

# Neurological Symptoms, Comorbidities, and Complications of COVID-19: A Literature Review and Meta-Analysis of Observational Studies

Kimia Vakili<sup>a</sup> Mobina Fathi<sup>a</sup> Mohammadreza Hajiesmaeili<sup>b</sup> Melika Salari<sup>c</sup>  
Diksha Saluja<sup>d</sup> Abbas Tafakhori<sup>e</sup> Fatemeh Sayehmiri<sup>a</sup>  
Mostafa Rezaei-Tavirani<sup>f</sup>

<sup>a</sup>Student Research Committee, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; <sup>b</sup>Critical Care Quality Improvement Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran; <sup>c</sup>Department of Psychology, International Branch of Hormozgan Payame Noor University, Kish, Iran; <sup>d</sup>Department of Pharmacology, ISF College of Pharmacy, Moga, India; <sup>e</sup>Iranian Center of Neurological Science, Tehran University of Medical Sciences, Tehran, Iran; <sup>f</sup>Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Keywords

Coronavirus disease 2019 · Neurological symptoms · Headache · Olfactory dysfunction · Gustatory dysfunction · Cerebrovascular disease

## Abstract

**Background:** Recently, it has been shown that coronavirus disease 2019 (COVID-19), which has caused a pandemic since December 2019, can be accompanied by some neurological disorders. This study aimed to assess the prevalence of the most common neurological symptoms and comorbidities and systematically review the literature regarding the most prevalent neurological complications of COVID-19 infection. **Methods:** All relevant studies had been collected from PubMed, Scopus, Embase, and Web of Science databases. All extracted data were analyzed using Stata version 11.2. The  $I^2$  index was applied, and a random-effects model or a fixed-effects model was used for pooled estimation to assess the heterogeneity of studies. Furthermore, Egger and Beeg's tests were used to evaluate the publication bias. **Results:** Fifty-seven studies (26 observational and 31 case reports) were included (including 6,597 COVID-19 patients). The most prevalent general symptoms were fever, cough,

and dyspnea with 84.6% (95% CI: 75.3–92.1;  $I^2 = 98.7\%$ ), 61.3% (95% CI: 55.3–67.0;  $I^2 = 94.6\%$ ), and 34.2% (95% CI: 25.6–43.4;  $I^2 = 97.7\%$ ), respectively. Neurological symptoms observed among COVID-19 patients were fatigue, gustatory dysfunction, anorexia, olfactory dysfunction, headache, dizziness, and nausea with 42.9% (95% CI: 36.7–49.3;  $I^2 = 92.8\%$ ), 35.4% (95% CI: 11.2–64.4;  $I^2 = 99.2\%$ ), 28.9% (95% CI: 19.9–38.8;  $I^2 = 96.3\%$ ), 25.3% (95% CI: 1.6–63.4;  $I^2 = 99.6\%$ ), 10.1% (95% CI: 2.7–21.0;  $I^2 = 99.1\%$ ), 6.7% (95% CI: 3.7–10.5;  $I^2 = 87.5\%$ ), and 5.9% (95% CI: 3.1–9.5;  $I^2 = 94.5\%$ ). The most prevalent neurological comorbidity in COVID-19 was cerebrovascular disease with 4.3% (95% CI: 2.7–6.3;  $I^2 = 78.7\%$ ). **Conclusion:** The most prevalent neurological manifestations of COVID-19 include fatigue, gustatory dysfunction, anorexia, olfactory dysfunction, headache, dizziness, and nausea. Cerebrovascular disorders can either act as a risk factor for poorer prognosis in COVID-19 patients or occur as a critical complication in these patients. Guillain-Barre syndrome, encephalitis, and meningitis have also been reported as complications of COVID-19.

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Kimia Vakili and Mobina Fathi contributed equally to the manuscript.

## Introduction

The novel coronavirus disease 2019 (COVID-19) outbreak had infected 6,663,304 cases and caused 392,802 deaths worldwide by June 6, 2020 [1]. As the responsible virus, coronavirus 2 (SARS-CoV-2) is a highly transmissible pathogen. The most prevalent symptoms of COVID-19 are respiratory failure, fever, and dry cough [2]. Although coronaviruses do not usually cause neurological diseases, several reports indicate that the new virus can cause direct or indirect central nervous system (CNS) infections [3–5]. Moreover, several reports have shown the possible involvements of the CNS [6–8] or peripheral nervous system (PNS) [9–11], and multiple studies have revealed the presence of some neurologic symptoms [12–14]. These symptoms can be categorized into several groups, including acute cerebrovascular disease, intracranial infection (such as headache, epilepsy, and consciousness impairment), PNS involvement (such as olfactory and gustatory impairment), and neuromuscular symptoms (fatigue, myalgia, muscle cramp, or increased muscle enzyme levels). Some patients may also experience sensory abnormalities, sphincter impairment, and neuralgia [15].

The structure of the viral capsid of SARS-CoV-2 involves a receptor-binding domain, which specifically recognizes the human angiotensin-converting enzyme-2 receptor [16]. ACE2, as an entrance key for SARS-CoV-2, has an approximately ubiquitous expression in different human organs, including lung parenchyma, airway epithelia, nasal mucosa, gastrointestinal tract, urinary tract, reproductive organs, lymphoid tissues, vascular endothelia, and brain [17]. Under normal conditions, the ACE2 expression level in the brain is low; therefore, ACE2 alone does not seem enough to make brain cells susceptible to infection [18].

In a study conducted by Li et al. [19], potential neuroinvasion routes of SARS-CoV-2 were introduced based on data of previous respiratory viruses, with a neuroinvasive propensity and neurological symptoms of COVID-19. Two major anatomical infection routes are discovered through which SARS-CoV-2 can enter the CNS, a neural pathway through the PNS and a fluid body pathway through blood, lymph, and CSF.

1. Peripheral nerves route: contagion via droplets is almost the main transmission route of SARS-CoV-2 (close contact can also be considered an essential route of infection); therefore, the mechanism of olfactory loss and gustatory impairment may be clarified by investigating potential intranasal and oral routes of

SARS-CoV-2 to enter the CNS. In this pathway, the virus enters a nerve terminal and replicates, and then finds its route back to the CNS retrogradely [19]. Besides, SARS-CoV-2 can adhere to the nasal mucosa and directly disturb olfactory sensory neurons and olfactory epithelium by pro-inflammatory cytokines [20].

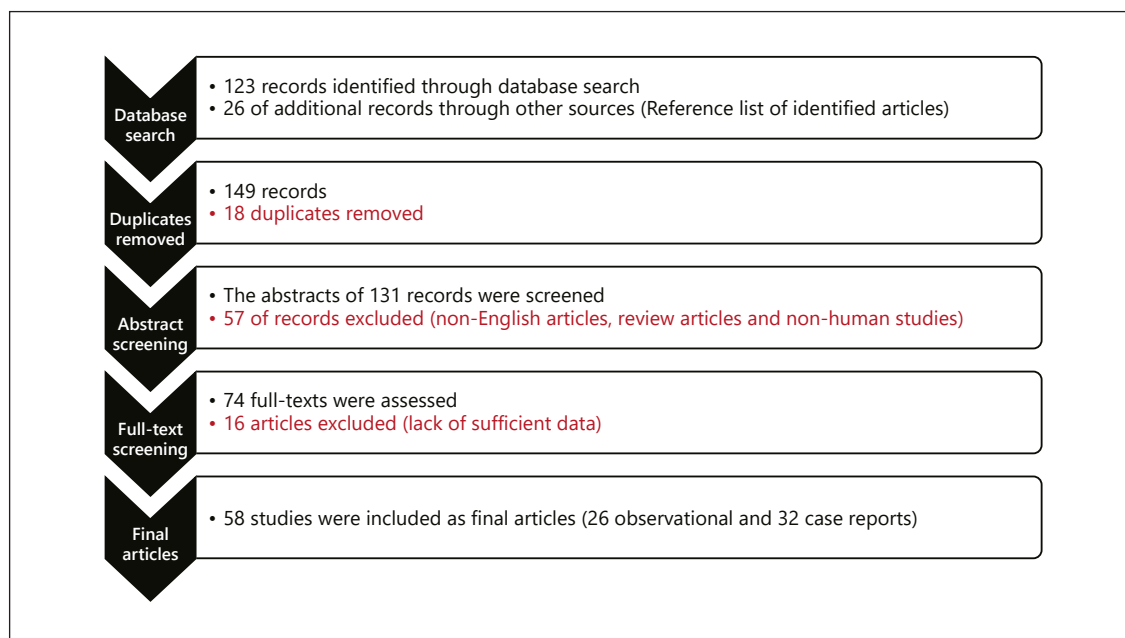
2. Hematogenous route: in a hematogenous invasion, the viruses disturb the endothelial cells in the blood-brain barrier or the blood-cerebrospinal fluid barrier and then find their way toward the CNS. In a transgenic mouse model expressing human ACE2 infected by SARS-CoV, the olfactory nerve was the main neuroinvasion route for the virus; however, some infected sites were observed in their brain indirectly connected with the olfactory bulb. Consequently, non-neuronal routes of viral infection, such as the hematogenous route, were suggested [21].
3. Lymphatic drainage of the cerebrospinal fluid route: Pathological conditions, such as viral infections, can destroy the lymphatic drainage system of the brain [22], leading to brain edema and alterations in brain structure and function, and ultimately leading to viral overflow into the perivascular space and CSF. This phenomenon may result in CNS symptoms in critical COVID-19 patients [23].

Another relationship between neurologic diseases and COVID-19 is about neurologic diseases that can coexist with COVID-19 as an underlying condition. Initial reports have revealed that cerebrovascular disease might play a substantial role in infected patients. They proposed that comorbid cerebrovascular disease, as a clinical significance, can lead to a worse prognosis in COVID-19 patients [24]. The present study aimed to investigate the relationship between COVID-19 infection and neurologic diseases by reviewing the most recent articles conducted on neurologic manifestations in COVID-19 infection, neurologic comorbidities in COVID-19 patients, and neuroinvasion mechanisms of SARS-CoV-2. The related data are analyzed to get a more quantitative perspective on these topics.

## Methods

### Study Selection

A Web search was conducted in PubMed, Scopus, Embase, and Web of Science databases to find eligible studies (cross-sectional, case-control, and case report) published until 17 April 2020. Two of the authors conducted the search process independently to promote accuracy. Neurological symptoms, neurologic complications, and CNS-related comorbidities in COVID-19 patients were explored using search queries, including ([Neuro-] OR [brain]) AND (COVID-19), (Neurological symptoms)



**Fig. 1.** Study flow diagram.

AND (COVID-19), and (Neurological complications) AND (COVID-19). At first, eligible studies were selected based on article titles. Subsequently, the reference lists of all related reviews (narrative and systematic) were searched to find more related articles.

#### *Inclusion and Exclusion Criteria*

All relevant data about neurological symptoms, neurologic complications, and CNS-related comorbidities in COVID-19 were screened to include in the final analysis. Other exclusion criteria were non-human studies, systematic review and meta-analysis studies, non-English publications, and duplicate publications.

#### *Data Extraction*

All data, including general information about the study and research team (the name of the first author, date of publication, location of publication, sample size), demographic data about the subjects (age and gender), the prevalence of general symptoms (fever, cough, and dyspnea), neurological symptoms (headache, nausea, dizziness, fatigue, Olfactory dysfunction, gustatory dysfunction, and anorexia), neurological complications (seizure, status epilepticus, Guillain-Barre syndrome [GBS], meningitis, and encephalitis), and CNS-related comorbidities (cerebrovascular disease and other nervous system diseases), were extracted from all included studies.

#### *Statistical Analysis*

The effect size was the prevalence of neurological symptoms and complications and CNS-related comorbidities; therefore, the variance was estimated using the binomial distribution. Furthermore, the average weight value was assigned to each study to combine the prevalence of various studies. The heterogeneity was as-

sessed utilizing  $Q$  statistics and  $I^2$  index ( $\alpha$  significance level was  $>10\%$ ). For heterogeneous studies, the random-effects model was applied when  $p$  was near 0 or meta prop command in STATA was used for the stability of variance and after the calculation of Freeman-Tukey Double Arcsine Transformation pool estimation for this proportion [25]. STATA version 11.2 was used for data analysis. Ethical approval was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics code: IR.SBMU.RETECH.REC.1399.082).

#### *Publication Bias*

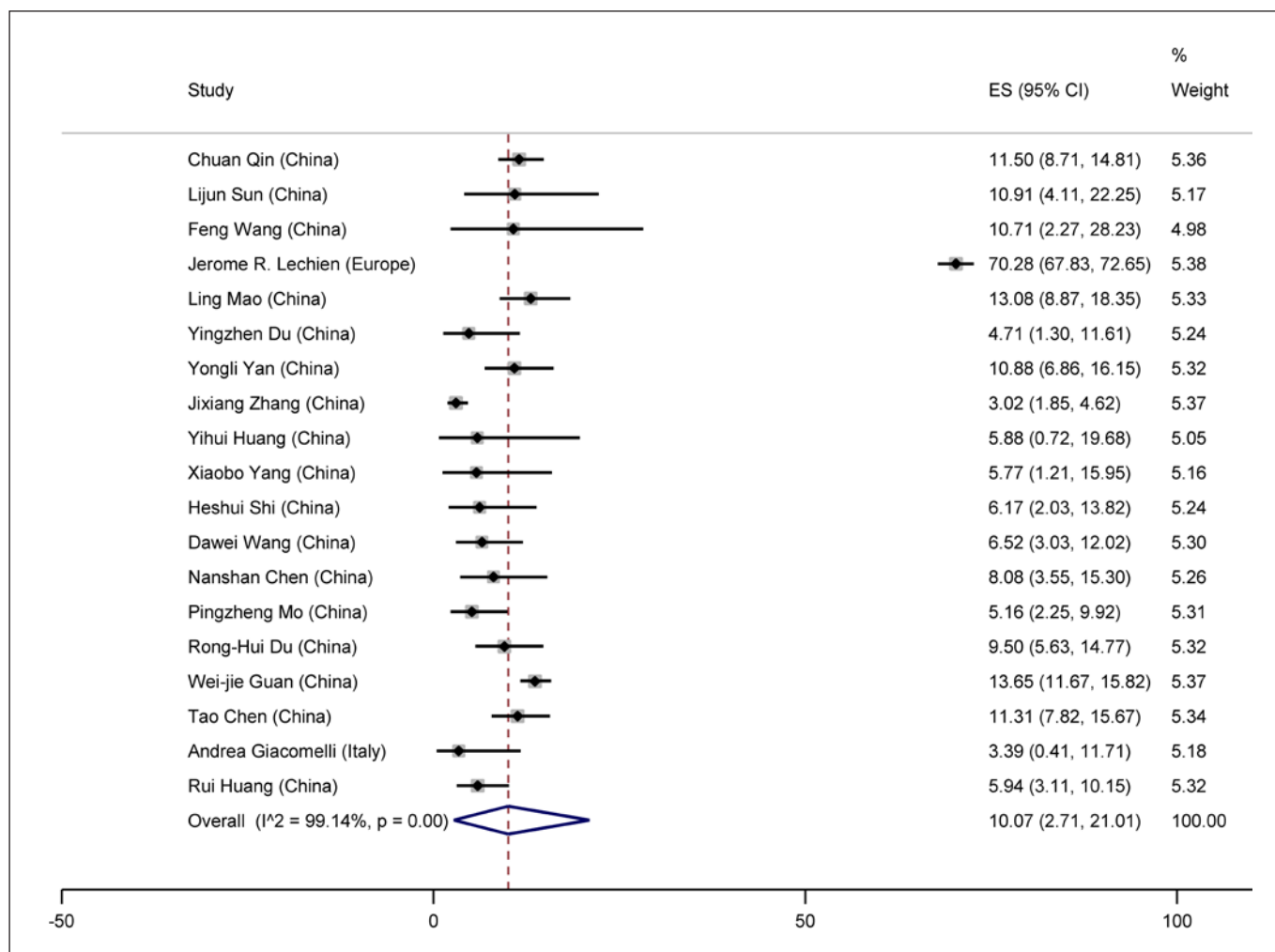
Publication bias was graphically detected by the Funnel plot. This funnel plot is a scatter plot with 2 variates ( $x, y$ ), evaluating the study effect size estimates against its sample size. A linear regression analysis, including both intercept and slope parameters, was conducted for publication bias. It was calculated based on the following equation:

$$y_i = \alpha + \beta_{xi} + \varepsilon_i$$

$i = 1, \dots, r$  ( $r$  = the number of studies),  $y_i$  = standardized estimate,  $x_i$  = precision of studies, and  $\varepsilon_i$  = error terms.

#### *Quality Assessment*

The Newcastle-Ottawa Scale was employed to evaluate the quality of each included study [26] utilizing 8 assessment items, including selection, comparability, and outcome, based on the Ottawa checklist for cross-sectional studies. Based on the Newcastle-Ottawa Scale score standards, studies can be divided into 3 groups, including high quality (scores  $\geq 7$ ), moderate quality (scores of 5–6), and low quality (scores of 0–4) the table is accessible in Appendix; see [www.karger.com/doi/10.1159/000516258](http://www.karger.com/doi/10.1159/000516258) for all online suppl. material).



**Fig. 2.** Forest plot of the prevalence of headache in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random-effects model). COVID-19, coronavirus disease 2019.

## Results

### Study Selection

This study has been conducted based on the PRISMA checklist [27]. One hundred twenty-three studies were identified after the initial database exploration. Moreover, 26 more studies were obtained from other sources (mostly by investigating a reference list of identified studies). From these 149 studies, 18 studies were duplicated and were excluded. In the next step, 57 other articles were excluded after the abstract screening. Subsequently, the full-texts of 74 remaining articles were reviewed, in which 16 articles were excluded due to the lack of appropriate data. Finally, 58 articles published from February 2020

until April 2020, including 26 observational studies and 32 case reports, were included for final analysis (Fig. 1; Table 1).

### Demographic Characteristics of Subjects

Pooled together, 6,597 COVID-19 confirmed patients were included in the present study. The mean age of patients were 54.2 (95% CI: 48.4–58.0;  $I^2 = 99.7\%$ ). Furthermore, 55% (95% CI: 50–60;  $I^2 = 100.0\%$ ) of the patients were male.

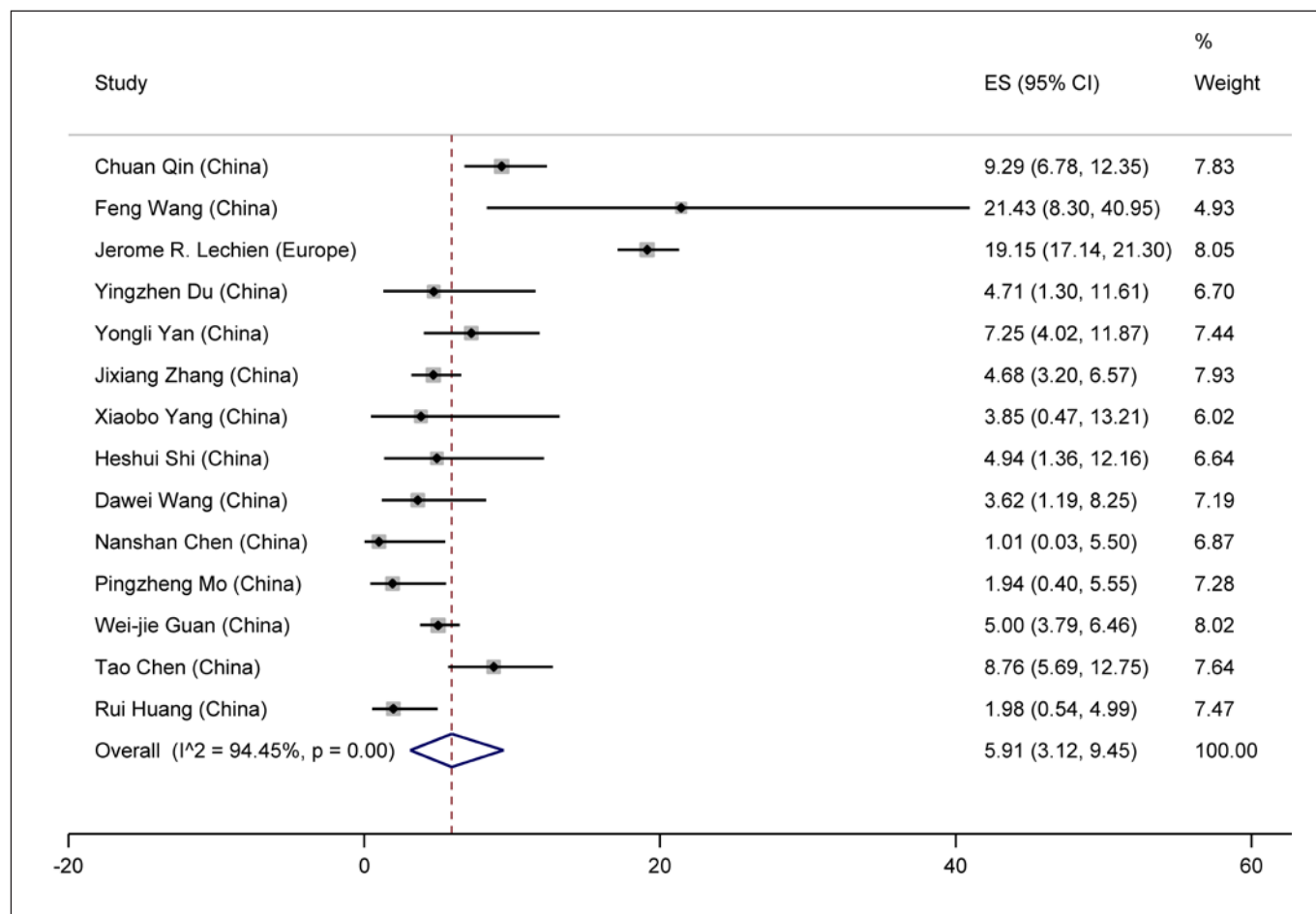
### General Symptoms

The most prevalent general symptoms observed among COVID-19 patients were fever (4,093/5,991),

**Table 1.** Baseline characteristics of included studies

Study [ref.]	Place	Patients, n			Mean age (SD)	General symptoms, %			Neurological symptoms, %					Comorbidities, %				
		all	male	female		fever	cough	dyspnea	fatigue	gustatory dys-function	anorexia	olfactory dys-function	haedache	dizziness	nausea	all	nervous system diseases	cerebro-vascular disease
Huang et al. [1]	China	34	14	20	56.24 (17.14)	94.1	50	14.7	64.7					5.9				
Yang et al. [2]	China	52	35	17	59.7 (13.30)	98	77	63.5	11.5					6		4		
Yang et al. [3]	China	92	49	43	69.8 (14.50)											70.7	10.9	
Wu et al. [4]	China	201	128	73		93.5	81.1	39.8	32.3								3.5	
Mo et al. [5]	China	155	86	69		81.3	62.6	2.4	73.2		31.7			9.8	2.4	3.7	4.5	
Mao et al. [6]	China	214	87	127	52.7 (15.50)	61.7	50			5.6	31.8	5.1	13.1	16.8		38.8		
Cao et al. [7]	China	199	120	179		91.5											6.5	
Shi et al. [8]	China	81	42	39	49.5 (11)	73	59	42			1			6	2	5	26	7
Wang et al. [9]	China	18	10	8		94.4	55.6	22.2						5.6		5.6		
Liu et al. [10]	China	109	59	50		82.6	61.5		56.9								5.5	
Du et al. [11]	China	179	97	82	57.6 (13.70)	98.9	81.6	49.7	39.7				9.5					
Du et al. [12]	China	85	62	23	65.8 (14.20)	91.8	22.4	70.6	58.8		56.5			4.7		4.7	68.2	8.2
Guan et al. [13]	China	1,099	637	459		43.8	67.8	18.7	38.1					13.6		5	23.7	1.4
Wang et al. [14]	China	138	75	63		98.6	59.4	31.2	69.6		39.9			6.5	9.4	3.6	46.4	5.1
Giacomelli et al. [15]	Italy	59	40	19		72.8	37.3	25.4		10.2		5.1	3.4					
Chen et al. [16]	China	99	67	32	55.5 (13.10)	83	82	31						8		1	1	
Lechien et al. [17]	Europe	417	154	263	36.9 (11.40)	45	79		58	88.8	52	85.6	45			21		
Yan et al. [18]	China	193	114	79		89.6	69.9	59.6	52.3		35.2			10.9		7.3	48.7	4.1
Qin et al. [19]	China	452	235	217		92.6	33.3	50.8	46.4		21			11.4	8.1	9.2	44	2.4
Sun et al. [20]	China	55	31	24		81.8	47.3	5.5	25.5		12.7			10.9	10.9		32.7	
Beltrán-Corbellini et al. [21]	Spain	79	48	31	61.6 (17.40)					35.44		31.65						
Wang et al. [22]	China	28	21	7	68.6 (9.00)	92.9	82.1	57.1	64.3		57.1			10.7		21.4	60.7	14.3
Chen et al. [23]	China	274	171	103		91	68	44	5		24			11	8	9	49	1
Lechien et al. [24]	Europe	1,420	458	962	39.17 (12.09)	45.4	63.2	49.1		54.2	45.7	84.37	70.3			19.2	0.9	
Huang et al. [25]	China	202	116	86		77.2	59.4	9.4	21.8					5.9		2	27.2	1.5
Zhang et al. [26]	China	663	321	342	55.6	79.5	61.8	24.3	31.4					3	3.5	4.7		

<sup>1</sup>Huang Y, et al. Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: A retrospective single center analysis. *Travel medicine and infectious disease*. 2020. <sup>2</sup>Yang X, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*. 2020. <sup>3</sup>Yang F, et al. Analysis of 92 deceased patients with COVID-19. *Journal of medical virology*. 2020. <sup>4</sup>Wu C, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA internal medicine*. 2020. <sup>5</sup>Mo P, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clinical Infectious Diseases*. 2020. <sup>6</sup>Mao L, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA neurology*. 2020. <sup>7</sup>Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*. 2020. <sup>8</sup>Shi H, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *The Lancet Infectious Diseases*. 2020. <sup>9</sup>Wang L, et al. The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China. *European Respiratory Journal*. 2020. 55(4). <sup>10</sup>Liu Y, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. *MedRxiv*. 2020. <sup>11</sup>Du R-H, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *European Respiratory Journal*. 2020;55(5). <sup>12</sup>Du Y, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. *American journal of respiratory and critical care medicine*. 2020;201(11):1372–1379. <sup>13</sup>Guan W-j, et al. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*. 2020;382(18):1708–1720. <sup>14</sup>Wang D, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. <sup>15</sup>Giacomelli A, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clinical Infectious Diseases*. 2020. <sup>16</sup>Chen N, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507–513. <sup>17</sup>Lechien JR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *European Archives of Oto-Rhino-Laryngology*. 2020;1–11. <sup>18</sup>Yan Y, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. *BMJ Open Diabetes Research and Care*. 2020;8(1):e001343. <sup>19</sup>Qin C, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical Infectious Diseases*. 2020. <sup>20</sup>Sun L, et al. Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China. *Journal of Medical Virology*. 2020. <sup>21</sup>Beltrán-Corbellini A, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. *European journal of neurology*. 2020. <sup>22</sup>Wang F, et al. Clinical characteristics of 28 patients with diabetes and COVID-19 in Wuhan, China. *Endocrine Practice*. 2020. <sup>23</sup>Chen T, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368. <sup>24</sup>Lechien JR, et al. Clinical and epidemiological characteristics of 1,420 European patients with mild-to-moderate coronavirus disease 2019. *Journal of internal medicine*. 2020. <sup>25</sup>Huang R, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: A retrospective, multicenter study. *PLOS Neglected Tropical Diseases*. 2020;14(5):e0008280. <sup>26</sup>Zhang J, et al. Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China. *Clinical Microbiology and Infection*. 2020.



**Fig. 3.** Forest plot of the prevalence of nausea in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random-effects model). COVID-19, coronavirus disease 2019.

cough (3,582/5,792), and dyspnea (1,960/5,469) with 84.6% (95% CI: 75.3–92.1;  $I^2 = 98.7\%$ ), 61.3% (95% CI: 55.3–67.0;  $I^2 = 94.6\%$ ), and 34.2% (95% CI: 25.6–43.4;  $I^2 = 97.7\%$ ), respectively.

#### Neurological Symptoms

Neurological symptoms in COVID-19 patients were fatigue (1,583/3,919), gustatory dysfunction (1,158/2,189), anorexia (1,100/3,095), olfactory dysfunction (1,594/2,189), headache (1,379/5,482), dizziness (140/2,032), and nausea (467/4,941) with 42.9% (95% CI: 36.7–49.3;  $I^2 = 92.8\%$ ), 35.4% (95% CI: 11.2–64.4;  $I^2 = 99.2\%$ ), 28.9% (95% CI: 19.9–38.8;  $I^2 = 96.3\%$ ), 25.3% (95% CI: 1.6–63.4;  $I^2 = 99.6\%$ ), 10.1% (95% CI: 2.7–21.0;  $I^2 = 99.1\%$ ), 6.7% (95% CI: 3.7–10.5;  $I^2 = 87.5\%$ ), and 5.9%

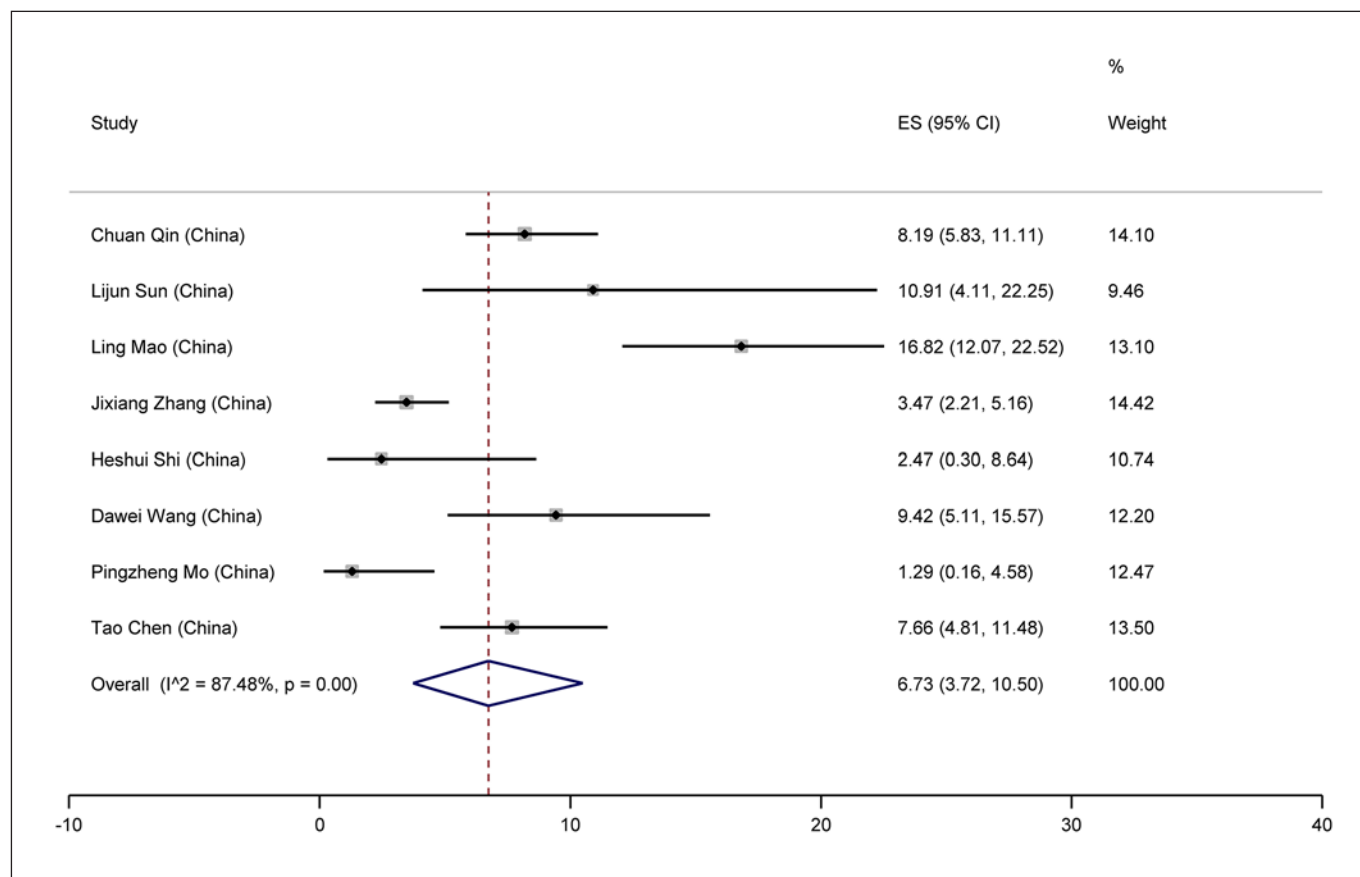
(95% CI: 3.1–9.5;  $I^2 = 94.5\%$ ), respectively (Fig. 2–8; Table 2).

#### Neurological Complications

Neurological complications of COVID-19 have been mostly reported in the case report articles; therefore, the data were extracted from these articles and pooled together, as presented in Table 3.

#### CNS-Related Comorbidities

A great number of COVID-19 patients had comorbid conditions (1,070/2,913) 43.9% (95% CI: 35.1–53.1;  $I^2 = 95.2\%$ ). The prevalence of underlying nervous system disease among these patients was (21/1,720) 1.5% (95% CI: 0.3–3.6;  $I^2 = 69.6\%$ ), while the most prevalent neurologi-



**Fig. 4.** Forest Plot of the prevalence of dizziness in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random-effects model). COVID-19, coronavirus disease 2019.

cal comorbidity was cerebrovascular disease (101/3,107) 4.3% (95% CI: 2.7–6.3;  $I^2 = 78.7\%$ ) (Fig. 9).

#### Publication Bias

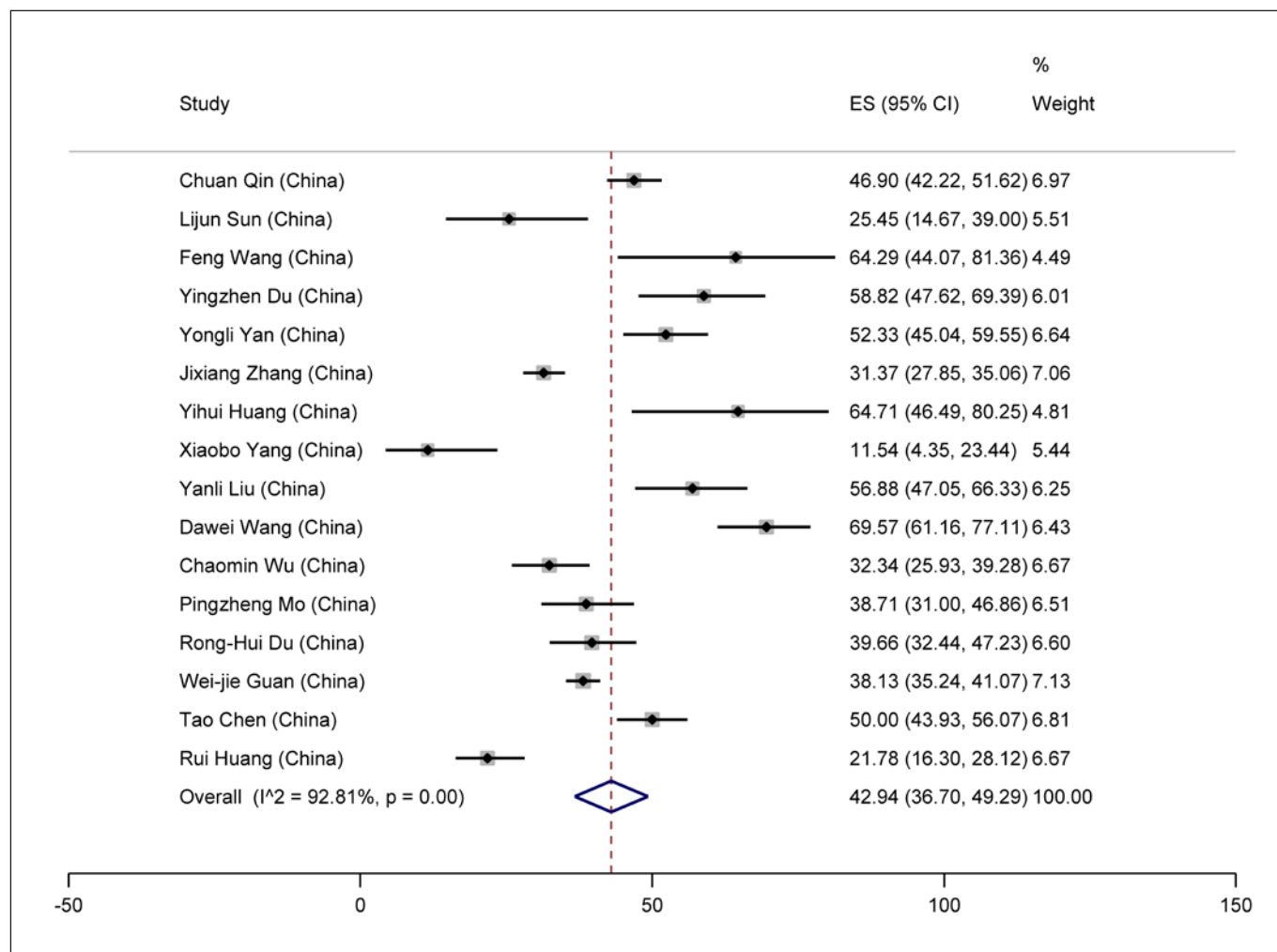
Figure 10 demonstrates the Begg's funnel plot for related studies. The plot interpretation revealed a sign of publication bias ( $p = 0.03$ ), indicating that both negative and positive results have not been published (Fig. 10).

#### Discussion

COVID-19 has rapidly spread throughout the world [28]. A wide range of symptoms and signs of COVID-19, including fever, cough, dyspnea, fatigue, diarrhea, and vomiting, have been reported in previous studies. However, some COVID-19 patients are asymptomatic [29].

The incubation period of this disease is approximately between 2 and 11 days, and its mortality rate is about 2–4% [30, 31]. In this study, the calculated prevalence of the most common general symptoms of this disease, including fever, cough, and dyspnea, was 84.6% (95% CI: 75.3–92.1;  $I^2 = 98.7\%$ ), 61.3% (95% CI: 55.3–67.0;  $I^2 = 94.6\%$ ), and 34.2% (95% CI: 25.6–43.4;  $I^2 = 97.7\%$ ), respectively, which is in good agreement with previous measures [32].

This disease can cause acute respiratory distress syndrome in severe cases, which can be a lethal condition. Other aspects of this disease, such as cardiovascular manifestations and renal complications, are being identified every day. Although most articles imply that COVID-19 mainly affects the respiratory and cardiovascular system, growing pieces of evidence are showing that neurological symptoms (such as fatigue, headache, dizziness,



**Fig. 5.** Forest plot of the prevalence of fatigue in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random-effects model). COVID-19, coronavirus disease 2019.

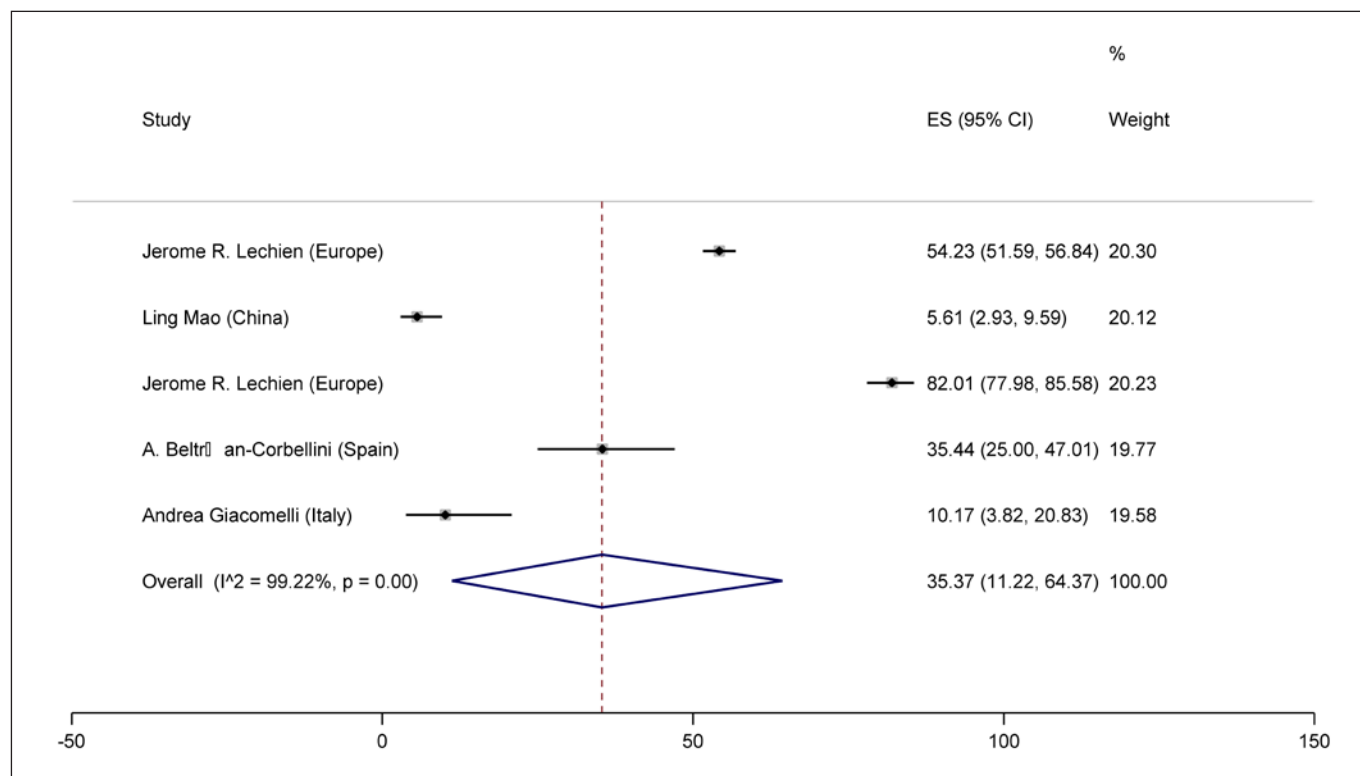
hypogeusia/hyposmia, and impaired consciousness) and complications (such as [Meningo]-encephalopathy, cerebrovascular diseases, PNS disorders, and skeletal muscle injuries) [12, 33] are likely to occur in COVID-19 patients.

As mentioned before, coronaviruses are mostly known for upper respiratory tract infections; however, it has recently been observed that they can be correlated with inflammatory neurological diseases [34]. For this purpose, many animal studies have been conducted. Murray et al. [35] revealed that oligodendrocyte lysis and further demyelination in the CNS could occur during the acute phase in primate brains due to murine coronavirus repli-

cation. Besides,  $Il-1\beta$ ,  $Il-6$ , and  $TNF-\alpha$  levels increased in the spinal cord of infected subjects. Butler et al. [36] showed that intranasal infection with HCoV-OC43 could lead to retrograde dissemination of the virus and infect the brainstem and pyriform cortex. According to these findings, the risk of neural involvement by SARS-CoV-2 should not be overlooked.

Various neurotropic mechanisms, such as ACE2 receptor expression in neural tissue, are designated for COVID-19. Following previous reports, ACE2 receptors are expressed in both glial cells and neurons. On the other hand, SARS-CoV-2 has around 20-fold higher receptor affinity than ACE2 receptors than SARS-CoV [37], indi-

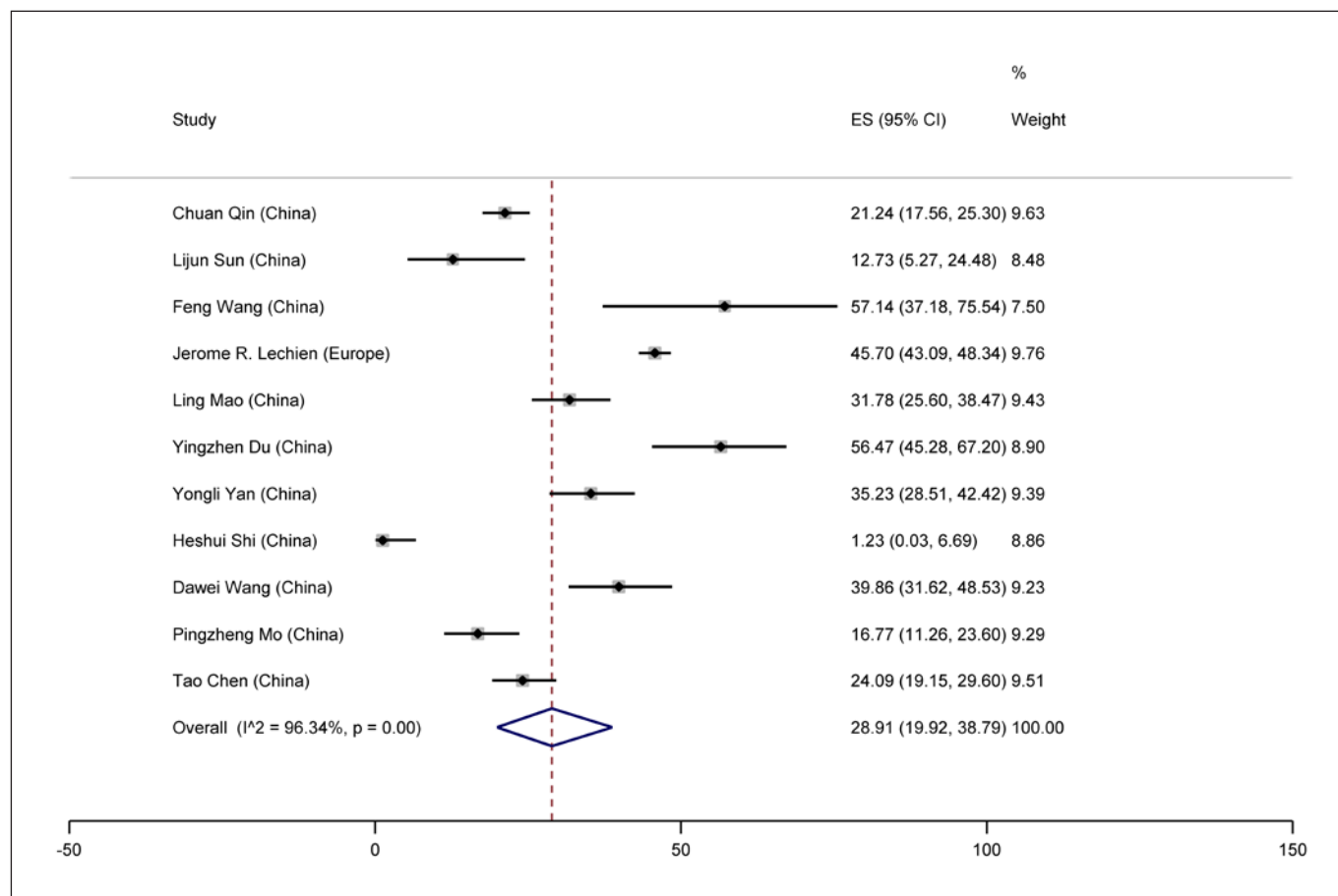




**Fig. 6.** Forest plot of the prevalence of gustatory dysfunction in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random-effects model). COVID-19, coronavirus disease 2019.

**Table 2.** Statistical analysis of reviewed studies

	Study, <i>n</i>	Patients, <i>n</i>	Prevalence, % (95% CI)	$I^2$ , %	<i>p</i> value for heterogeneity
<i>Gender</i>					
Female	26	3,277/6,694	45 (40–50)	100	0.00
Male	26	3,417/6,694	55 (50–60)	100	0.00
<i>General symptoms</i>					
Fever	24	4,093/5,991	84.61 (75.31–92.07)	98.67	0.00
Cough	23	3,582/5,792	61.26 (55.32–67.04)	94.57	0.00
Dyspnea	20	1,960/5,496	34.18 (25.56–43.35)	97.70	0.00
<i>Neurological symptoms</i>					
Fatigue	16	1,583/3,919	42.94 (36.70–49.29)	92.81	0.00
Gustatory dysfunction	5	1,158/2,189	35.37 (11.22–64.37)	99.22	0.00
Anorexia	11	1,100/3,095	28.91 (19.92–38.79)	96.34	0.00
Olfactory dysfunction	5	1,594/2,189	25.34 (1.58–63.41)	99.57	0.00
Headache	19	1,379/5,482	10.07 (2.71–21.01)	99.14	0.00
Dizziness	8	140/2,032	6.73 (3.72–10.50)	87.48	0.00
Nausea	14	467/4,941	5.91 (3.12–9.45)	94.45	0.00
<i>Comorbidities</i>					
Nervous system diseases	12	1,070/2,913	43.98 (35.06–53.11)	95.23	0.00
Cerebrovascular disease	3	21/1,720	1.52 (0.25–3.62)	69.61	0.00
	13	101/3,107	4.28 (2.65–6.25)	78.73	0.00



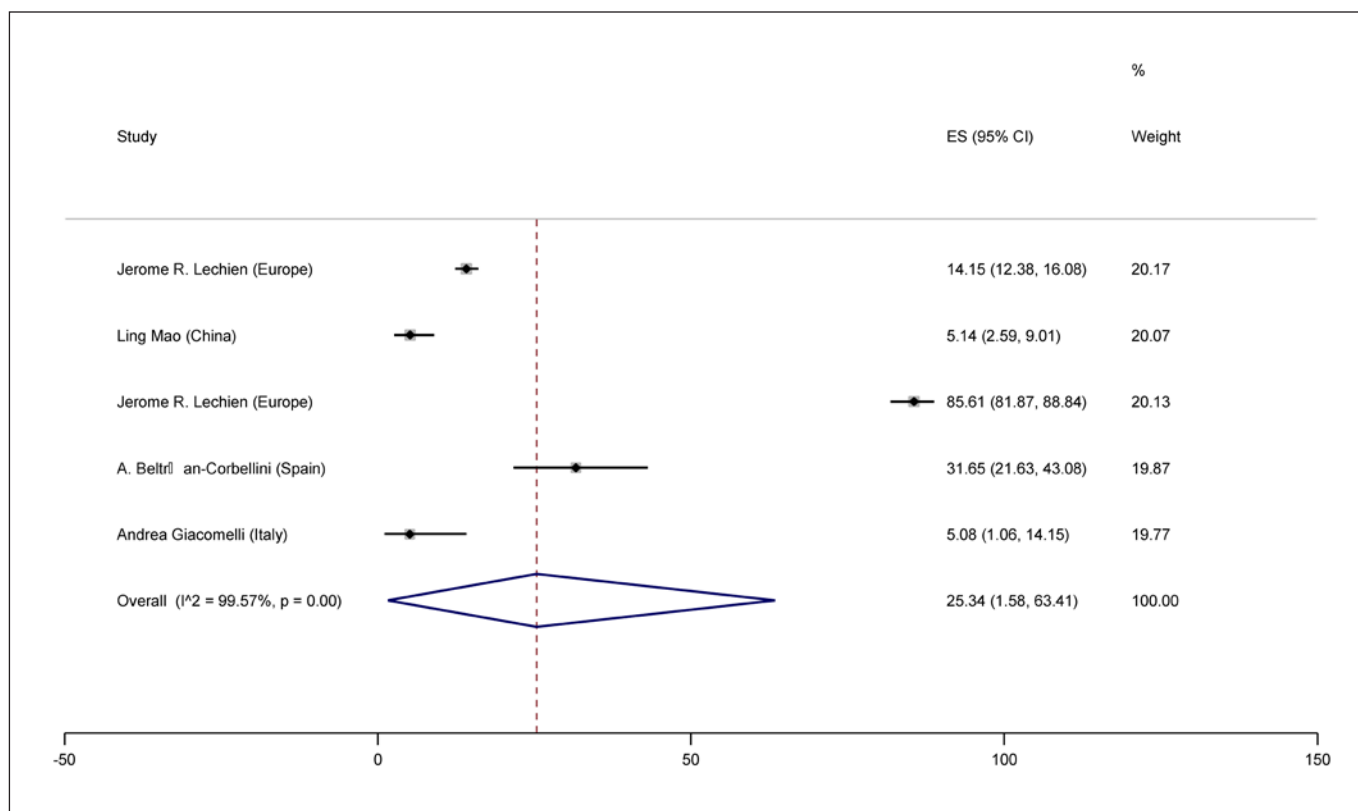
**Fig. 7.** Forest Plot of the prevalence of anorexia in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random-effects model). COVID-19, coronavirus disease 2019.

cating a higher risk of neurologic infection in COVID-19 patients.

Mainly, SARS-CoV-2 has 2 dissemination routes, through which it can infect the CNS: systemic circulation or ethmoid bone (i.e., olfactory nerve) [37]. When SARS-CoV-2 is present in general circulation, it can find its way through cerebral circulation, where slow blood flow through microcirculation can facilitate the interaction of its spike protein with ACE2 receptors on capillary endothelium. Subsequently, viral budding from the capillary endothelium and further endothelial disruption can support viral access to the brain [37]. This viral budding can also happen in neuronal tissues and cause neuronal damage without significant inflammation. It is also important to note that long before this neuronal damage occurs, the endothelial disruption in the capillaries of the brain can lead to bleeding within the cerebral tissue and

cause critical consequences. Cribriform plate (near olfactory bulb) can be considered another entrance gate for SARS-CoV-2. Viral invasion through this pathway can be related to olfactory dysfunction observed among COVID-19 patients. As was evident, 25.3% (95% CI: 1.6–63.4;  $I^2 = 99.6\%$ ) of patients represented different degrees of olfactory dysfunction from mild hyposmia to complete anosmia.

Gustatory dysfunction was also reported in 35.4% (95% CI: 11.2–64.4;  $I^2 = 99.2\%$ ) of patients, which can be related to olfactory impairment or be directly related to the renin-angiotensin system (RAS). It has been revealed that RAS components (also ACE-2) are expressed in mouse taste organs [38]. In addition to the regulatory role of these components in the activity of taste organs, the presence of ACE-2 in these structures might explain gustatory dysfunction in COVID-19 patients [39].



**Fig. 8.** Forest plot of the prevalence of olfactory dysfunction in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names (based on a random-effects model). COVID-19, coronavirus disease 2019.

Anorexia was also another symptom observed in 28.9% (95% CI: 19.9–38.8;  $I^2 = 96.3\%$ ) of patients. This loss of appetite can have different reasons. As Kinnaired et al. [40] reported that altered taste sensitivity could disturb taste processing in anorexia nervosa, appetite loss can have different reasons, such as gustatory dysfunction. Alternatively, it can be a result of the immune responses of the patient. The role of a dysfunctional immune system has been proved in both COVID-19 and anorexia nervosa (AN) [41]. For example, patients with AN have significantly increased TNF- $\alpha$ , IL-1, IL-6, and TNF-receptor II levels, reducing the levels of C-reactive protein and IL-6 receptor. Increased levels of TNF-alpha and IL-6 have also been reported in COVID-19 [42]. Nevertheless, there is still more evidence needed to support this theory.

Moreover, headache was reported in 10.1% (95% CI: 2.7–21.0;  $I^2 = 99.1\%$ ) of patients. According to initial reports, the intensity of headaches in the symptomatic COVID-19 patients was moderate to severe and new-onset (sudden to gradual). Their headache was bilateral with

pulsating or pressing quality in the periorbital, forehead, or temporoparietal region [43]. The potential pathophysiological mechanisms that can lead to headache are direct activation of peripheral trigeminal nerve endings, increased pro-inflammatory cytokines in the cerebral circulation, vasculopathy, and hypoxia [43].

As one of the most common symptoms in many neurologic diseases [44], fatigue was reported in 42.9% (95% CI: 36.7–49.3;  $I^2 = 92.8\%$ ) of COVID-19 patients. Fatigue can be considered a general symptom in most diseases; however, it must be taken more seriously in COVID-19 patients due to certain potential risks of neurologic involvement. Like many other respiratory infections, COVID-19 can lead to a state of malaise and severe acute fatigue [45]. Moreover, chronic fatigue can happen with a prevalence of about 10% (within 3 months) due to COVID-19 [46]. Studies on post-viral fatigue have revealed that the development of chronic fatigue can be predicted by blood levels of IL-6 and IL-10 in the acute phase of the disease [47]. These pro-inflammatory mediators (IL-6

**Table 3.** Study characteristics of case reports

Study [ref.]	Place	Patients, n	Gender (M/F)	Age, yr	General symptoms (yes/no)					Neurological symptoms (yes/no)					Neurological complications
					fever	cough	dyspnea	headache	fatigue	altered mental status	olfactory dysfunction	gustatory dysfunction			
Ye et al. [1]	China	1	M	-	Yes	-	Yes	-	Yes	Yes	-	-	-	-	Encephalitis
Duong et al. [2]	USA	1	F	41	Yes	-	-	Yes	-	No	-	-	-	-	Meningoencephalitis without respiratory failure
Toscanao et al. [3]	Italy	5	(1)	-	Yes	Yes	-	-	-	-	-	-	Yes	-	GBS
		(2)	-	-	Yes	-	-	-	-	-	-	-	-	-	
		(3)	-	-	Yes	Yes	-	-	-	-	-	-	-	-	
		(4)	-	-	-	Yes	-	-	-	-	Yes	-	-	-	
		(5)	-	-	-	Yes	-	-	-	-	Yes	-	Yes	-	
Gutiérrez-Ortiz et al. [4]	Spain	2	(1)	M	50	Yes	Yes	-	Yes	Yes	No	-	-	-	Miller Fisher syndrome and polyneuritis cranialis
		(2)	F	39	Yes	No	No	No	No	-	-	-	-	-	
Zhao et al. [5]	China	1	F	61	No	No	-	-	Yes	-	-	-	-	-	GBS
Sedaghat et al. [6]	Iran	1	M	65	Yes	Yes	Yes	-	-	-	-	-	-	-	GBS
Poyiadji et al. [7]	USA	1	F	-	Yes	Yes	-	-	-	Yes	-	-	-	-	ANE
Moriguchi et al. [8]	Japan	1	M	24	Yes	-	-	Yes	Yes	-	-	-	-	-	Meningitis/encephalitis
Balloy et al. [9]	France	1	M	59	Yes	Yes	Yes	Yes	-	-	-	-	-	-	Nonlesional status epilepticus
Coen et al. [10]	Switzerland	1	M	70	-	Yes	-	-	Yes	-	-	-	-	-	GBS
Kaya et al. [11]	Turkey	1	M	38	Yes	-	Yes	-	-	No	-	-	-	-	Transient cortical blindness (a PRES-like syndrome)
Viguiet et al. [12]	France	1	M	66	Yes	Yes	Yes	-	-	Yes	-	-	-	-	Acute ischemic stroke complicating common carotid artery thrombosis
Mermelstein [13]	Brazil	1	F	27	No	Yes	Yes	Yes	Yes	-	Yes	-	-	-	Acute anosmia
Sachs et al. [14]	USA	1	M	59	Yes	-	Yes	-	-	-	-	-	-	-	Leukoencephalopathy
Padroni et al. [15]	Italy	1	F	70	Yes	Yes	-	-	-	-	-	-	-	-	GBS

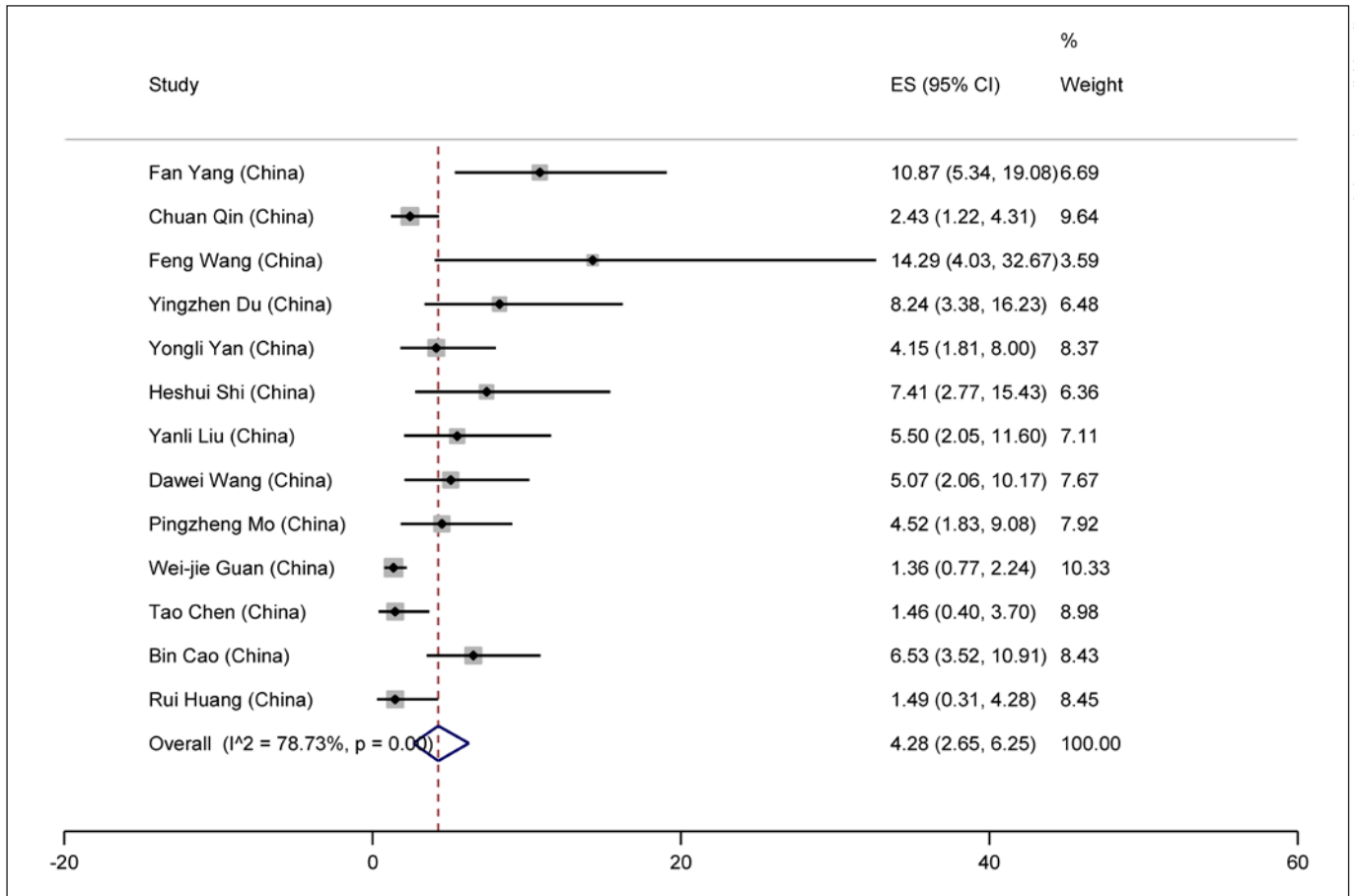
**Table 3** (continued)

Study [ref.]	Place	Patients, n	Gender (M/F)	Age, yr	General symptoms (yes/no)				Neurological symptoms (yes/no)				Neurological complications	
					fever	cough	dyspnea	headache	fatigue	altered mental status	olfactory dysfunction	gustatory dysfunction		
Dinkin et al. [16]	USA	(1)	M	36	Yes	Yes	-	-	Yes	-	-	-	-	Ophthalmoparesis
		(2)	F	71	Yes	Yes	-	-	-	-	-	-	-	
Pfefferkorn et al. [17]	Germany	1	M	51	Yes	Yes	-	-	Yes	-	-	-	-	Acute polyradiculoneuritis with locked-in syndrome
Zanin et al. [18]	Italy	1	F	54	-	-	-	-	-	-	-	-	-	Demyelinating lesions in the brain and spine
Ottaviani et al. [19]	Italy	1	F	66	Yes	Yes	-	-	-	-	-	-	-	Early GBS
Kong et al. [20]	China	1	F	53	No	No	-	No	-	No	-	-	-	Dizziness
Wong et al. [21]	UK	1	M	40	Yes	Yes	Yes	-	Yes	-	-	-	-	Rhombencephalitis
Filatov et al. [22]	USA	1	M	74	Yes	Yes	-	Yes	-	Yes	-	-	-	Encephalopathy
Alberti et al. [23]	Italy	1	M	71	Yes	-	-	-	-	-	-	-	-	GBS
Bernard-Valnet Switzerland et al. [24]		(1)	F	64	No	Yes	-	-	Yes	-	-	-	-	Acute meningoencephalitis
		(2)	F	67	-	Yes	Yes	Yes	-	-	-	-	-	
Scheidl et al. [25]	Germany	1	F	54	No	No	No	-	-	-	No	No	-	GBS
Avula et al. [26]	USA	(1)	M	73	Yes	-	Yes	-	-	Yes	-	-	-	Stroke
		(2)	F	83	Yes	-	-	-	-	Yes	-	-	-	
		(3)	F	80	No	No	-	-	-	-	-	-	-	
		(4)	F	88	-	-	-	-	-	-	-	-	-	
Goldberg et al. [27]	USA	1	M	64	Yes	-	Yes	-	-	-	-	-	-	Cerebrovascular disease
El Otmami et al. [28]	Morocco	1	-	70	No	Yes	No	-	-	-	-	-	-	GBS
Huang et al. [29]	USA	1	F	40	Yes	-	-	-	-	-	-	-	-	Encephalitis
Sohal et al. [30]	USA	1	M	72	-	-	Yes	-	-	Yes	-	-	-	Seizures

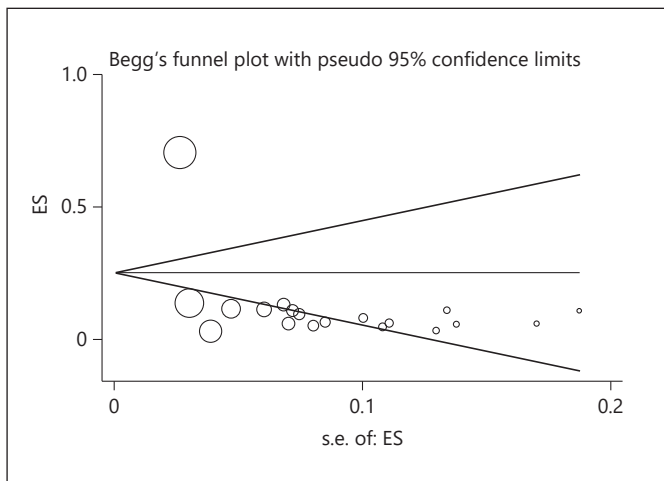
**Table 3** (continued)

Study [ref.]	Place	Patients, n (M/F)	Age, yr	General symptoms (yes/no)				Neurological symptoms (yes/no)				Neurological complications			
				fever	cough	dyspnea	headache	fatigue	altered mental status	olfactory dysfunction	gustatory dysfunction				
Muhammad et al. [31]	Germany	1	F	60	-	-	-	-	-	-	-	-	-	-	Severe brain hemorrhage
Zoghi et al. [32]	Iran	1	M	21	Yes	Yes	-	No	Yes	-	No	No	No	No	Demyelinating event of the CNS

ANE, acute hemorrhagic necrotizing encephalopathy; CNS, central nervous system; GBS, Guillain-Barre syndrome. <sup>1</sup> Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain, behavior, and immunity*. 2020. <sup>2</sup> Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain, behavior, and immunity*. 2020. <sup>3</sup> Toscano G, et al. Guillain-Barre syndrome associated with SARS-CoV-2. *New England Journal of Medicine*. 2020. <sup>4</sup> Gutierrez-Ortiz C, et al. Miller Fisher Syndrome and polyneuropathy cranialis in COVID-19. *Neurology*. 2020. <sup>5</sup> Zhao H, et al. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? *The Lancet Neurology*. 2020;19(5):383–384. <sup>6</sup> Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. *Journal of Clinical Neuroscience*. 2020. <sup>7</sup> Poyiadji N, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology*. 2020;201:1187. <sup>8</sup> Moriguchi T, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases*. 2020. <sup>9</sup> Balloy G, et al. Non-lesional status epilepticus in a patient with coronavirus disease 2019. *Clinical Neurophysiology*. 2020. <sup>10</sup> Coen M, et al. Guillain-Barre syndrome as a complication of SARS-CoV-2 infection. *Brain, behavior, and immunity*. 2020. <sup>11</sup> Kaya Y, et al. Transient cortical blindness in COVID-19 pneumonia; a PRES-like syndrome: Case report. *Journal of the Neurological Sciences*. 2020;413:116858. <sup>12</sup> Viguier A, et al. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. *Journal of neurology*. 2020. <sup>13</sup> Mermelstein S. Acute anosmia from COVID-19 infection. *Practical Neurology*. 2020;practneurol-2020-002583. <sup>14</sup> Sachs JR, et al. COVID-19-Associated Leukoencephalopathy. *Radiology*. 2020;201:753. <sup>15</sup> Padroni M, et al. Guillain-Barre syndrome following COVID-19: new infection, old complication? *Journal of neurology*. 2020;1. <sup>16</sup> Dinkin M, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology*. 2020. <sup>17</sup> Pfeifferkorn T, et al. Acute polyradiculoneuritis with locked-in syndrome in a patient with Covid-19. *Journal of Neurology*. 2020;1. <sup>18</sup> Zanin L, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochirurgica*. 2020;1–4. <sup>19</sup> Ottaviani D, et al. Early Guillain-Barre syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital. *Neurological Sciences*. 2020;1. <sup>20</sup> Kong Z, et al. 2019 novel coronavirus pneumonia with onset of dizziness: a case report. *Annals of Translational Medicine*. 2020;8(7). <sup>21</sup> Wong PF, et al. Lessons of the month 1: A case of rhombencephalitis as a rare complication of acute COVID-19 infection. *Clinical Medicine*. 2020;20(3):293–294. <sup>22</sup> Filatov A, et al. Neurological complications of coronavirus disease (COVID-19): encephalopathy. *Cureus*. 2020;12(3). <sup>23</sup> Alberti P, et al. Guillain-Barre syndrome related to COVID-19 infection. *Neurology-Neuroimmunology Neuroinflammation*. 2020;7(4). <sup>24</sup> Bernard-Valnet R, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. *European Journal of Neurology*. 2020. <sup>25</sup> Scheidl E, et al. Guillain-Barre syndrome during SARS-CoV-2 pandemic: a case report and review of recent literature. *Journal of the Peripheral Nervous System*. 2020. <sup>26</sup> Avula A, et al. COVID-19 presenting as stroke. *Brain, behavior, and immunity*. 2020. <sup>27</sup> Goldberg MF, et al. Cerebrovascular Disease in COVID-19. *American Journal of Neuroradiology*. 2020. <sup>28</sup> El Otmani H, et al. Covid-19 and Guillain-Barre syndrome: More than a coincidence! *Revue neurologique*. 2020. <sup>29</sup> Huang YH, Jiang D, Huang JT. SARS-CoV-2 Detected in Cerebrospinal Fluid by PCR in a Case of COVID-19 Encephalitis. *Brain Behav Immun*. 2020;87:149. <sup>30</sup> Sohal S, Mossammat M. COVID-19 Presenting with Seizures. *IDCases*. 2020;e00782. <sup>31</sup> Muhammad S, et al. Letter to editor: Severe brain haemorrhage and concomitant COVID-19 Infection: A neurovascular complication of COVID-19. *Brain, Behavior, and Immunity*. 2020. <sup>32</sup> Zoghi A, et al. A case of possible atypical demyelinating event of the central nervous system following COVID-19. *Multiple sclerosis and related disorders*. 2020;102324.



**Fig. 9.** Forest Plot of the prevalence of cerebrovascular disease in COVID-19 patients. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author’s names (based on a random-effects model). COVID-19, coronavirus disease 2019.



**Fig. 10.** Begg’s funnel plot for publication bias.

and IL-10) are present in the cytokine that occurs in severe cases of COVID-19 and suggests an immunologic pattern for this chronic fatigue [48]. Dizziness 6.7% (95% CI: 3.7–10.5;  $I^2 = 87.5\%$ ) and nausea 5.9% (95% CI: 3.1–9.5;  $I^2 = 94.5\%$ ) have also been reported in COVID-19 patients. These symptoms can also predict neurological involvement in COVID-19 patients, as they are common symptoms of encephalitis [49].

As the most prevalent neurological comorbidity in COVID-19, the cerebrovascular disease with 4.3% (95% CI: 2.7–6.3;  $I^2 = 78.7\%$ ) can put COVID-19 patients at significant risk. Cerebrovascular manifestations can also occur in patients as a result of COVID-19. This phenomenon can have different causes [24], including (1) ACE2 expression within venous and arterial tissues of the brain can make these structure susceptible for SARS-CoV-2 in-

vasion [50], (2) cardiac arrhythmia as a result of COVID-19 can lead to cardio-embolism formation [13], (3) coagulation impairments as a result of COVID-19 can predispose to thromboembolic events [51], (4) preexisting cerebrovascular disorder can lead to intracranial stenosis (and hypo-perfused brain areas), which can increase the risk of ischemic stroke after COVID-19 severe infection [51].

Based on the case reports, the most critical COVID-related neurological complications were cerebrovascular diseases, encephalopathy, GBS, and seizure. As observed, the critical patients had more propensity to develop cerebrovascular diseases; their D-dimer levels were also higher than nonsevere patients. This can somehow justify the higher rate of cerebrovascular diseases in these patients [52]. In addition to this elevated level of d-dimer, intracranial cytokine storm has been found guilty in the pathophysiology of stroke/cerebrovascular disease [53]. Seizures were also reported in some cases. It has been hypothesized that this epileptic event can happen due to decreased seizure threshold caused by cytokine storm [54]. It seems unlikely that this virus can cause seizures directly. Patients with prolonged presence in ICU had a higher rate of encephalopathic complications than usually expected. Previous studies stated that this issue could be caused by prolonged administration of high doses of sedatives and anesthetics (to manage severe respiratory disease) [52]. It has also been reported that viremia and hypoxia can exacerbate these encephalopathic situations in COVID-19 patients [31]. GBS (alongside another inflammatory demyelinating polyneuropathy, like Miller Fisher syndrome) has also been reported in multiple cases of COVID-19. The pathophysiology of this phenomenon might be secondary to the neuroinvasive nature of SARS-CoV-2 and its ability to precipitate the demyelination process [55]. This peripheral demyelination can also be triggered by aberrant immune responses caused by viral infection-related inflammatory environments [56]. Finally, it should be noted that all of the scenarios described lately are hypotheses and require further studies to be confirmed.

## Conclusions

The neuroinvasive propensity of SARS-CoV-2 has been reported in previous studies. This neuroinvasion can be associated with different neurologic symptoms, directly or indirectly. The most prevalent neurologic manifestations of COVID-19 are fatigue, gustatory dysfunc-

tion, anorexia, olfactory dysfunction, headache, dizziness, and nausea. Cerebrovascular disorders can either be a risk factor for poorer prognosis in COVID-19 patients or occur as a critical complication in these patients. Although neurologic complications had not been reported in any observational study yet, GBS, encephalitis, and meningitis have been introduced as complications of COVID-19 in multiple case reports.

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## Statement of Ethics

This study was conducted under the approval of Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics code: IR.SBMU.RETECH.REC.1399.082).

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

The authors did not receive any funding.

## Author Contributions

K.V. and M.F. conceived of the presented idea, searched electronic databases, and collected the data. K.V. wrote the manuscript. F.S. performed the computation and analytical methods. M.H. and M.R supervised the findings of this work. A.T., M.S., M.H., and D.S. critically revised the manuscript. All authors discussed the results and contributed to the final manuscript.

## Availability of Data and Material

All data analyzed or generated during this study are included in published articles available in Tables 1 and 3.



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