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Prevalence and Mortality Risk of Neurological Disorders during the COVID-19 Pandemic: An Umbrella Review of the Current Evidence

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Keywords
COVID-19 · Central nervous system diseases · Prevalence · Mortality

Abstract
Introduction: Coronavirus disease 2019 (COVID-19), a global pandemic, has infected approximately 10% of the world's population. This comprehensive review aimed to determine the prevalence of various neurological disorders in COVID-19 without overlapping meta-analysis errors. ***Methods:*** We searched for meta-analyses on neurological disorders following COVID-19 published up to March 14, 2023. We obtained 1,184 studies, of which 44 meta-analyses involving 9,228,588 COVID-19 patients were finally included. After confirming the forest plot of each study and removing overlapping individual studies, a re-meta-analysis was performed using the random-effects model. ***Results:*** The summarized combined prevalence of each neurological disorder is as follows: stroke 3.39% (95% confidence interval, 1.50–5.27), dementia 6.41% (1.36–11.46), multiple sclerosis 4.00% (2.50–5.00), epilepsy 5.36% (−0.60–11.32), Parkinson's disease 0.67% (−1.11–2.45), encephalitis 0.66% (−0.44–1.77), and Guillain-Barré syndrome 3.83% (−0.13–7.80). In addition, the mortality risk of patients with comorbidities of COVID-19 is as follows: stroke OR 1.63 (1.23–2.03), epilepsy OR 1.71 (1.00–2.42), dementia OR 1.90 (1.31–2.48), Parkinson's disease OR 3.94 (−2.12–10.01). ***Conclusion:*** Our results show that the prevalence and mortality risk may increase in some neurological diseases during the COVID-19 pandemic. Future studies should elucidate the precise mechanisms for the link between COVID-19 and neurological diseases, determine which patient characteristics predispose them to neurological diseases, and consider potential global patient management.

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Introduction

Since the outbreak of the novel coronavirus disease (COVID-19) in December 2019, the number of cross-border infections has increased rapidly, posing a serious threat to global health. Globally, as of March 15, 2023, there have been 760,897,555 confirmed cases of COVID-19, including 6,874,585 deaths, reported to the WHO. As of March 11, 2023, a total of 13,232,780,775 vaccine doses have been administered [1, 2]. The symptoms of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are not limited to the respiratory tract but affect the entire body [3]. These symptoms include cutaneous, respiratory, cardiovascular, musculoskeletal, mental health, neurologic, and renal symptoms, which may be prolonged [4].

To date, several systematic reviews and meta-analysis studies related to various neurological complications caused by COVID-19 have been published. However, previous meta-analyses have described several studies with a small sample of subjects, each reporting a different prevalence rate and odds ratio [5–8]. In addition, existing papers often examine only simple symptoms (e.g., myalgia, smell impairment, taste dysfunction, headache, vomiting, nausea, dizziness). Therefore, information on diseases (stroke, epilepsy, Parkinson's disease, dementia, encephalitis, Guillain-Barré syndrome, multiple sclerosis, etc.) other than simple symptoms is limited. The growing number of individually reviewed studies, reporting disparate results, and, to date, meta-analysis studies focusing on symptoms rather than disease make it difficult for clinicians to track and obtain sufficient information. Additionally, previous studies did not comprehensively compare the increased mortality in COVID-19 patients with neurological disorders. In addition, few reviews report a relationship between viral mutations and neurological disease.

Therefore, an umbrella review of meta-analysis is an attempt to bridge the gap pointed out in the existing literature through two contributions. As a first contribution, we will estimate the summarized prevalence and mortality of neurological disorders in patients with COVID-19 without overlapping errors to make the data easier for clinicians to understand. Our next contribution was to look at the temporal evolution of the impact of COVID-19 on neurological diseases by identifying how viral mutations affect mortality in COVID-19 patients with neurological diseases.

Methods

This umbrella meta-analysis study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9, 10]. We registered this review protocol in the International Prospective Register of Systematic Reviews with the registration number CRD42022330401. The PRISMA checklist is provided in Supplementary Material S1 (for all online suppl. material, see https://doi.org/10.1159/000530536).

Search Strategy

Relevant studies were systematically searched in electronic databases, including MEDLINE, Embase, Cochrane, Scopus, PsycINFO, and Google Scholar, from December 1, 2019, to Nov 5, 2022, and we updated our search on March 14, 2023. The search strategy was as follows: ("COVID-19" or "SARS-CoV-2" or "coronavirus disease-19" or "new coronavirus" or "2019-nCoV" or "novel corona virus" or "novel coronavirus" or "nCoV-2019" or "novel coronavirus pneumonia" or "2019 novel coronavirus" or "coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2") AND ("Nervous System Diseases" or "Neurodegenerative Diseases" or "Stroke" or "Cerebrovascular Disorders" or "Dementia" or "Epilepsy" or "Parkinson Disease" or "Encephalitis" or "Guillain-Barre Syndrome (GBS)" or "Multiple Sclerosis" or "neurologic disorder") AND (meta-analysis) (online suppl. Material S2).

Inclusion and Exclusion Criteria

The Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework was used to establish the study's inclusion criteria. The study focused on COVID-19 patients (P) and examined the relationship between the presence of neurological disorders (stroke, epilepsy, Parkinson's disease, dementia, encephalitis, Guillain-Barré syndrome, multiple sclerosis, etc.) (I). The study evaluated the prevalence rate of neurological disorders, mortality, and ICU admission (O). Systematic meta-analysis studies written in English and published in a peer-reviewed journal between December 1, 2019, and March 14, 2023, were included in the study design (S). Only meta-analyses that reported individual studies and their outcomes in a forest plot were included for re-meta-analysis. We excluded studies with the following criteria: (1) meta-analysis studies with insufficient data, (2) narrative reviews, (3) studies on specific groups, such as children or neonates/pregnant women, (4) when re-meta-analysis is not possible because there is no report on individual studies, (5) studies written in languages other than English.

Two reviewers (J.M.P. and W.G.W.) selected the papers through title/abstract/full-text review according to the above criteria. Disagreements between authors were resolved in consultation with third author (Y.W.K.).

Data Extraction

Two reviewers (J.M.P. and W.G.W.) independently extracted the relevant information, including the first author, publication year, the timeframe of literature search, mean age, sex (female, %), number of COVID-19 patients, articles included in each meta-analysis. The primary endpoint of the quantitative meta-analysis was the prevalence rate of neurological disorders in COVID-19 patients. The authors extracted prevalence rate of single

neurological disorder reported in each trial. We considered mortality and risk of ICU admission as secondary endpoints for patients with COVID-10 with neurological disease. At this time, the diagnosis period of the neurological disease includes both before and after SARS-CoV-2 infection. Patients with coexisting SARS-CoV-2 infection and neurological disease at the time of investigation were included. Data on mortality were extracted as the odds ratio and relative risk ratio.

Quality Assessment

The quality of each eligible systematic meta-analysis study was independently analyzed by two reviewers (J.M.P. and W.G.W.). If the evaluation was unclear, a third author (YWK) was consulted to arrive at an agreement. The Assessment of Multiple Systematic Reviews (AMSTAR-2) tool was used to assess the methodological quality of the included studies [11]. AMSTAR-2 consists of a total of 16 items and is a rating system that classifies the quality level of all reviews into critically low, low, moderate, and high. The definition of each grade is as follows: high: no or one noncritical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest; moderate: more than one noncritical weakness but no critical flaws – it may provide an accurate summary of the results of the available studies that were included in the review; low: one critical flaw with or without noncritical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest; and critically low: more than one critical flaw with or without noncritical weaknesses – the review has more than one critical flaw and should not be relied upon [11].

Statistical Analysis

Re-meta-analysis was performed in the following order. First, the forest plot of each included meta-study was checked to extract the author, year, and results of each study included in the forest plot. Second, the included meta-studies were classified by year and author name to check whether individual studies overlap with previous studies. Duplicates of individual studies were excluded based on author name, publication year, and outcome value. Third, a meta-analysis was conducted by collecting individual studies excluding duplicates. Fourth, reanalyzed meta-analyses were collected and finally meta-analysis was performed for each neurological disease. Because the included studies were sampled from populations with different countries and medical histories, a high degree of heterogeneity was expected, so a restricted maximum likelihood randomized effect meta-analysis was performed. For each meta-analysis, individual studies were reanalyzed to estimate the summary effects, 95% confidence interval (CI), and p values. In this study, the mortality odds ratio and relative risk ratio were meta-analyzed together with reference to the previous study that found that odds ratio and relative risk ratio are close in the case of less than 20%, which is relatively rare [12]. Nonoverlapping study data were integrated to obtain the prevalence rate and mortality odds ratio for each neurological disorder and presented as forest plots. All re-analyses in this study were performed using Stata (17.0; Stata Corporation, College Station, TX, USA). Subgroup analyses were performed by distinguishing strains from the original strain of SARS-CoV-2. We also performed a sensitivity analysis based on the AMSTAR-2 tool by selecting high- or moderate-quality studies. The heterogeneity of individual studies was assessed using the inconsistency of the I^2 metric and the p value of the Cochrane Q test. Publication bias was analyzed by funnel plots and Egger's test. The metatrim command in Stata was utilized to apply the trim-and-fill method for investigating the potential of publication bias [13]. All statistical tests were two sided; p values <0.05 were considered statistically significant.

Results

Study Identification and Characteristics

A total of 1,184 studies were retrieved, of which 101 were duplicates. A total of 597 and 213 studies were excluded after reading the titles and abstracts, respectively. 202 papers were excluded from the full-text evaluation, leaving 71 papers. Of these, 27 papers were excluded due to lack of detailed data, systematic review without meta-analysis, and failure to secure individual research data from forest plot, leaving 44 final papers. The study selection flowchart and reasons for exclusion are shown in Figure 1. Altogether, 44 studies involving 9,228,588 patients with COVID-19 were included for this meta-analysis, including 28, 7, 4, 7, 3, 4, and 1 study on stroke, epilepsy, Parkinson's disease, dementia, encephalitis, GBS, and multiple sclerosis, respectively. The detailed characteristics and quality of the included studies for meta-analysis are listed in Table 1.

Considering the methodological quality of AMSTAR-2 tool items, 15 [6, 8, 14–26] and 1 [27] studies were rated as being of high and moderate quality, respectively. Overall, 16 [7, 24, 28–41] and 12 [5, 42–52] studies were rated as being of low and critically low quality (online suppl. Material S3 Table 1). In a total of 28 low-quality and very low-quality studies, unsatisfactory items were ranked as follows: (1) description of risk of bias for individual studies (82.1%), (2) conducting additional research on publication bias and discussing its impact on the results (53.6%), (3) assessment of the impact of risk of bias in individual studies on the meta-analysis composite outcome (42.9%), and (4) a sufficient explanation for the heterogeneity observed in the results (25%), respectively.

Prevalence of Neurological Disorders during the COVID-19 Pandemic

Figure 2 shows the forest plot of studies on the prevalence of neurological disorders in COVID-19 patients pooled after excluding duplicate data. The summarized pooled prevalence rate of stroke was estimated as 3.39% (95% CI = 1.50 to 5.27, I^2 = 99.7%). In addition, the summarized pooled prevalence rates of ischemic and

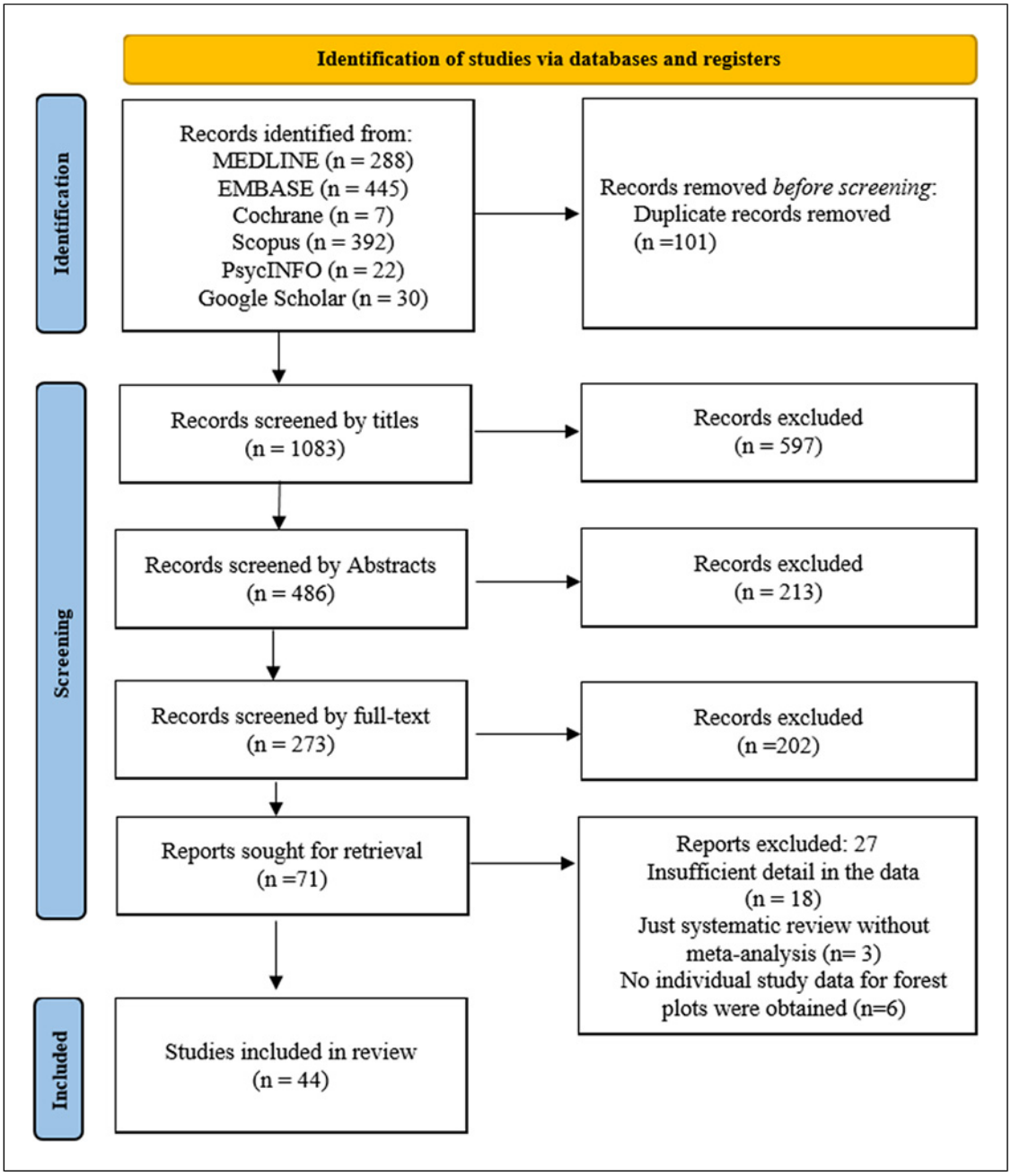

Fig. 1. PRISMA flowchart of study screening and selection process.

hemorrhagic strokes were estimated as 1.36% (95% CI = 1.07 to 1.64, I^2 = 18.8%) and 0.49% (95% CI = 0.28 to 0.69, I^2 = 74.9%), respectively. The following is a list of summarized pooled prevalence rates of other neurological disorders: epilepsy: 5.36% (95% CI = −0.60 to 11.32, I^2 = 99.2%), Parkinson's disease: 0.67% (95% CI = −1.11 to 2.45, I^2 = 56.4%), dementia: 6.41% (95% CI = 1.36 to 11.46, I^2 = 76.5%), encephalitis: 0.66% (95% CI = −0.44 to 1.77, I^2 = 98.5%), GBS: 3.83% (95% CI = −0.13 to 7.80, I^2 = 97.1%), and multiple sclerosis 4.00% (95% CI = 2.50 to 5.50, I^2 = 0.0%). When overall neurological disorders were combined, the summarized pooled prevalence rate was estimated at 2.80% (95% CI = 1.84 to 3.75, I^2 = 99.9%). The prevalence rate of neurological disorders during the COVID-19

Table 1. Meta-analyses reporting neurological disorders in patients with COVID-19

Disorder/First author (date of publication)	Study period	Number of studies/ participants	Age, mean (range), years	Sex (female), %	Random effects (reported) (ES, 95% CI)	Radom effects (re-analyzed) (ES, 95% CI)	Q test *p* value	I^2 statistic	Egger *p* value	Quality assessment AMSTAR-2
Stroke										
Abdullahi et al. (2020) [42]	Nov 2019–17 Apr 2020	60/11,069	(24–95)	55.30	Stroke prevalence 3.00% (1.00–5.00)	Stroke prevalence 3.00% (1.00–5.00)	0.579	0.0%	0.126	Critically low
Favas et al. (2020) [15]	Nov 2019–Jun 2020	74/30,159	N/R	N/R	Stroke prevalence 2.30% (1.00–3.60) Ischemic stroke prevalence 2.10% (0.90–3.30) Hemorrhagic stroke prevalence 0.40% (0.20–0.60)	Stroke prevalence 2.71% (1.28–4.13) Ischemic stroke prevalence 2.10% (0.90–3.30) Hemorrhagic stroke prevalence 0.40% (0.20–0.60)	<0.001 <0.001 0.009	88.2% 88.4% 74.0%	0.049 0.055 0.391	High
Yamakawa et al. (2020) [18]	Nov 2019–Oct 2020	26/6,368	66.6	34.40	Stroke prevalence 1.10% (0.60–1.60)	Stroke prevalence 0.78% (0.49–1.07)	0.045	58.9%	0.073	High
Zhang et al. (2020) [30]	N/R	47/16,143	N/R	N/R	Stroke prevalence 3.00% (2.00–4.00)	Stroke prevalence 2.93% (1.79–4.08)	<0.001	80.7%	0.024	Low
Beyrouti et al. (2021) [5]	Nov 2019–12 Dec 2020	4/98	60	36.00	Hemorrhagic stroke prevalence 0.38% (0.22–0.58)	Hemorrhagic stroke prevalence 0.27% (0.17–0.37)	<0.001	82.4%	0.002	Critically low
Cheruiyot et al. (2021) [44]	Nov 1 2019–Aug 14 2020	23/13,741	(21–79)	34.20	Hemorrhagic stroke prevalence 0.70% (0.50–0.90)	Hemorrhagic stroke prevalence 0.73% (0.54–0.92)	0.078	43.5%	0.651	Critically low
Vitalakumar et al. (2021) [87]	Nov 11 2019–Sep 3 2020	240/190,785	N/R	N/R	Stroke prevalence 9.90% (6.80–13.40)	Stroke prevalence 7.30% (5.72–8.87)	<0.001	96.8%	<0.001	High
He et al. (2021) [33]	Jan 1 2020–Apr 30 2021	168/292,693	N/R	N/R	Stroke prevalence 12.00% (8.00–16.00) Hemorrhagic stroke prevalence 5.00% (3.00–9.00)	Stroke prevalence 12.00% (8.00–16.00) Hemorrhagic stroke prevalence 5.00% (3.00–9.00)	<0.001 <0.001	98.9% 95.6%	<0.001 <0.001	Low
Nannoni et al. (2021) [47]	Nov 11 2019–Sep 14 2020	61/108,571	65.3	37.60	Stroke prevalence 1.40% (1.00–1.90)	Stroke prevalence 1.03% (0.84–1.21)	<0.001	80.3%	0.003	Critically low
Parsay et al. (2021) [48]	Nov 11 2019–Jul 12 2020	17/25,586	N/R	N/R	Ischemic stroke prevalence 1.70% (1.30–2.35)	Ischemic stroke prevalence 1.43% (1.12–1.74)	<0.001	68.1%	0.011	Critically low
Siow et al. (2021) [37]	Nov 11 2019–Jul 8 2020	30/55,176	65.5	29.50	Stroke prevalence 1.74% (1.09–2.51)	Stroke prevalence 3.14% (1.06–5.22)	<0.001	83.8%	0.058	Low
Syahrul et al. (2021) [24]	Nov 2019–Nov 8 2020	18/58,104	N/R	N/R	Ischemic stroke prevalence 1.11% (1.03–1.22) Hemorrhagic stroke prevalence 0.46% (0.40–0.53)	Ischemic stroke prevalence 1.15% (0.84–1.46) Hemorrhagic stroke prevalence 0.43% (0.22–0.65)	<0.001 <0.001	89.0% 81.6%	0.012 0.001	Low

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Table 1 (continued)

Disorder/First author (date of publication)	Study period	Number of studies/ participants	Age, mean (range), years	Sex (female), %	Random effects (reported) (ES, 95% CI)	Radom effects (re-analyzed) (ES, 95% CI)	Q test *p* value	I^2 statistic	Egger *p* value	Quality assessment AMSTAR-2
Vakili et al. (2021) [27]	Nov 2019–Apr 17 2020	57/6,597	54.2	45.00%	Stroke prevalence 4.28% (2.65–6.25)	Stroke prevalence 3.85% (2.36–5.35)	0.001	63.8%	<0.001	Moderate
Ganesh et al. (2022) [38]	Nov 2019–May 13 2021	59/17,452	52.8	50.40%	Ischemic stroke prevalence 3.00% (3.00–4.00)	Ischemic stroke prevalence 4.19% (0.66–7.71)	<0.001	99.1%	0.209	Low
Luo et al. (2022) [52]	Nov 2019–Mar 24 2021	10/26,691	(48–75)	35.10	Ischemic stroke prevalence 2.00% (1.00–2.00)	Ischemic stroke prevalence 1.50% (−0.30–3.30)	<0.001	88.7%	0.012	Critically low
Nagraj et al. (2022) [40]	Nov 2019–Jul 31 2021	77/38,732	55	38.00	Stroke prevalence 0.01% (0.01–0.02)	Stroke prevalence 0.13% (0.10–0.16)	0.750	0.0%	<0.001	Low
Schmidbauer et al. (2022) [7]	Nov 2019–Mar 5 2021	79/477	61	34.50	Hemorrhagic stroke prevalence 0.85% (0.36–1.99)	Hemorrhagic stroke prevalence 1.22% (−0.15–2.60)	<0.001	90.3%	<0.001	Low
Aggarwal et al. (2020) [43]	Dec 2019–Mar 31 2020	7/1,829	(52–67)	N/R	Mortality OR 2.33(0.77–7.04)	Mortality OR 1.77 (−0.89–4.43)	0.857	0.0%	<0.001	Critically low
Florez-Perdomo et al. (2020) [16]	N/R	7/3,244	(30–88)	N/R	Mortality OR 2.78 (1.42–5.46)	Mortality OR 1.59 (0.96–2.21)	0.640	0.0%	0.381	High
Pranata et al. (2020) [28]	Nov 2019–Apr 10 2020	16/4,448	(44–72)	N/R	Mortality RR 2.38 (1.92–2.96)	Mortality RR 2.38 (1.92–2.96)	0.457	0.0%	0.869	Low
Wang et al. (2020) [57]	Dec 2019–Apr 30 2020	8/1,374	(51–77)	N/R	Mortality OR 4.78 (3.24–7.03)	Mortality OR 4.21(−1.95–10.36)	0.531	0.0%	0.344	Low
Biswas et al. (2020) [14]	Nov 2019–May 21 2020	20/64,676	(52–69)	50.00	Mortality RR 4.78 (3.39–6.76)	Mortality RR 5.43 (2.89–7.97)	0.495	0.0%	0.147	High
Fernández Villalobos et al. (2021) [32]	Dec 2019–May 28 2020	74/44,672	N/R	N/R	Mortality RR 2.70 (1.70–4.10)	All results are duplicates	0.389	5.0%	0.061	Low
Gao et al. (2021) [19]	Nov 2019–Mar 11 2020	69/17,879	(39–74)	N/R	Mortality OR 3.45 (2.46–4.84)	Mortality OR 1.61 (0.97–2.24)	0.960	0.0%	0.002	High
Katzenschlager et al. (2021) [35]	Dec 2019–May 31 2020	88/69,762	N/R	N/R	Mortality OR 3.45 (2.42–4.91) ICU care OR 5.88 (2.35–14.73)	Mortality OR 2.11 (1.07–3.16)	0.995	0.0%	0.004	Low
Siepmann et al. (2021) [23]	Nov 2019–Apr 11 2020	11/1,906	66	48.50	Mortality RR 2.18 (1.75–2.70) ICU care RR 2.79 (1.83–4.24)	Mortality RR 2.79 (1.32–5.90)	0.598	0.0%	0.073	High
Li et al. (2022) [39]	Nov 2019–Nov 22 2021	47/7,267,055	N/R	N/R	Mortality OR 1.30 (1.16–1.44)	Mortality OR 1.25 (1.12–1.37)	<0.001	83.8%	0.336	Low

Table 1 (continued)

Disorder/First author (date of publication)	Study period	Number of studies/ participants	Age, mean (range), years	Sex (female), %	Random effects (reported) (ES, 95% CI)	Radom effects (re-analyzed) (ES, 95% CI)	Q test *p* value	I^2 statistic	Egger *p* value	Quality assessment AMSTAR-2
Quintanilla-Sánchez et al. (2022) [41]	Nov 2019–Aug 2020	16/11,886	N/R	N/R	Mortality OR 3.85 (1.08–13.70)	Mortality OR 1.71 (−9.35–12.77)	0.998	0.0%	0.174	Low
Epilepsy										
Favas et al. (2020) [15]	Nov 2019–Jun 2020	74/30,159	N/R	N/R	Prevalence 1.10% (0.70–1.70)	Prevalence 1.10% (0.70–1.70)	0.012	69.0%	0.448	Moderate
Vitalakumar et al. (2021) [87]	2019.11–2020.9.3	240/190,785	N/R	N/R	Prevalence 4.05% (2.50–5.80)	Prevalence 2.55% (1.73–3.37)	<0.001	92.2%	<0.001	High
He et al. (2021) [33]	Jan 1 2020–Apr 30 2021	168/292,693	N/R	N/R	Prevalence 4.00% (2.00–5.00)	Prevalence 4.00% (2.00–5.00)	<0.001	98.1%	<0.001	Low
Kubota et al. (2021) [6]	Nov 2019–Sep 19 2020	12/308	(45–65)	N/R	Prevalence 2.05% (0.02–6.04)	Prevalence 2.05% (0.02–6.04)	0.149	30.3%	0.017	High
Kuroda et al. (2022) [51]	Nov 2019–Feb 13 2021	24/6,492	N/R	61.00%	Prevalence 18.5% (13.9–23.6)	Prevalence 18.5% (13.9–23.6)	<0.001	96.4%	0.006	Critically low
Gao et al. (2021) [19]	Nov 2019–Mar 11 2020	69/17,879	(39–74)	N/R	Mortality OR 2.08 (0.08–50.91)	Mortality OR 2.08 (0.08–50.91)	0.335	0.0%	<0.001	High
Siahaan et al. (2021) [22]	Nov 2019–Jun 30 2021	13/67,131	(47–77)	N/R	Mortality OR 1.71 (1.14–2.56)	Mortality OR 1.71 (1.14–2.56)	0.842	0.0%	0.126	High
Parkinson's disease										
El-Qushayri et al. (2022) [26]	Nov 2019–Mar 12 2021	12/8,649	(63–79)	N/R	Prevalence 2.12% (0.75–5.98)	Prevalence 2.12% (0.75–5.98)	0.003	78.9%	0.110	High
Khoshnood et al. (2022) [50]	Nov 2019–Sep 2021	30/64,434	(60–82)	N/R	Prevalence 5.00% (4.00–6.00)	Prevalence 0.10% (0.08–0.12)	<0.001	98.0%	0.001	Critically low
Chambergo-Michilot et al. (2021) [31]	Nov 2019–Apr 1 2021	6/5,429	65	50.0	Mortality OR 11.23 (3.92–32.18)	Mortality OR 11.23 (3.92–32.18)	0.914	0.0%	<0.001	Low
Putri et al. (2021) [21]	Nov 2019–Dec 25 2020	12/103,874	(55–84)	N/R	Mortality OR 2.63 (1.50–4.60)	Mortality OR 2.63 (1.50–4.60)	<0.001	90.2%	0.496	High
Dementia										
Liu et al. (2020) [17]	Nov 2019–Aug 1 2020	10/119,218	(36–97)	60.00	Prevalence 9% (6–13) Mortality OR 5.17 (2.31–11.59)	Prevalence 9% (6–13) Mortality OR 5.17 (2.31–11.59)	<0.001 <0.001	87.0% 98.4%	0.058 0.818	High
Soysal et al. (2022) [8]	Nov 2019–Jun 2 2021	7/420	75	60.00	Prevalence 3.85% (0.43–7.27)	Prevalence 3.85% (0.43–7.27)	<0.001	82.3%	0.534	High
Hariyanto et al. (2021) [45]	Nov 2019–Oct 25 2020	24/46,391	(47–85)	N/R	Mortality RR 2.62 (2.45–2.04)	Mortality RR 2.65 (2.07–3.22)	<0.001	91.6%	0.026	Critically low
		10/56,577	(50–85)	N/R			<0.001	90.4%	0.333	Low

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Table 1 (continued)

Disorder/First author (date of publication)	Study period	Number of studies/ participants	Age, mean (range), years	Sex (female), %	Random effects (reported) (ES, 95% CI)	Radom effects (re-analyzed) (ES, 95% CI)	Q test *p* value	I^2 statistic	Egger *p* value	Quality assessment AMSTAR-2
July and Pranata (2021) [34]	Nov 2019–Sep 24 2020				Mortality OR 2.80 (1.85–4.24)	Mortality OR 1.80 (0.86–2.73)				
Saragih et al. (2021) [36]	Nov 2019–Nov 29 2020	15/27,952	(67–86)	N/R	Mortality OR 2.96 (2.00–4.38)	Mortality OR 2.86 (1.02–7.73)	0.350	9.9%	0.973	Low
Yang, et al. (2021) [49]	Jan 1 2020–Feb 1 2021	34/182,280	(48–86)	N/R	Mortality OR 1.84 (1.57–2.16)	Mortality OR 1.70 (1.39–2.00)	<0.001	90.1	0.109	Critically low
Axenhus et al. (2022) [25]	Jan 1 2020–Mar 2022	11/N/R	N/R	N/R	Mortality RR 1.25 (1.21–1.29)	Mortality OR 1.27 (1.14–1.39)	<0.001	99.6	0.766	High
Encephalitis										
Vitalakumar et al. (2021) [87]	Nov 2019–Sep 3 2020	240/190,785	N/R	N/R	Prevalence 0.2% (0.06–0.44)	Prevalence 0.2% (0.06–0.44)	0.001	70.0%	0.006	High
He et al. (2021) [33]	Jan 12020–Apr 30 2021	168/292,693	N/R	N/R	Prevalence 2.00% (1.00–3.00)	Prevalence 2.00% (1.00–3.00)	<0.001	90.3%	<0.001	Low
Siow et al. (2021) [37]	Nov 2019–Oct 24 2020	23/129,008	(43–80)	N/R	Prevalence 0.22% (0.06–0.44)	Prevalence 0.09%(–0.03–0.22)	<0.001	69.4%	<0.001	Low
Guillain-Barré syndrome										
Vitalakumar et al. (2021) [87]	Nov 2019–Sep 3 2020	240/190,785	N/R	N/R	Prevalence 6.90% (2.30–13.70)	Prevalence 6.90% (2.30–13.70)	<0.001	97.8%	0.867	High
He et al. (2021) [33]	Jan 1 2020–Apl 30 2021	168/292,693	N/R	N/R	Prevalence 1.00%(0.00–3.00)	Prevalence 1.00%(0.00–3.00)	<0.001	89.5%	<0.001	Low
Palaiodimou et al. (2021) [20]	Dec 30 2019–Dec 18 2020	18/136,746	58	27.40	Prevalence 1.50% (0.00–4.90)	Prevalence 0.51% (–0.17–1.19)	<0.001	95.5%	0.082	High
Ganesh et al. (2022) [38]	Nov 2019–May 31 2021	59/17,452	52.8	50.40	Prevalence 4.00% (3.00–5.00)	Prevalence 8.00% (6.85–9.15)	<0.001	98.6%	N/R	Low
Multiple sclerosis										
Moghadasi et al. (2021) [46]	Nov 2019–Apr 11 2021	12/16,577	(35–54)	N/R	Prevalence 4.00% (2.00–5.00)	Prevalence 4.00% (2.00–5.00)	<0.001	96.0%	0.078	Critically low

N/R, not recorded.

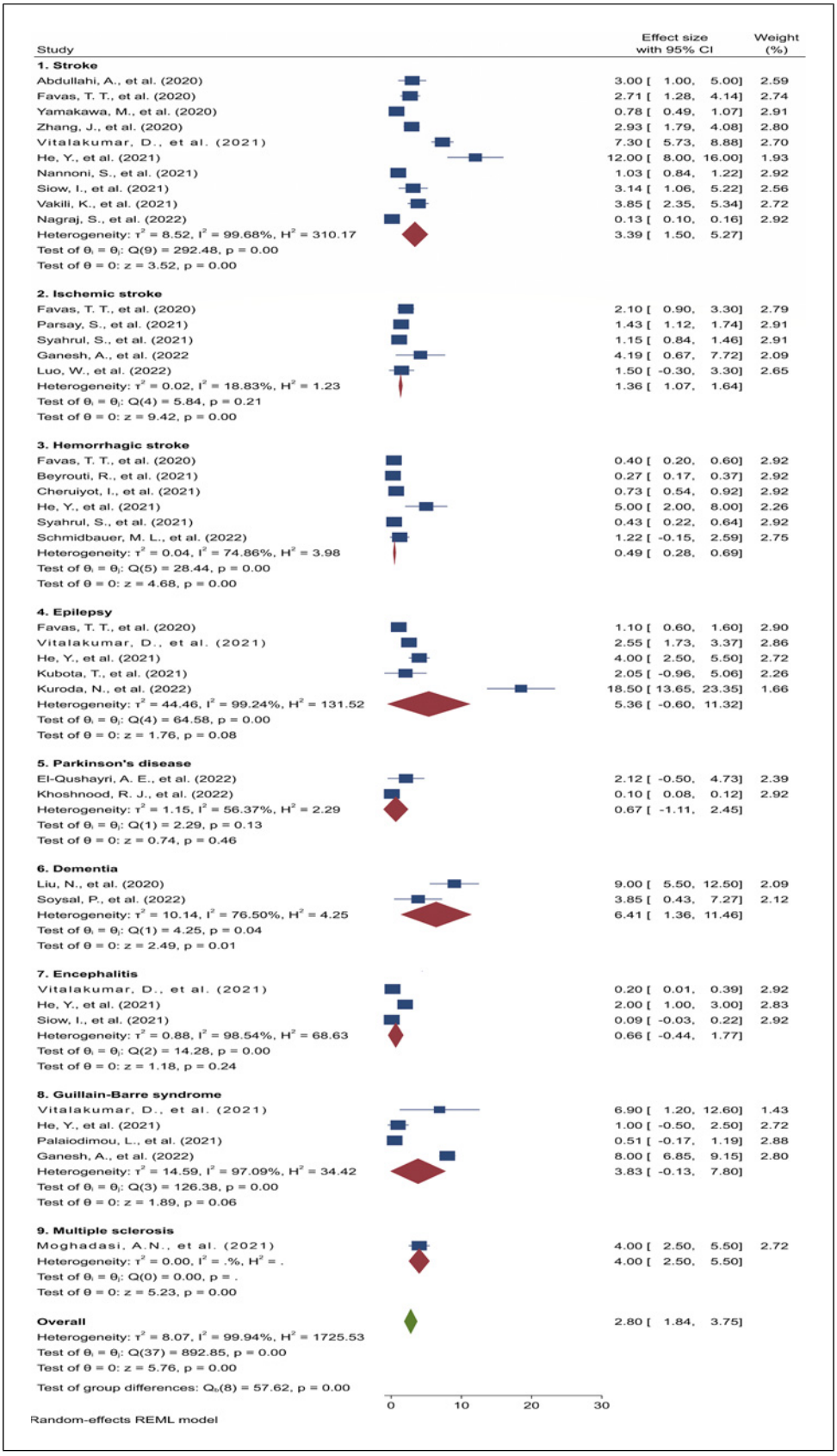

Fig. 2. Forest plot of studies regarding the prevalence rate (%) of neurological disorders in patients with COVID-19.

Table 2. Prevalence rates and mortality risk of neurological disorder during the COVID-19 pandemic

	After COVID-19 outbreak prevalence rates, % (95% CI)	Sensitivity analysis of prevalence rates, % (95% CI)	Mortality, OR (95% CI)	Sensitivity analysis of mortality, OR (95% CI)
Stroke	**3.39 (1.50, 5.27)**	**3.60 (0.90, 6.29)**	**1.63 (1.23, 2.03)**	**2.47 (1.00, 3.95)**
Ischemic stroke	**1.36 (1.07, 1.64)**	**2.10 (0.90, 3.30)**	–	–
Hemorrhagic stroke	**0.49 (0.28, 0.69)**	**0.40 (0.20, 0.60)**	–	–
Epilepsy	5.36 (−0.60, 11,.32)	**1.81 (0.65, 2.96)**	**1.71 (1.00, 2.42)**	**1.71 (1.00, 2.42)**
Parkinson's disease	0.67 (−1.11, 2.45)	2.12 (−0.50, 4.73)	3.94 (−2.12, 10.01)	**2.63 (1.08, 4.18)**
Dementia	**6.41 (1.36, 11.46)**	**6.41 (1.36, 11.46)**	**1.90 (1.31, 2.48)**	2.50 (−1.05, 6.06)
Encephalitis	0.66 (−0.44, 1.77)	**0.20 (0.01, 0.39)**	–	
GBS	3.83 (−0.13, 7.80)	3.05 (−3.08, 9.18)	–	
Multiple sclerosis	**4.00 (2.50, 5.00)**	–	–	

pandemic is presented in Table 2. Funnel plots (online suppl. Material S3 Fig. 1) and Egger's test p values ($p < 0.001$) confirm the presence of publication bias. Thus, we recalculated the pooled prevalence rate using the trim-and-fill method. After addition of 33 missing studies, pooled prevalence rate estimate was decreased and nonsignificant (0.15%, 95% CI = −0.88–1.17) (online suppl. Material S3 Fig. 2).

Mortality of COVID-19 Patients with Neurological Disorders

Our meta-analysis showed that some neurological disorders were significantly associated with an increased risk of mortality in COVID-19 patients on the basis of a random-effects model (Fig. 3). In our meta-analysis after excluding duplicate data, stroke was associated with a higher mortality risk OR 1.63 (95% CI = 1.23 to 2.03, I^2 = 37.9%) in COVID-19 patients. In addition, the mortality risk of patients with comorbidities of COVID-19 was OR 1.71 (95% CI = 1.00 to 2.42, I^2 = 0.0%) for epilepsy and OR 1.90 (95% CI = 1.31 to 2.48, I^2 = 85.9%) for dementia (Table 2). However, Parkinson's disease was not statistically significant with an OR 3.94 (95% CI = −2.12 to 10.01, I^2 = 28.9%), and ischemic stroke, hemorrhagic stroke, encephalitis, GBS, and multiple sclerosis were not analyzed due to lack of data. When overall neurological disorders were combined, the summarized mortality risk was estimated at OR 1.79 (95% CI = 1.48 to 2.11, I^2 = 78.2%). Funnel plots (online suppl. Material S3 Fig. 3) and Egger's test p values ($p = 0.001$) confirm the presence of publication bias. The addition of the nine missing studies imputed after using the trim-and-fill method slightly reduced the effect size of the pooled estimate (OR 1.48, 95% CI = 1.09–1.87), although it maintained a significant positive relationship (online suppl. Material S3 Fig. 4).

ICU Care of COVID-19 Patients with Neurological Disorders

Among the included meta-analysis papers, there were two papers expressing ICU treatment odds ratio or relative risk ratio as adverse events other than mortality. ICU care of COVID-19 patients with stroke is described by Katzenschlager et al. [35], OR 5.88 (95% CI = 2.35–14.73, I^2 = 16.3%) and Siepmann et al. [23] RR 2.79 (95% CI = 1.83–4.24, I^2 = 35.3%) [23, 35]. Re-meta-analysis was not performed due to the small number of studies.

Effects of SARS-CoV-2 Original Strain versus Variant on Stroke

Stroke is the most common and studied neurological disorder in COVID-19 patients. We performed a subgroup analysis to determine whether the prevalence rates and mortality odds ratios were different when differentiating between the original strain and variants of SARS-CoV-2. According to the US Centers for Disease Control and Prevention (CDC), the high transmission period for the original strain of coronavirus was from December 1, 2020, to February 28, 2021. The high transmission period of the Delta variant was from July 15, 2021, to October 31, 2021. The Omicron variant was

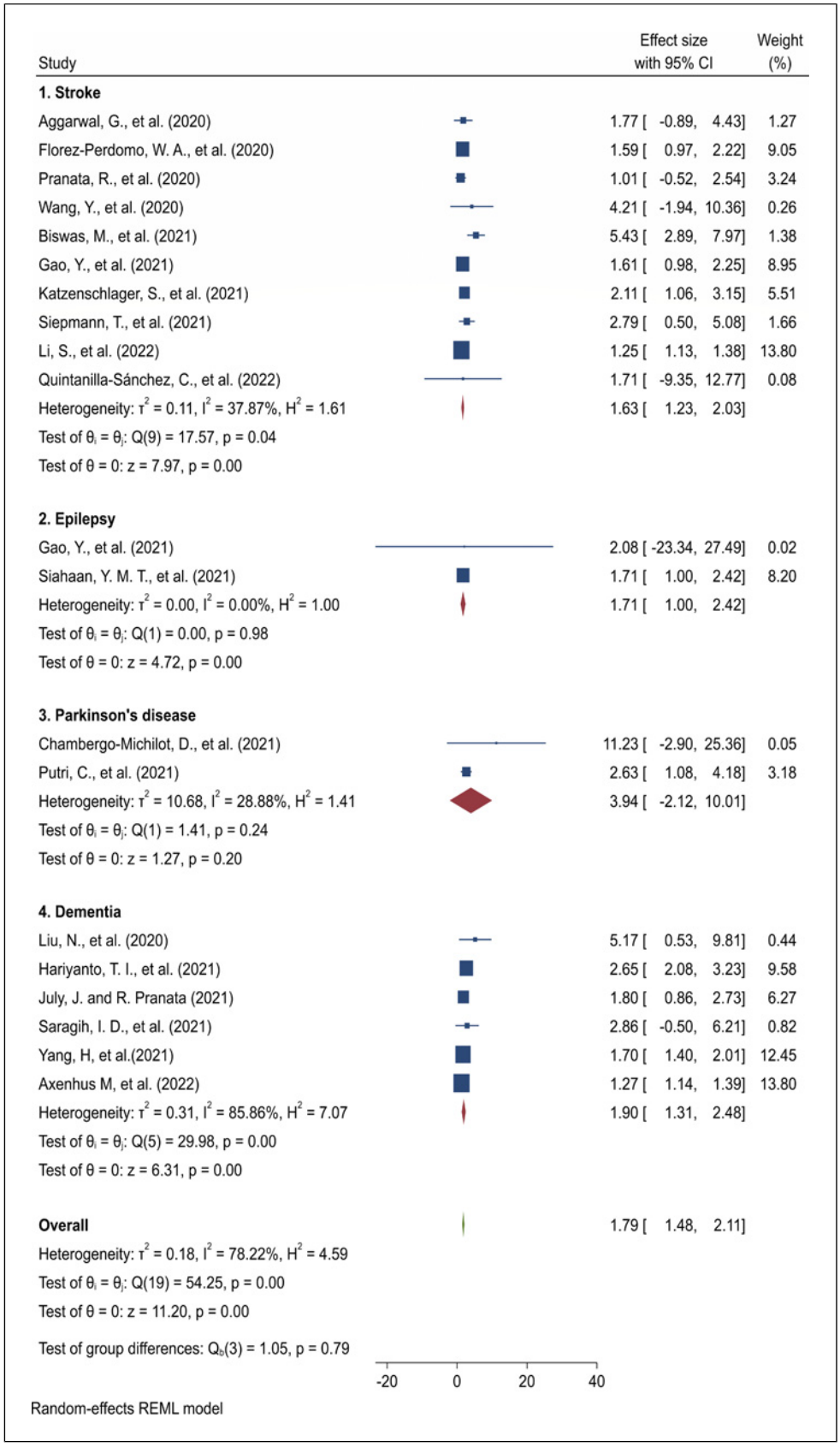

Fig. 3. Forest plot of studies regarding mortality odds ratio of neurological disorders in patients with COVID-19.

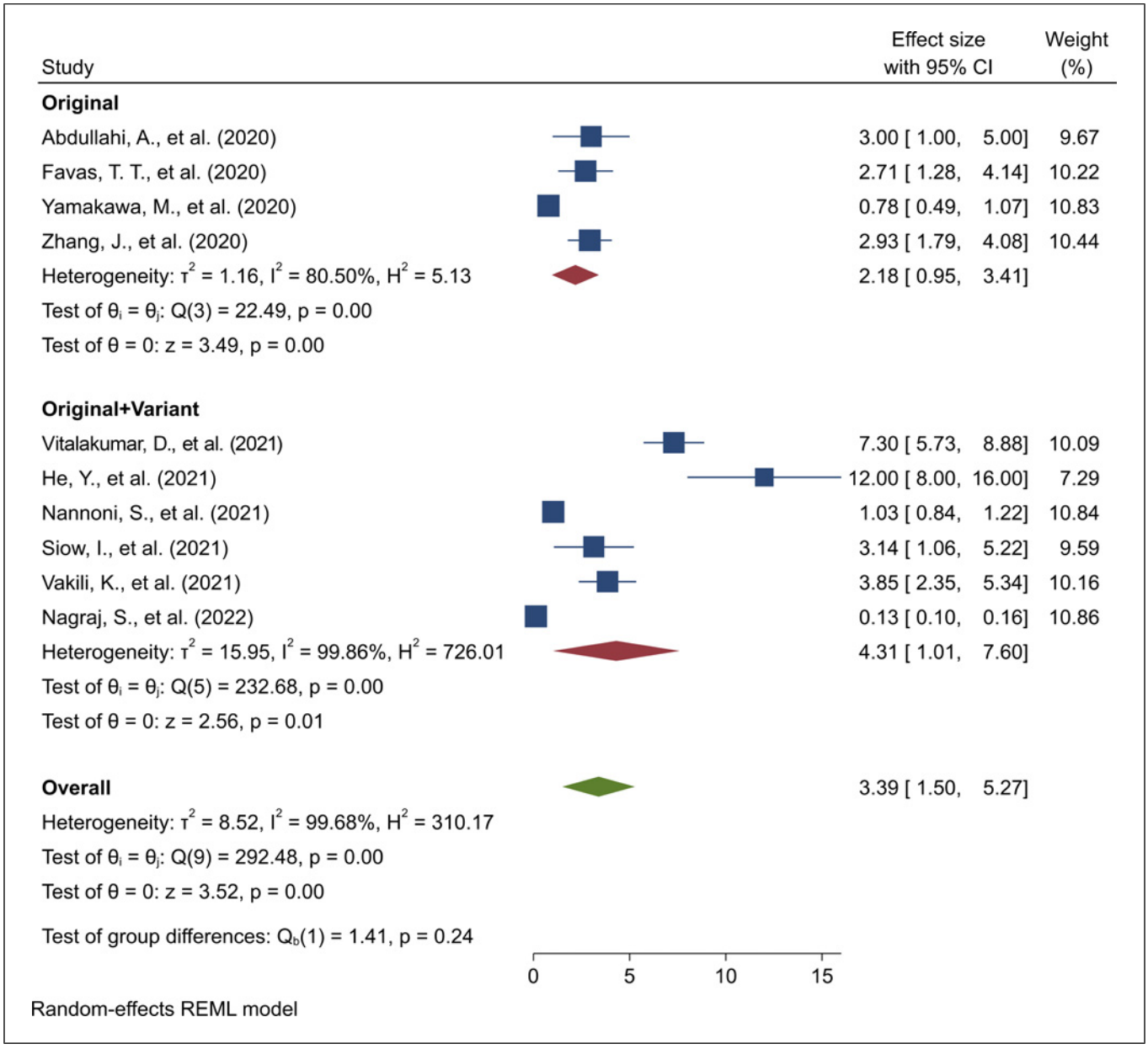

Fig. 4. Effects of SARS-CoV-2 original strain versus variant on stroke prevalence.

prevalent from December 19, 2021, to January 15, 2022 [53]. Therefore, studies published in 2020 mainly dealt with the original coronavirus strain; additionally, studies published in 2021 assumed that the original strain and variant were analyzed together. A subgroup analysis was conducted based on the year of issue to confirm whether there was a difference due to the SARS-CoV-2 variant. The stroke prevalence was 2.18% (95% CI = 0.95 to 3.41, I^2 = 80.5%) in the original strain and 4.31% (95% CI = 1.01 to 7.60, I^2 = 99.9%) when analyzed with variants (Fig. 4). Funnel plots (online suppl. Material S3 Fig. 5) and Egger's test p values ($p < 0.001$) confirm the presence of publication bias. The addition of the one missing study imputed after using the trim-and-fill method slightly reduced the effect size of the pooled estimate (2.72%, 95% CI = 0.35–5.10), although it maintained a significant positive relationship (online suppl. Material S3 Fig. 6).

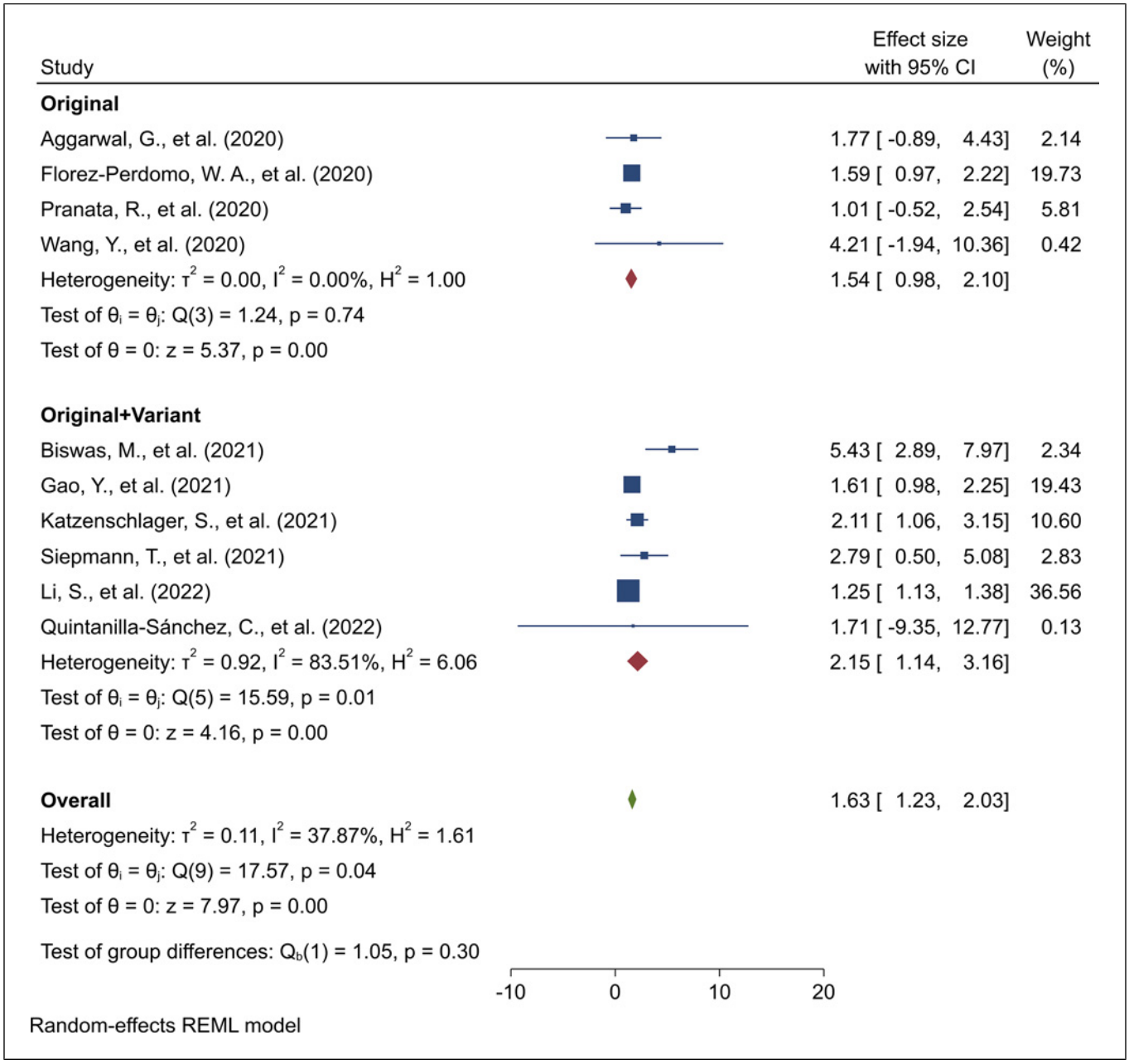

Fig. 5. Effects of SARS-CoV-2 original strain versus variant on stroke patient mortality odds ratio.

The mortality in patients with stroke comorbidity was OR 1.54 (95% CI = 0.98 to 2.10, I^2 = 0.0%) for the original strain and OR 2.15 (95% CI = 1.14 to 3.16, I^2 = 83.5%) when analyzed as mutations (Fig. 5). Funnel plots (online suppl. Material S3 Fig. 7) and Egger's test p values (p = 0.019) confirm the presence of publication bias. The addition of the three missing studies imputed after using the trim-and-fill method slightly reduced the effect size of the pooled estimate (OR 1.47, 95% CI = 1.10–1.84), although it maintained a significant positive relationship (online suppl. Material S3 Fig. 8). Prevalence and mortality in stroke patients tend to increase when the original strains of SARS-CoV-2 exist together with variant rather than when original strain is present alone.

Sensitivity Analysis

Sensitivity analysis on high- or moderate-quality studies based on AMSTAR-2 tool in the prevalence

rates showed an increasing trend: stroke (3.60%, 95% CI = 0.90–6.29), ischemic stroke (2.10%, 95% CI = 0.90–3.30), hemorrhagic stroke (0.40%, 95% CI = 0.20–0.60), epilepsy (1.81%, 95% CI = 0.65–2.96), encephalitis (0.20%, 95% CI = 0.01–0.39), Parkinson's disease (2.12%, 95% CI = −0.50–4.73), dementia (6.41%, 95% CI = 1.3- to 11.46), and gBS (3.06%, 95% CI = −3.08–9.18) (online suppl. Material S3 Fig. 9). Funnel plots (online suppl. Material S3 Fig. 10) and Egger's test p values ($p < 0.001$) confirm the presence of publication bias. The addition of the four missing studies imputed after using the trim-and-fill method slightly reduced the effect size of the pooled estimate (1.58%, 95% CI = 0.02–3.14), although it maintained a significant positive relationship (online suppl. Material S3 Fig. 11).

Sensitivity analysis of mortality odds ratios showed an increasing trend: stroke (OR 2.47, 95% CI = 1.00–3.95), epilepsy (OR 1.71, 95% CI = 1.00–2.42), Parkinson's disease (OR 2.63, 95% CI = 1.08–4.18), and dementia (OR 2.50, 95% CI = −1.05–6.06) (online suppl. Material S3 Fig. 12). Funnel plots (online suppl. Material S3 Fig. 13) and Egger's test p values ($p = 0.003$) confirm the presence of publication bias. The addition of the seven missing studies imputed after using the trim-and-fill method slightly reduced the effect size of the pooled estimate (OR 1.31, 95% CI = 0.58–2.05), although it maintained a significant positive relationship (online suppl. Material S3 Fig. 14).

Discussion

This study is the first umbrella review to synthesize current meta-analysis studies on the prevalence of neurological disorders after COVID-19. We estimated the summarized pooled prevalence rate and mortality odds ratio of neurological disorders in patients with COVID-19. Our findings suggest that the prevalence and mortality of stroke (including ischemic stroke and hemorrhagic stroke), epilepsy, dementia, and multiple sclerosis increased significantly during the COVID-19 pandemic. In addition, in the case of stroke patients, these results tended to be greater when the SARS-CoV-2 original strain coexisted with variant than when the SARS-CoV-2 original strain was present alone. In existing laboratory and clinical studies, COVID-19 is found to affect both the central nervous system (CNS) and the peripheral nervous system as well as thromboembolism, neuroinflammation, and neurodegenerative mechanisms.

Stroke

Cerebrovascular disease is the most commonly reported neurological disorder in people with COVID-19. COVID-19 triggers a systemic inflammatory response and increases the levels of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-2R [54]. This inflammatory response results in diffuse endothelial cell damage, abnormal hemodynamics, and uncontrolled platelet activation, leading to ischemic stroke with thrombotic complications [55]. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors and induces a cytokine storm, damaging the endothelial cells in arteries and veins. It raises blood pressure and damages cerebrovascular endothelial function, causing cerebral hemorrhage [56, 57]. Stroke and comorbidities of COVID-19 also increase disease severity and mortality. The first explanation is that stroke increases the risk of pulmonary complications such as pneumonia, which can have fatal consequences for people with COVID-19 [58]. Another possibility is that stroke is part of multi-organ failure and systemic coagulation disorders that increase mortality in COVID-19 patients [59].

Epilepsy

Studies have shown that an increase in the pro-inflammatory mediators, such as IL-1B and TNFα, triggers epileptic seizures [60]. In addition, the results of previous studies have shown that inflammatory factors and virus particles break the blood-brain barrier and subsequently penetrate the CNS and cause seizures due to brain damage [61, 62]. An increase in the frequency and severity of seizures causes hypoxemia [63]. Hypoxemia can be fatal in COVID-19 patients with impaired respiratory function. Therefore, people with epilepsy have an increased risk of severe hypoxemia and an increased risk of death from COVID-19 [64].

Dementia

COVID-19 and Alzheimer's disease are associated with ACE2 receptors, and interleukin-1 (IL-1), IL-6, cytoskeletal-associated protein 4 (CKAP4), galectin-9 (GAL-9 or Gal-9), and APOE4 alleles are known to share a common link, suggesting that COVID-19 may cause dementia [65]. In addition to the pathophysiological factors of both diseases, other factors also play a role. First, the majority of people with dementia are older and have other comorbidities that can increase the severity of the infection. Older people often have atypical symptoms, such as afebrile, non-respiratory symptoms and delirium. These atypical COVID-19 symptoms impede early diagnosis of the disease and increase disease spread and

mortality [66]. Second, due to cognitive decline, it is impossible to perform preventive measures such as wearing a mask and washing hands by oneself; care and support from caregivers are required, and the risk of developing COVID-19 increases in the absence of care [67].

Multiple Sclerosis

Multiple sclerosis is a chronic immune-mediated neurodegenerative disease that can be caused by genetic or environmental factors. The cytokine storm induced by SARS-CoV-2 infection disrupts glial cell interactions within the CNS and ultimately induces multiple sclerosis through microglia phagocytic function, hypoxia-mediated mitochondrial dysfunction, and neurodegeneration [68, 69]. The pre-existing immune status of people with multiple sclerosis is also relevant. Multiple sclerosis patients treated with B-cell-depleting drugs often develop serious infections, but previous studies believed there was no relationship between the type of drug a patient was taking and their susceptibility to COVID-19 [70]. However, hospitalization rates were 25% higher, suggesting a link between disease progression and death and COVID-19 [70, 71]. In this umbrella review, PD, encephalitis, and GBS did not yield statistically significant results, but several previous studies describe an association with COVID-19 [21, 72–75].

Parkinson's Disease

Biochemical pathways, such as those involving interactions with the brain dopaminergic system via dopamine decarboxylase, systemic inflammatory responses via ACE2 receptors, changes in the gut microbiome, oxidative stress, inflammation, and protein aggregation, are associated with Parkinson's disease and COVID-19. It shares the same pathway, suggesting that Parkinson's disease may develop after COVID-19 [74, 75]. PD also appears to be associated with an increased risk of severity and increased mortality from COVID-19 [21]. The first reason is that people with PD are older and have other comorbidities that can increase the severity of the infection. The second reason is "immune senescence." These reduced neutrophil phagocytosis, oxidative burst, macrophage chemotaxis, phagocytosis, number of peripheral naïve T and B cells which reduce ability to respond to new antigen [72]. Third, the COVID-19 pandemic will worsen the results by disrupting treatment, exercise, and social activities related to PD [73].

Encephalitis

There are three proposed mechanisms in the pathophysiology of COVID-19 that cause encephalitis: direct involvement of the nervous system, systemic inflammation, and molecular mimicry. First, direct invasion includes hematogenous invasion by disruption of the blood-brain barrier and trans-synaptic propagation. Synaptic propagation involves binding of SARS-CoV-2 to ACE 2 receptors on the cell membrane of peripheral neurons, entering the cell, and then traveling retrograde to the CNS, primarily via olfactory nerve epithelium [76]. A second mechanism explains that encephalitis is caused by a systemic inflammatory response that appears as a pro-inflammatory condition in cerebrospinal fluid analysis and serology [77]. A third proposed mechanism is molecular mimicry. The host antibodies and lymphocytes expand in response to SARS-CoV-2 infection. These immune molecules must be specific for SARS-CoV-2 antigens; however, some immune molecules are cross-reactive and can attack self-antigens [78]. Although the incidence of encephalitis in COVID-19 patients is relatively low (<1%), Siow et al. [78] found a significant increase in the incidence of critically ill patients, higher frequency of use of intensive care units and ventilators, and higher mortality rates.

Guillain-Barré Syndrome

Guillain-Barré syndrome is a malfunction of the body's immune system that attacks the peripheral nervous system, also known as acute inflammatory demyelination, and usually occurs after a respiratory/gastrointestinal infection. Viral particles have similar epitopes at the molecular level, which in turn activate autoreactive B or T cells, causing the immune system to produce antibodies that destroy the peripheral nervous system. Coronaviruses are also thought to cause this process [79, 80]. All types of GBS such as acute inflammatory demyelinating polyradiculoneuropathy, critical illness myopathy and neuropathy, peripheral polyneuropathies, acute motor axonal neuropathy, and acute motor sensory axonal neuropathy have been reported in patients with COVID-19 [81]. Magnetic resonance imaging of COVID-19 patients with GBS showed enhancement in the nerve root or in the facial or trigeminal nerve [82]. This suggests that demyelination is a major cause of the correlation between COVID-19 and GBS.

For the above reasons, SARS-CoV-2 binds to the ACE2 receptor, triggering a cytokine storm and systemic inflammatory response associated with various neurological diseases and increasing mortality [54, 56, 60, 65, 68,

74, 76, 78, 79]. However, further studies are needed to elucidate the exact mechanism.

Strengths and Limitations

One of the strengths of this umbrella review is that it provides the most comprehensive and up-to-date analysis with minimal overlapping data. Overlapping meta-analyses of the same subject are becoming a significant issue [83–85]. This is because, if the initial research data are repeatedly used, the 95% CI decreases and the effect size increases due to statistical problems, which may cause errors in reflecting the actual effect size. However, even in the recent meta-analysis, it is necessary to include all previous individual studies despite a broad exploratory strategy; however, there are some missing studies. Therefore, an umbrella review of meta-analysis was required. We overcame the previous problem of overlapping meta-analyses and performed a re-analysis by pooling all of the individual study datasets together with the analysis for each meta-analysis for a comprehensive review. Among the included meta-analyses, there were a minimum of 9.0% and a maximum of 100% of duplicate individual studies for each neurological disorder. A re-analysis after removing duplicate data reduced most effect sizes and slightly increased the 95% CIs. A second strength of this umbrella review is that it attempted to determine if there were any changes due to COVID-19 mutations in the subgroup analysis. A third strength of this umbrella review is that this most comprehensive and up-to-date analysis provides clinicians with an easy-to-understand relationship between COVID-19 and neurological disorders. This allows clinicians to treat patients with neurological disorders and a history of COVID-19 knowing that they have a different prognosis than other patients. It also suggests that the occurrence of neurological disorders in a large number of patients with a history of COVID-19 should be looked at more closely. Last strength of this umbrella review is that results of this paper also suggest that for epidemiologists, the presence or absence of a COVID-19 history can act as an important cofactor in the epidemiological investigation of neurological diseases.

This study has some limitations. First, only re-analyzable meta-analysis studies were included. Even studies that can be reanalyzed may contain errors in individual studies and potential confounders between individual studies. Second, there is a high degree of heterogeneity and publication bias in this study. This is due to differences in the number of patients, racial differences, disease severity, comorbidities, publication biases, and study methods. For publication bias, further analysis using the trim-and-fill method found that unpublished trials tended to reduce effect sizes. Therefore, these results should be interpreted with caution.

Third, in the subgroup analysis, the effect of the SARS-CoV-2 mutation was analyzed by considering the peak prevalence period of each mutation rather than targeting patients accurately classified by genome sequencing, and only stroke was analyzed due to the lack of literature. Therefore, the distinction between the SARS-CoV-2 original strain and variants is not clear, which weakens the degree of correlation. Fourth, the effect of vaccination was not considered. The impact of vaccines on the association between COVID-19 and neurological disease is unknown, as most of the included meta-analysis studies did not consider vaccination. Vaccination began in the USA on December 14, 2020, and has since started in several countries [86]. However, since vaccination varies by country and income, additional research considering these issues is needed. Fifth, in the qualitative evaluation of a total of 44 registered studies, 28 studies were evaluated at a low or very low level. Sensitivity analyses performed on the high-medium-quality study pool tended to increase effect sizes, so caution should be exercised in the interpretation of this study. Lastly, looking at the prevalence rate, we can see a correlation between COVID-19 and neurological disorders; however, the causal relationship is not clear. Based on these limitations, future studies should first identify which characteristics of COVID-19 patients are associated with neurological diseases, determine whether they change with SARS-CoV-2 mutations and vaccination, and clarify the pathophysiology through molecular-level studies.

Conclusions

Our study found an increase in the prevalence and mortality of several neurological diseases during the COVID-19 pandemic, suggesting an association between COVID-19 and neurological diseases. Although we are still in the midst of the COVID-19 pandemic, we must prepare for the long COVID syndrome and complications that may occur after the pandemic is over. Additional clinical and experimental studies in the future should provide strong evidence for the mechanism. This should help prevent the long-term neurological complications of COVID-19 and develop screening and treatment plans for potential patients.

Conflict of Interest Statement

The authors have declared that no competing interest exists.

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Authors' Contributions

Jong Mi Park, Jae Il Shin, and Yong Wook Kim developed the idea, designed the study, had full access to all data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Jong Mi Park and Wongi Woo ran the search strategy, selected articles, extracted data, and evaluated the quality of the literature. Jong Mi Park, Wongi Woo, Sang Chul Lee, Seoyeon Park, Dong Keon Yon, Seung Won Lee, Lee Smith, Ai Koyanagi, Jae Il Shin, and Yong Wook Kim wrote the manuscript. All the listed authors reviewed and approved the final manuscript.

Data Availability Statement

All the data relevant to the study are included in the article or uploaded as supplementary information. The data are available by accessing the published studies listed in Table 1 (see also [87]).

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