1:1.6 |
| 149 | Lersy et al., 2020 | 58 | France | Retrospective | 62(55−70) | 1:1.9 |
| 150 | Levinson et al., 2020 | 42 | Israel | Prospective | 34(15−82) | 1:1.2 |
| 151 | Li et al., 2020 | 99 | Wuhan, China | Cross-sectional | 51.4(11.9) | 1:1.2 |
| 152 | Li et al., 2020 | 204 | China | Retrospective | 68(60−95) | 1.04:1 |
| 115 | Lian et al., 2020 | 788 | Zhejiang, China | Retrospective | NC[a] | 1:1.06 |
| 153 | Liang et al., 2020 | 86 | China | Retrospective | 25.5(6−57) | 1:1.04 |
| 154 | Lin et al., 2020 | 161 | Shanghai, China | Retrospective | 45(34−61) | 1:1 |
| 155 | Liotta et al., 2020 | 509 | Chicago, USA | Retrospective | 58.5(16.9) | 1:1.2 |



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**Table 1. continued**

| ref | study | sample ($n$) | setting | study design | mean or median age (SD or range) | female/male ratio |
|---|---|---|---|---|---|---|
| 156 | Liu et al., 2020 | 72 | Shaanxi, China | Retrospective | 46.2(15.6) | 1:1.18 |
| 157 | Lodigiani et al., 2020 | 388 | Milan, Italy | Retrospective | 66(55−75) | 1:2.1 |
| 158 | Luigetti et al., 2020 | $C$ = 218<br>$P$ = 213 | Italy | Case control | $C$ = 75.9(12.6)<br>$P$ = 70.2(13.9) | $C$ = 1:1.8<br>$P$ = 1:1.1 |
| 159 | Lv et al., 2020 | 196 | China | Retrospective | 50.6(13.8) | 1.2;1 |
| 161 | M. Huang et al., 2020 | 60 | Jiangsu, China | Retrospective | 57(26−97) | 1:1.4 |
| 162 | M. Shi et al., 2020 | 161 | China | Multicentric retrospective | 59.3(16.5) | 1:1.8 |
| 163 | M. Wu et al., 2020 | 1989 | Hubei, China | Retrospective | NC[a] | 1.9:1 |
| 164 | Ma et al., 2020 | 523 | China | Retrospective | 44(32−54) | 1:1.23 |
| 165 | Maechler et al., 2020 | 333 | Berlin, Germany | Cross-sectional | 34(28−47) | 1:1.3 |
| 166 | de Magalhães et al., 2020 | 557 | Brazil | Retrospective | 47(32−68) | 1.2:1 |
| 40 | Mahammedi et al., 2020 | 108 | Italy | Retrospective | 71(60.5−79) | 1:1.7 |
| 167 | Mao et al., 2020 | 214 | Wuhan, China | Retrospective | 52.7(15.5) | 1.4:1 |
| 168 | Martín-Sánchez et al., 2020 | 1379 | Spain | Retrospective | 62(18) | 1:1.15 |
| 169 | Mcloughlin et al., 2020 | 71 | London, U.K. | Point prevalence study | 61(24−91) | 1:6.1 |
| 170 | Membrilla et al., 2020 | 145 | Spain | Cross-sectional | 42.7(21−70) | 1.7:1 |
| 171 | Meng et al., 2020 | 168 | Wuhan, China | Retrospective | 56.7(15.1) | 1:1.04 |
| 36 | Meppiel et al., 2020 | 222 | France | Retrospective | 65(53−72) | 1:1.58 |
| 172 | Mo et al., 2020 | 155 | Wuhan, China | Retrospective | 54(42−66) | 1:1.2 |
| 173 | Mohamud et al., 2020 | 60 | Mogadishu, Somalia | Retrospective | 45.7(13.5) | 2.3:1 |
| 174 | Moon et al., 2020 | 352 | Korea | Retrospective | 57(38−72) | 1.4:1 |
| 175 | Mukherjee et al., 2020 | 137 | New York, USA | Retrospective | 59(51−70) | 1:2.6 |
| 176 | Muñoz et al., 2020 | 100 | Madrid, Spain | Retrospective | 61.5(39.5−82) | 1:1.08 |
| 177 | N. Yan et al., 2020 | 1682 | Wuhan, China | Retrospective | 50(39−58) | 1.04:1 |
| 178 | Nakagawara et al., 2020 | 57 | Japan | Retrospective | 35.4(13.6) | 1.28:1 |
| 179 | Nascimento et al., 2020 | 28854 | Brazil | Retrospective | 44.18 | 1.2:1 |
| 180 | Nowak et al., 2020 | 169 | Poland | Retrospective | 63.7(19.6) | 1:1.06 |
| 181 | P. Shi et al., 2020[181] | 134 | Wuhan, China | Retrospective | 46(34−58) | 1.06:1 |
| 182 | Paderno et al., 2020 | 508 | Brescia, Italy | Cross-sectional | 55(15) | 1:1.2 |
| 183 | Paderno et al., 2020a | 151 | Italy | Prospective | 45(18−70) | 1.6:1 |
| 184 | Paterson et al., 2020 | 43 | United Kingdom | Retrospective | NC[a] | 1:1.26 |
| 185 | Peng et al., 2020 | 49 | Wuhan, China | Retrospective | 63(53−73) | 1.8:1 |
| 186 | Petrocelli et al., 2020 | 300 | Bologna, Italy | Prospective | 43.6(12.2) | 3:1 |
| 187 | Poncet-Megemont et al., 2020 | 139 | France | Retrospective | 48.5(15.3) | 1.6:1 |
| 188 | Popov et al., 2020 | 138 | Sofia, Bulgaria | Retrospective | 52.9(16.4) | 1:1.7 |
| 189 | Q. Chen et al., 2020 | 145 | Zhejiang, China | Retrospective | 47.5(14.6) | 1:1.19 |
| 190 | Q. Wang et al., 2020 | 43 | Weifang, China | Retrospective | 42.82(11.24) | 1:1.15 |
| 191 | Qin et al., 2020 | 1875 | Wuhan, China | Retrospective | 63(51−70) | 1:1.01 |
| 192 | Qiu et al., 2020 | 36 | Zhejiang, China | Observational cohort study | 8.3(3.5) | NR[a] |
| 160 | R. Huang et al., 2020 | 202 | Jiangsu, China | Retrospective | 44(33−54) | 1:1.3 |
| 193 | Raberahona et al., 2020 | 1288 | Madagascar | Retrospective | 38(26−52) | 1.05:1 |
| 41 | Radmanesh et al., 2020 | 242 | New York, USA | Retrospective | 68.6(16.5) | 1:1.6 |
| 194 | Rajkumar et al., 2020 | 230 | Chennai, India | Cross-sectional | 43.56(4.6) | 1:1.7 |
| 195 | Rifino et al., 2020 | 137 | Bergamo, Italy | Retrospective | 64.9(14) | 1:1.9 |
| 196 | Rojas-Lechuga et al., 2020 | 197 | Spain | Cross-sectional | 46.5(14.5) | 1.7:1 |
| 23 | Romero-Sánchez et al., 2020 | 841 | Spain | Retrospective | 66.42(14.96) | 1.2:1 |
| 197 | Rubio-Rivas et al., 2020 | 12066 | Spain | Retrospective | 68(56−79) | 1:1.4 |
| 32 | S. Xiong et al., 2020 | 116 | Wuhan, China | Retrospective | 58.5(47−69) | 1:2.2 |
| 27 | Salahuddin et al., 2020 | 574 | USA | Retrospective | 62.83(17.55) | 1.0:1 |
| 198 | Salmon Ceron et al., 2020 | 55 | Paris, France | Prospective | 34(28−43) | 1.29:1 |
| 199 | Sarangi et al., 2020 | 50 | Pune, India | Cross-sectional | 6(2−12) | 1:2.3 |
| 200 | Scullen et al., 2020 | 27 | New Orleans, USA | Retrospective cross-sectional | 59.8(35−91) | 1:1.08 |
| 201 | Shah et al., 2020 | 33 | USA | Retrospective | 63(50−75) | 1.09:1 |
| 202 | Shang et al., 2020 | 307 | Jiangsu, China | Retrospective | 46(33−55) | 1:1.14 |
| 203 | Shekhar et al., 2020 | 90 | USA | Retrospective | NR[a] | NR[a] |



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**Table 1. continued**

| ref | study | sample (*n*) | setting | study design | mean or median age (SD or range) | female/male ratio |
|---|---|---|---|---|---|---|
| 204 | Shi et al., 2020 | 81 | Wuhan, China | Retrospective | 49.5(11) | 1:1.07 |
| 205 | Song et al., 2020 | 69 | China | Retrospective | 52(37−63) | 1.4:1 |
| 206 | Speth et al., 2020 | 103 | Switzerland | Cross-sectional | 46.8(15.9) | 1.06:1 |
| 207 | Spiteri et al., 2020 | 38 | Germany, Spain, Finland, France, Italy, Sweden, Russia, Belgium | Retrospective | 42(2−82) | 1:1.9 |
| 37 | Studart-Neto et al., 2020 | 89 | Brazil | Retrospective | 57.4(15.9) | 1:1.6 |
| 208 | Sun et al., 2020 | 84 | China | Retrospective | 46(37−53) | 1.2:1 |
| 209 | Sung et al., 2020 | 3060 | Korea | Retrospective | 43(26−57) | 1.29:1 |
| 210 | Swann et al., 2020 | 651 | United kingdom | Prospective | 4.6(0.3−13.7) | 1:1.2 |
| 211 | T. Chen et al., 2020 | 132 | Wuhan, China | Retrospective | 32(29−41) | 2.3:1 |
| 212 | T. L. Chen et al., 2020 | 203 | Wuhan, China | Retrospective | 54(20−91) | 1:1.13 |
| 213 | Tabata et al., 2020 | 104 | Japan | Retrospective | 68(47−75) | 1:1.08 |
| 212 | Tao Chen et al., 2020 | 274 | China | Retrospective | 62(44−70) | 1:1.6 |
| 214 | Tenforde et al., 2020 | 350 | USA | Retrospective | 43(32−57) | 1:1.12 |
| 215 | Tham et al., 2020 | 1065 | Singapore | Cross-sectional | 34(28−42) | 1:7 |
| 216 | Timothée Klopfenstein et al., 2020 | 70 | France | Retrospective | 57(19) | 1.4:1 |
| 217 | Tomlins et al., 2020 | 95 | United kingdom | Retrospective | 75(59−82) | 1:1.7 |
| 218 | Tostmann et al., 2020 | 90 | Netherlands | Prospective | NR[a] | 3.7:1 |
| 219 | Trigo et al., 2020 | 576 | Spain | Retrospective | 67.2(14.7) | 1:1.3 |
| 220 | Vacchiano et al., 2020 | 108 | Bologna, Italy | Prospective | 59(18−83) | 1:1.3 |
| 45 | Vaira et al., 2020 | 345 | Milan, Bologna, Italy | Prospective | 48.5(23−88) | 1.3:1 |
| 46 | Vaira et al., 2020a | 72 | Sassari, Italy | Prospective | 49.2(26−90) | 1.6:1 |
| 221 | Vaira et al., 2020b | 33 | Bologna, Italy | Prospective | 47.2(26−64) | 2:1 |
| 50 | Vaira et al., 2020b | 106 | London, United Kingdom | Prospective | 49.6(8.5) | 1:1 |
| 38 | Varatharaj et al., 2020 | 153 | United Kingdom | Retrospective | 71(23−94) | 1:1.6 |
| 222 | Vee et al., 2020 | 247 | Malaysia | Retrospective | 28(20−45) | 1:2.2 |
| 223 | Vena et al., 2020 | 317 | Genoa, Italy | Retrospective | 71(60−82) | 1:2.04 |
| 224 | Villarreal et al., 2020 | 230 | Spain | Prospective | 43(18−62) | 5.7:1 |
| 225 | W. Li et al., 2020 | 97 | China | Retrospective | 45(18) | 1.15:1 |
| 226 | W. Wang et al., 2020 | 123 | Wuhan, China | Retrospective | 68(56.5−78) | 1.05:1 |
| 227 | W. Yang et al., 2020 | 149 | Zhejiang, China | Retrospective | 45.11(13.35) | 1:1.19 |
| 228 | W. Zhang et al., 2020 | 91 | Beijing, China | Retrospective | 74.9(65−94) | 1.3:1 |
| 229 | Wang et al., 2020 | 28 | Wuhan, China | Retrospective | 68.6(9) | 1:3 |
| 230 | Wang et al., 2020 | 199 | Fujian, China | Retrospective | 46.3(16.4) | 1:1.1 |
| 231 | Wang et al., 2020 | 59 | China | Retrospective | 67.4(11.3) | 1:1.8 |
| 232 | Wang et al., 2020 | 293 | Wuhan, China | Retrospective | 59.2(42.8−73.1 | 1.12:1 |
| 233 | Wang et al., 2020 | 56 | Liaoning, China | Retrospective | 45(21−80) | 1.3:1 |
| 234 | Wang et al., 2020 | 421 | China | Retrospective | 52(39−61) | 1:1.03 |
| 235 | Wei et al., 2020 | 566 | China | Retrospective | 69(65−76) | 1:1 |
| 236 | Wu et al., 2020 | 148 | Wuhan, China | Retrospective | 7(1.5−10.25) | 1.4:1 |
| 237 | X. Liu et al., 2020 | 104 | China | Retrospective | 42(31−55) | 1:1.5 |
| 238 | X. Wang et al., 2020 | 1012 | Fangcang, China | Prospective | 50(16−89) | 1:1.07 |
| 239 | X. Xu et al., 2020 | 90 | Guangzhou, China | Retrospective | 50(18−86) | 1.3:1 |
| 240 | X. Y. Zhao et al., 2020 | 91 | Hubei, China | Retrospective | 46(46−91) | 1:1.16 |
| 241 | X. Yan et al., 2020 | 218 | China | Retrospective | 43(32−52) | 1:1.27 |
| 242 | Xie et al., 2020 | 733 | China | Retrospective | 65(56−73) | 1:1.8 |
| 243 | Xiong et al., 2020 | 917 | China | Retrospective | 48.7(17.1) | 1:1.2 |
| 244 | Xu et al., 2020 | 50 | China | Retrospective | 43.9(16.8) | 1:1.3 |
| 245 | Y. Chen et al., 2020 | 51 | Hebei, China | Retrospective | 58.9(13.7) | 1:1.12 |
| 246 | Y. Li et al., 2020 | 219 | Wuhan, China | Retrospective | 53.3(15.9) | 1.4:1 |
| 247 | Y. Li et al., 2020 | 132 | Wuhan, China | Retrospective | 65(57−71) | 1:1.14 |
| 248 | Y. Liu et al., 2020 | 12 | Shenzhen, China | Prospective | 62.5(10−72) | 1:2 |
| 249 | Y. nan Han et al., 2020 | 25 | China | Retrospective | 44(22−70) | 1.08:1 |
| 250 | Y. Wang et al., 2020 | 189 | China | Retrospective | 44(14) | 1:1.12 |
| 251 | Y. Wei et al., 2020 | 276 | Hubei, China | Retrospective | 51(41−58) | 1:1.2 |
| 252 | Y. Wu et al., 2020 | 71 | China | Retrospective | 61(49−69) | 1:1.7 |
| 253 | Y. Zheng et al., 2020 | 73 | China | Retrospective | 43(21−76) | 1:1.21 |
| 254 | Yan et al., 2020 | 59 | California, USA | Cross-sectional | NC[a] | 1:1 |
| 246 | Yanan Li et al., 2020 | 219 | China | Retrospective | 53.3(15.9) | 1.5:1 |



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**Table 1. continued**

| ref | study | sample ($n$) | setting | study design | mean or median age (SD or range) | female/male ratio |
|---|---|---|---|---|---|---|
| 255 | Yang et al., 2020 | 52 | Wuhan, China | Retrospective | 59.7(13.3) | 1:2.05 |
| 256 | Yao et al., 2020 | 108 | Huanggang, China | Retrospective | 52(37−58) | 1.5:1 |
| 257 | Yoon et al., 2020 | 150 | Boston, England | Retrospective | 63.6(16) | 1:1.8 |
| 258 | Yoshimura et al., 2020 | 17 | Japan | Retrospective | 69(10) | 1.1:1 |
| 259 | Yu et al., 2020 | 141 | China | Retrospective | 81(78−85) | 1.4:1 |
| 260 | Yue et al., 2020 | 86 | Gansu, China | Retrospective | 41(31−54.3) | 1.2:1 |
| 261 | Z. Chen et al., 2020 | 32 | China | Multicenter Retrospective | 9.5(0.1−18) | 1:1.9 |
| 262 | Z. Wang et al., 2020 | 69 | Wuhan, China | Retrospective | 42(35−62) | 1.15:1 |
| 263 | Zerah et al., 2020 | 821 | France | Retrospective | 86 | 1.3:1 |
| 31 | Zhan et al., 2020 | 405 | Wuhan, China | Retrospective | 56(17−95) | 1.17:1 |
| 264 | Zhang et al., 2020 | 221 | Wuhan, China | Retrospective | 55(39−66.5) | 1.04:1 |
| 265 | Zhao et al., 2020 | 101 | Hunan, China | Retrospective | 44.44(17−75) | 1:1.2 |
| 266 | Zheng et al., 2020 | 52 | South China | Retrospective | 9(4−12) | 1:1.1 |
| 267 | Zhong et al., 2020 | 48 | China | Retrospective | 44.35(15.76) | 1:1.8 |
| 268 | Zhou et al., 2020 | 118 | Wuhan, China | Retrospective | NC[a] | 1.2:1 |

[a]NC = not clear. NR = not reported. $C$ = control. $P$ = patients.

**Table 2. Neurological Manifestations in COVID-19 Patients**

| nonspecific | CNS manifestations | PNS manifestations |
|---|---|---|
| Headache | Altered mental status | Olfactory dysfunction |
| Fatigue | Encephalitis | Gustatory dysfunction |
| Myalgia | Encephalopathy | Neuralgia |
| Dizziness | Hypoxic ischemia | Arthralgia |
| Nausea | Agitation | Dysautonomia |
| Vomiting | Confusion | Guillain−Barre syndrome |
| Malaise | Bradypsychia | Paraesthesia |
| | Acute confusional syndrome | Facial palsy |
| | Anxiety | Peripheral neuropathy |
| | Depression | Focal neurologic deficits |
| | Psychosis | Vision impairment |
| | Movement disorders | AIDP |
| | Shock | Hyper |
| | Orthostatic hypertension | Rhabdomyolysis |
| | Balance disorder | Myopathy |
| | Delirium | |
| | Tremors | |
| | Myelitis | |
| | Syncope | |
| | Ataxia | |
| | Seizure | |
| | Cerebrovascular disease | |
| | Sleep disorders | |
| | Cranial neuropathy | |
| | Cerebral venous sinus thrombosis | |
| | Posterior reversible encephalopathy syndrome (PRES) | |

and visualized using a funnel plot (L'Abbé plot). The analysis was done using Stats Direct statistical analysis software (version 3).

## 3. RESULTS

A total of 75 454 articles were identified in the searched databases. After the removal of duplicates, 59 580 titles and abstracts were screened. From these, 59 133 articles were excluded and 447 full-text articles were screened for eligibility. After screening, 246 studies were included in the qualitative synthesis whereas 240 studies were included in the quantitative synthesis. The scheme of selection of studies for analysis is shown in Figure 1.

**3.1. Study Characteristics.** The included studies were prospective and retrospective observational cohort studies, cross-sectional studies, and case-control studies. The demographic characteristics including study design, sample size, study setting, age, and sex ratio in patients of included studies are shown in Table 1.

**3.2. Quality Assessment.** All cohort, cross-sectional and, case-control studies with one protocol assessed for methodological quality on the NOS were found to be good, fair, and poor quality, based on the scores of the study in selection,


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Table 3. Prevalence of Neurological Manifestations in COVID-19 Patients

| event | studies | sample size | cases | prevalence (95% CI) |
|---|---|---|---|---|
| Malaise | 12 | 4855 | 2805 | 57.8 [56.4−59.2] |
| Arthralgia | 34 | 29116 | 7168 | 24.6 [24.1−25.1] |
| Fatigue | 147 | 83827 | 15862 | 18.9 [18.7−19.2] |
| Myalgia | 154 | 118491 | 20161 | 17.0 [16.8−17.2] |
| Olfactory dysfunction | 89 | 83575 | 9641 | 11.5 [11.3−11.8] |
| Gustatory dysfunction | 74 | 75915 | 8131 | 10.7 [10.5−10.9] |
| Headache | 176 | 163052 | 16221 | 9.9 [9.8−10.1] |
| Encephalopathy | 12 | 6607 | 690 | 10.4 [9.7−11.2] |
| Sleep disorder | 5 | 1269 | 150 | 11.8 [10.0−13.6] |
| Altered mental status | 30 | 17277 | 1484 | 8.6 [8.2−9.0] |
| Nausea | 100 | 77035 | 4454 | 5.8 [5.6−5.9] |
| Confusion | 13 | 5356 | 342 | 6.4 [5.7−7.0] |
| Vomiting | 104 | 89355 | 4704 | 5.3 [5.1−5.4] |
| Movement disorders | 9 | 9108 | 178 | 2.0 [1.7−2.2] |
| Dizziness | 50 | 62623 | 800 | 1.3 [1.2−1.4] |
| Cerebrovascular disease | 28 | 62959 | 669 | 1.1 [1.0−1.1] |
| Neuralgia | 7 | 2777 | 50 | 1.8 [1.3−2.3] |
| Seizure | 24 | 62446 | 335 | 0.5 [0.5−0.6] |
| Guillain−Barre syndrome | 7 | 6804 | 57 | 0.8 [0.6−1.1] |
| Encephalitis | 8 | 53981 | 30 | 0.1[ 0.04−0.1] |

Table 4. Meta-Analysis, Summary Estimate of Pooled Prevalence, and Heterogeneity of Each Neurological Manifestation

| event | studies ($N$) | summary estimate (%) | 95% CI | $I_2$ (inconsistency) |
|---|---|---|---|---|
| Malaise | 12 | 38.3 | [24.7, 52.9] | 97.2 |
| Fatigue | 147 | 33.6 | [29.5, 37.8] | 99.3 |
| Gustatory dysfunction | 74 | 27.2 | [22.3, 32.3] | 99.5 |
| Olfactory dysfunction | 89 | 26.4 | [21.8, 31.3] | 99.5 |
| Encephalopathy | 12 | 23.5 | [14.3, 34.1] | 98.1 |
| Myalgia | 154 | 21.4 | [18.8, 24.1] | 99.1 |
| Arthralgia | 34 | 19.9 | [15.3, 25.0] | 98.8 |
| Altered mental status | 30 | 17.1 | [12.3, 22.5] | 98.6 |
| Sleep disorder | 5 | 14.9 | [1.9, 36.8] | 98.5 |
| Headache | 176 | 14.6 | [12.2, 17.2] | 99.4 |
| Confusion | 13 | 14.2 | [6.9, 23.5] | 98.5 |
| Cerebrovascular disease | 28 | 9.9 | [6.8, 13.4] | 98.7 |
| Nausea | 100 | 9.8 | [8.1, 11.7] | 98.2 |
| Guillain−Barre syndrome | 7 | 6.9 | [2.3, 13.7] | 97.9 |
| Vomiting | 104 | 6.7 | [5.5, 8.0] | 97.8 |
| Dizziness | 50 | 6.7 | [4.7, 9.1] | 98.0 |
| Movement disorders | 9 | 5.2 | [1.7, 10.4] | 98.6 |
| Seizure | 24 | 4.05 | [2.5, 5.8] | 97.7 |
| Neuralgia | 7 | 2.4 | [0.8, 4.7] | 90.3 |
| Encephalitis | 8 | 0.6 | [0.2, 1.3] | 92.5 |

comparability, and outcome subscales. Out of 457 studies, 150 were of good quality, 96 were of fair quality, and 211 studies were of poor quality on the NOS. Only articles of good and fair quality (240) were included for quantitative analysis (Table 2).

**3.3. Neurological Manifestations and COVID-19.** The neurological manifestations in COVID-19 patients were categorized into nonspecific, CNS, and PNS manifestations depending upon the symptoms. The neurological manifestations found in COVID-19 patients are enlisted in Table 2.

*3.3.1. Nonspecific Symptoms.* The most common problems reported in COVID-19 patients were nonspecific symptoms such as headache, fatigue, myalgia, dizziness, nausea, vomiting, etc. Headache was reported in 176 studies with a pooled proportion of 14.6% (2.2−17.2). Fatigue, myalgia, and malaise were reported with pooled proportion of 33.6% (29.5−37.8), 21.4% (18.8−24.1), and 38.3% (24.7−52.9), respectively. The dizziness was found to be significant with a pooled proportion of 6.7% (4.7−9.1). Nausea and vomiting were also found prominent in COVID-19 patients with pooled proportions of 9.8% (8.1−11.7) and 6.7% (5.5−8.0), respectively. The forest plot of individual nonspecific symptoms in selected studies is presented in Figures S2−S7.

*3.3.2. CNS Manifestations.* The CNS manifestations were also highly reported in COVID-19 patients. The seizure was reported in 24 studies with a pooled proportion of 4.05% (2.5−5.8). Both encephalitis and encephalopathy were reported with pooled proportions of 0.6% (0.2−1.3) and 23.5% (14.3−34.1), respectively. Altered mental status was reported in 30 studies with a pooled proportion of 17.1% (12.3−22.5). Cerebrovascular diseases were reported in 28 studies with a pooled proportion of 9.9% (6.8−13.4). Sleep disorders were reported in 5 studies with a pooled proportion


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of 14.9% (1.9−36.8), whereas confusion was reported in 13 studies with a pooled proportion of 14.2% (6.9−23.5). Movement disorders were reported in 9 studies with a pooled proportion of 5.2% (1.7−10.4). The individual and pooled proportion of CNS manifestations in individual studies is presented in Figures S8−S15.

**3.4. PNS Manifestations.** The peripheral nervous system is thought to be involved in COVID-19 pathogenesis as COVID-19 symptoms include PNS manifestations. Among them, smell and taste disturbances had been widely reported. Olfactory dysfunction was reported in 89 studies with a pooled proportion of 26.4% (21.8−31.3), whereas gustatory dysfunction was reported in 74 studies with a pooled proportion of 27.2% (22.3−32.3). Guillain−Barre syndrome was reported in 7 studies with a pooled proportion of 6.9% (2.3−13.7). Neuralgia was reported in 7 studies with a pooled proportion of 2.4% (0.8−4.7). Arthralgia was reported in 34 studies with a pooled proportion of 19.9% (15.3−25.0). The forest plot is presented in Figures S16−S20.

Apart from these, some manifestations that are reported rarely are listed in Table 2. The prevalence of neurological manifestations in COVID-19 patients is shown in Table 3. The meta-analysis, summary estimate of pooled prevalence, and heterogeneity of the same are shown in Table 4.

**3.5. Heterogeneity.** The heterogeneity among all included studies was found to be high for all the neurological manifestations with an $I_2$ value ranging from 90.3% to 99.5%.

**3.6. Publication Bias.** The funnel plot has indicated the involvement of publication bias in the majority of studies related to neurological manifestations. The publication bias was further confirmed by Eggers's test ($p > 0.05$). For arthralgia, sleep disorders, malaise, movement disorders, and Guillain−Barre syndrome, the $p$-value was found to be more than 0.05, which indicates no significant publication bias. However, for all other manifestations, the $p$-value for the Egger test was found to be less than 0.05, which indicates significant publication bias (Figures S23−S42).

## 4. DISCUSSION

The present study analyzed 240 studies with data of 190 785 patients to determine the association between the occurrence of neurological problems and COVID-19 infection. The neurological manifestations were broadly classified into nonspecific, CNS, and PNS manifestations. The nonspecific manifestations could be the systemic features of viral infection and indicators of disturbed homeostasis. Headache, fatigue, nausea, vomiting, myalgia, dizziness, and malaise were the commonly reported nonspecific manifestations.[19,20] The current analysis results have shown headache, fatigue, myalgia, dizziness, nausea, and vomiting as highly reported neurological manifestations in COVID-19 patients.

Central nervous system involvement in COVID-19 pathophysiology is evident, as COVID-19 patients are diagnosed with several CNS manifestations. Altered mental status or disturbances in consciousness was found to be a significant manifestation in COVID-19 patients.[21,22] Our analysis has also found altered mental status as a significant manifestation in COVID-19 patients with a pooled proportion of 17.1% (12.3−22.5). The stupor, coma, and somnolence were the specific manifestations associated with consciousness; additionally, bradypsychia and the acute confusional syndrome were also reported.[23] In a brain imaging study, the brain images of patients with altered mental status showed white matter microangiopathic changes, chronic infracts, and incidental meningioma.[24] The involvement of CNS in SARS-Cov-2 infection is confirmed.[22] Encephalitis including limbic encephalitis radiological acute disseminated encephalomyelitis, cytotoxic lesions of the corpus callosum, and radiological acute hemorrhagic necrotizing encephalopathy was reported in COVID-19 patients. The brain imaging of these patients showed the typical feature of viral encephalitis such as leptomeningeal enhancement and elevated protein levels, but RT-PCR for SARS-CoV-2 was found negative in CSF samples.[25] Encephalopathies such as posthypoxic leukoencephalopathy, metabolic or toxic encephalopathy, septic encephalopathy, posterior reversible encephalopathy syndrome, and diffuse symmetric leukoencephalopathy were the major manifestations found in neuroimaging studies.[5,26−29] The results of our analysis have found encephalitis and encephalopathy with pooled proportions 0.6% (0.2−1.3) and 23.5% (14.3−34.1), respectively. In addition these behavioral manifestations such as agitation, confusion, anxiety, depression and psychosis were also reported in COVID-19 patients.[23,30] The confusion was reported in 13 studies with a pooled proportion of 14.2% (6.9−23.5). Sleep disorders reported were insomnia and pathological wakefulness.[30−32] We have found sleep disorders in 5 studies with a pooled proportion of 14.9% (1.9−36.8).

Seizure or epilepsy was reported in COVID-19 patients who had and who did not have a prior history of seizure.[26] In children, both febrile seizures and nonfebrile seizures were reported.[33] Magnetic resonance imaging showed perfusion abnormalities related to seizures in COVID-19 patients with seizures. The current analysis results have found seizures in 24 studies with a pooled proportion of 4.05% (2.5−5.8). The possible factors that can account for the occurrence of seizures can be iatrogenic, metabolic alterations, and potential changes related to encephalitis.[34] Proinflammatory cytokines, blood−brain barrier (BBB) disruption, mitochondrial disturbance, and abnormal coagulation in COVID-19 patients can contribute to epilepsy.[35] Movement disorders reported in COVID-19 patients were characterized by tremors, myoclonus, and nonspecific psychomotor agitation. Additionally, balance disorders were also reported in the same studies.[36,37] Our study has found significant involvement of movement disorders in COVID-19 patients.

Cerebrovascular diseases are the most commonly reported neurological manifestation in COVID-19 patients. Ischemic stroke, hemorrhagic stroke, cerebral vasculitis, and cerebral venous thrombosis are the majorly reported cerebrovascular diseases.[38−40] Neuroimaging studies showed subacute and acute ischemic infarct, acute hemorrhage, intracranial hemorrhage, and cranial nerves enhancement in COVID-19 patients with cerebrovascular diseases.[40,41] The ischemic stroke reported in COVID-19 patients can be classified as small vessel disease, large vessel disease, cardioembolic, and stroke of determined and undetermined origin.[42] In a retrospective case-control study it has been shown that COVID-19 is mainly associated with large vessel occlusion strokes rather than the small vessel occlusion strokes.[43] Current evidence suggests that the prothrombotic effect of the inflammatory response caused by cytokine storm in COVID-19 patients might account for the triggering of ischemic stroke.[40] Another study showed that COVID-19 patients with stroke have a higher in-hospital mortality rate.[39] It has also been reported that detection of acute stroke can be a strong prognostic marker of the poor


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patient outcome as it is the most common neuroimaging finding among the COVID-19 patients.[44] The results of the current analysis have also found significant cerebrovascular diseases in COVID-19 patients of 28 studies with a pooled proportion of 9.9% (6.8−13.4).

The results of our analysis have shown smell and taste disturbances as major PNS manifestations reported in COVID-19 patients. Hyposmia and anosmia were the main olfactory dysfunctions, and their severity ranges from mild to moderate to severe.[45,46] In a multicentric study it has been shown that the prevalence of olfactory dysfunctions was significantly higher in the mild form compared to moderate to critical forms and about 95% of patients recovered from olfactory dysfunction in 6 months.[47] The possible mechanism for olfactory dysfunction in COVID-19 infection can be nasal obstruction, loss of olfactory receptor neurons, brain infiltration affecting olfactory centers, and damage to the olfactory epithelium.[48] ACE-2 receptors are highly expressed in the nasal cavity and olfactory bulb, and this can be the potential pathway for olfactory dysfunction as SARS-CoV-2 has a greater affinity toward the ACE-2 receptor.[49] Olfactory dysfunction can be a prognostic marker for the prediction of severity of disease as persistent olfactory dysfunction at 20 days is associated with disease severity.[50] Olfactory dysfunctions are often reported together with gustatory dysfunction. Ageusia, dysgeusia, and hypogeusia were the main gustatory dysfunctions.[45] Neuralgia and arthralgia were prominent in COVID-19 patients.[51,52]

Guillain−Barre syndrome (GBS), an autoimmune disorder, has been reported in COVID-19 patients.[53,54] All the variants of GBS such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), critical illness myopathy and neuropathy (CRIMYNE), peripheral polyneuropathies (PNP), acute motor axonal neuropathy (AMAN), and acute motor-sensory axonal neuropathy (AMSAN) have been reported in COVID-19 patients.[17,22] Magnetic resonance imaging of COVID-19 patients with GBS showed enhancement of caudal nerve roots and enhancement of facial nerve bilaterally.[53] Demyelinating pattern in either facial or trigeminal nerve was seen in COVID-19 patients with GBS, suggesting the involvement of cranial nerve.[22] Demyelination was the main association between COVID-19 and GBS; COVID-19 GBS seems to be more severe than non-COVID-19 GBS, and care should be taken for proper diagnosis.[54] Our analysis has shown significant involvement of GBS in COVID-19 patients with a pooled proportion of 6.9% (2.3−13.7).

## 5. CONCLUSION

Our study demonstrates that neurological manifestations are significantly reported in COVID-19 patients. The most common neurological manifestations in COVID-19 patients were headache, fatigue, olfactory dysfunction, gustatory dysfunction, vomiting, nausea, dizziness, myalgia, seizure, cerebrovascular diseases, sleep disorders, altered mental status, neuralgia, arthralgia, encephalopathy, encephalitis, malaise, confusion, movement disorders, and Guillain−Barre syndrome depending upon the individual, which indicates the involvement of CNS as well as PNS.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acschemneuro.1c00353.

Forest plot for each neurological manifestation (pp S2−S21); funnel plots, $I_2$ (inconsistency), and Egger bias value for each neurological manifestation (pp S22−S41); PRISMA checklist (pp S42−S46); NIH quality assessment tools checklist (pp S47−S49) (PDF)

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### Author Contributions

V.K.D extracted the data and drafted the manuscript. A.S. cross-checked the screening of studies and extracted data. A.K. designed, analyzed, and interpreted the data. S.J.S.F. revised the manuscript.


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## ABBREVIATIONS

ACE2: angiotensin-converting enzyme 2
AIDP: acute inflammatory demyelinating polyradiculoneuropathy
AMAN: acute motor axonal neuropathy
AMSAN: acute motor-sensory axonal neuropathy
BBB: blood−brain barrier
COVID-19: coronavirus disease-19
CRIMYNE: critical illness myopathy and neuropathy
CNS: central nervous system

CSF: cerebrospinal fluid
GBS: Guillain−Barre syndrome
PNS: peripheral nervous system
PNP: peripheral polyneuropathies
RTPCR: reverse transcription polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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