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Pre-existing neurological conditions and COVID-19 co-infection: Data from systematic reviews, meta-analyses, and scoping reviews

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ABSTRACT

Background: Pre-existing neurological diseases have been identified as risk factors for severe COVID-19 infection and death. There is a lack of comprehensive literature review assessing the relationship between pre-existing neurological conditions and COVID-19 outcomes. Identification of high risk groups is critical for optimal treatment and care.

Methods: A literature review was conducted for systematic reviews, meta-analyses, and scoping reviews published between January 1, 2020 and January 1, 2023. Literature assessing individuals with pre-existing neurological diseases and COVID-19 infection was included. Information regarding infection severity was extracted, and potential limitations were identified.

Results: Thirty-nine articles met inclusion criteria, with data assessing >3 million patients from 51 countries. 26/51 (50.9%) of countries analyzed were classified as high income, while the remaining represented middle-low income countries (25/51; 49.0%). A majority of evidence focused on the impact of cerebrovascular disease (17/39; 43.5%) and dementia (5/39; 12.8%) on COVID-19 severity and mortality. 92.3% of the articles (36/39) suggested a significant association between neurological conditions and increased risk of severe COVID-19 and mortality. Cerebrovascular disease, dementia, Parkinson's disease, and epilepsy were associated with increased COVID severity and mortality.

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Conclusion: Pre-existing neurological diseases including cerebrovascular disease, Alzheimer's disease and other dementias, epilepsy, and Parkinson's disease are significant risk factors for severity of COVID-19 infection and mortality in the acute infectious period. Given that 61.5% (24/39) of the current evidence only includes data from 2020, further updated literature is crucial to identify the relationship between chronic neurological conditions and clinical characteristics of COVID-19 variants.

1. Introduction

With over 650 million individuals with confirmed infections and over 6.5 million deaths worldwide as of January 9th, 2023, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection has been associated with a wide range of acute and chronic sequelae across affected populations. The risk of severe COVID-19 infection and mortality is increased in older individuals and those with underlying health conditions. Data shows that compared to patients with no neurological comorbidities prior to infection, patients with chronic neurological conditions including Alzheimer's disease, Parkinson's disease, and epilepsy may be more vulnerable to severe infection [1]. In this narrative review we aim to summarize current trends in published literature regarding the relationship between COVID-19 outcomes and presence of pre-existing neurological disease. Additionally, we aim to establish whether underlying pre-existing neurological diseases serve as specific risk factors for COVID-19 severity and mortality, and identify potential gaps in the evidence. This can inform clinical risk stratification in vulnerable populations, guide public policy and support future pandemic preparedness. Continued identification of high risk groups is critical to the prioritization of preventative programs, including booster vaccination, immunoglobulin, isolation, along with optimization of treatment considerations, including antiviral and anti-inflammatory therapies in those who may not meet the respiratory criteria for treatment.

2. Methods

Early in the COVID-19 pandemic, the World Health Organization (WHO) commissioned a scientific review of literature to investigate the clinical course, severity, and outcome of COVID-19 in individuals with pre-existing neurological disease as part of the Neurology and COVID-19 Scientific Brief [42]. To assess the strength of the current body of evidence, this updated descriptive review focused specifically upon systematic reviews, meta-analyses, and scoping reviews. A narrative approach was chosen in an attempt to synthesize the most high-level evidence published on this and provide summarized associations of the major associations between pre-existing neurological disease and COVID-19 severity and mortality that have discussed in literature thus far.

2.1. Term Justification

Search strategy and selection criteria for this review were identified through searches conducted in PubMed and the WHO COVID-19 research database. The included terms were selected to reflect the top pre-existing neurological conditions reflected in the most updated Global Burden of Disease study [2]. The neurological conditions with the greatest disability adjusted life year rates (DALYs) included stroke, Alzheimer's disease and other dementias (vascular, frontotemporal, Lewy Body, mixed), epilepsy, spinal cord injury, traumatic brain injury, brain and other CNS cancer, migraine headache, tension type headache, meningitis, encephalitis, Parkinson's disease, and multiple sclerosis (MS). For the purposes of this review, we chose to focus on the relationship between pre-existing neurological disorders and COVID-19 infection risk and outcomes. Therefore, the search terms used for the search strings in both databases were as follows:

#	PubMed Search	
1 – Neurological conditions	"Dementia"[Mesh] OR "Epilepsy"[Mesh] OR "cerebrovascular-disorders"[tiab] OR "cerebrovascular disease"[tiab] OR "stroke"[tiab] OR "prior stroke"[tiab] OR "antecedent stroke"[tiab] OR "history of stroke"[tiab] OR "brain ischemia"[tiab] OR "headache disorders"[tiab] OR "migraine"[tiab] or "tension headache"[tiab] OR "dementia"[tiab] OR "alzheimer"[tiab] OR "alzheimer's disease"[tiab] OR "frontotemporal dementia"[tiab] OR "vascular dementia"[tiab] OR "lewy body dementia"[tiab] OR "mixed dementia"[tiab] OR "seizure disorder"[tiab] OR "parkinson's disease"[tiab] OR "multiple sclerosis"[tiab] OR "disseminated sclerosis"[tiab]	879,411
2 - COVID	"COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "corona virus"[tiab] OR "corona pandemic"[tiab] OR coronavir*[tiab] OR betacoronavir*[tiab] OR covid19[tiab] OR covid*[tiab] OR "severe acute respiratory syndrome"[tiab] OR "novel CoV"[tiab] OR nCoV*[tiab] OR hcov[tiab] OR "CoV 2"[tiab] OR CoV2[tiab] OR 2019nCoV[tiab] OR NCOV19[tiab] OR ncovid[tiab] OR sarscov2 [tiab] OR sars2[tiab] OR "sars 2"[tiab] OR "sars-cov"[tiab] OR "sarscov 2"[tiab] OR "sars cov 2"[tiab] OR "sars co v 2"[tiab] OR sarscov [tiab] OR "sars virus"[tiab]	368,995
#3	#1 AND #2	7284
#4	validat*[tiab] OR predict*[tiab] OR prognos* [tiab] OR history*[tiab] OR course[tiab] OR 'follow-up'[tiab] OR cohort*[tiab] OR longitudinal[tiab] OR prospective[tiab] OR history[tiab] OR surviv*[tiab] OR outcome [tiab] OR severity[tiab] OR observa*[tiab] OR scor*[tiab] OR clinical*[tiab] OR risk*[tiab] OR odds[tiab]	11,982,780
	#1 AND #2 AND #3	5191
#4	Date filter 2020–2022	4821

Only English language articles were selected within the search. The results from the searches in these two databases were screened for duplicates which were removed from the list of articles to be screened.

2.2. Eligibility criteria

Our literature search focused upon existing systematic reviews, meta-analyses, and scoping reviews analyzing COVID-19 severity. Studies were included if they investigated the impact of pre-existing neurological diseases on the clinical course of COVID-19 or the role of pre-existing neurological diseases as a risk factor for death in COVID-19 patients. The diagnosis of COVID-19 was defined as a positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 or strong clinical and radiological suspicion of a COVID-19 diagnosis (WHO). Pre-existing neurological conditions were defined as globally prevalent chronic disease of the nervous system that had onset prior to the diagnosis of COVID-19. Studies that included both pre-existing neurological and non-neurological diseases were included in the review, but only findings pertaining to pre-existing neurological conditions were included in the analysis. Systematic reviews, meta-analyses, and scoping reviews published between January 1, 2020 and January 1,

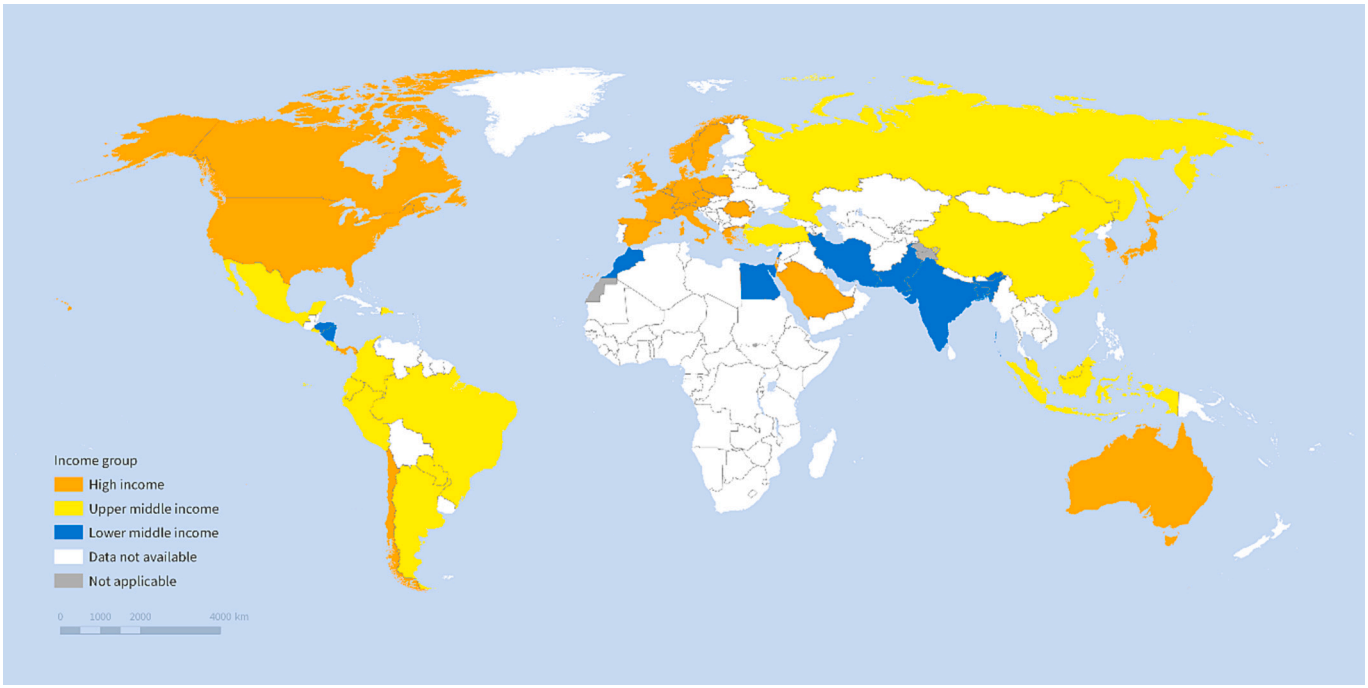

Fig. 1. Representation of Included Countries Stratified by Income Level. World Health Organization.
A majority of the evidence focused on the impact of cerebrovascular disease (17/39; 43.6%) and dementia (5/39; 12.8%) on COVID-19 severity and mortality. 92.3% of the articles (36/39) included for analysis suggested a significant association between neurological conditions and increased risk of severe COVID-19 and mortality.

Table 1
Selected articles assessing relationship between overall pre-existing neurological disease and COVID-19 infection severity.

Authors	Study Design	Data Collection Timeline	Conditions Studied	Total Studies Included	Total Cases	Countries	Pertinent Conclusions	Potential Confounders
Herman et al. (2020)	Scoping Review	1/1/2020–4/15/2020	CVD Stroke Dementia MCI PD Epilepsy	22	4014	China, Italy, France	Patients with underlying CVD and COVID-19 were more likely to require ICU admission (16.7% vs 1.0%), have delayed clinical improvement in the first 10 days of hospitalization (8.2% vs 0%), and develop ARDS. (11% vs 0%)	Age, cardiovascular comorbidities, hospitalized status
Gao et al. (2021)	Systematic Review	12/11/2019–6/27/2020	CVD Stroke Dementia Epilepsy	69	17,879	China, USA, South Korea, Italy, Austria, Iran, Israel, Saudi Arabia, Spain, Turkey, and UK	Presence of pre-existing nervous system disease, particularly CVD was associated with increased severity (OR = 3.19, 95%CI: 2.37 to 4.30, P < 0.001)and mortality of patient with COVID-19 (OR = 3.75, 95%CI: 2.68 to 5.25, *P* < 0.001)	Age, hospitalized status, additional clinical comorbidities
Kubota et al. (2021)	Systematic Review	Initiation-5/20/2020	CVD PD Dementia Epilepsy MS	26	2278	China, Netherlands	Patients with preexisting neurological disorders are more likely to develop severe COVID-19 (22.0% vs, 14.2–15.7% in general population. Patients with CVD or dementia comprised the majority of patients, who developed severe COVID-19 (19.3% & 22.2% respectively)	Age, additional comorbidities (diabetes, hypertension)
Liu 2021	Systematic review	Initiation-7/7/2021	Dementia Stroke Epilepsy PD	39	2,445,582	USA, Italy, South Korea, UK, China, Iran, Brazil, Spain, Turkey, Israel, Switzerland, Netherlands, Denmark, France, Belgium, Sweden, Russian, Peru, Germany, Malaysia, Poland	Pre-existing neurological disorders in COVID-19 patients were significantly associated with higher illness severity OR (95%CI) 1.43 (1.09–1.88)	Age, income regions

Table 2
Selected articles assessing relationship between cerebrovascular disease and COVID-19 infection severity.

Authors	Study Design	Data Collection Timeline	Conditions Studied	Total Studies Included	Total Cases	Countries	Pertinent Conclusions	Relative Risk (95% CI)
Aggarwal et al. (2020)	Meta Analysis	Up to Mar 31, 2020	CVD	6	49	USA	Patients with history of CVD had 2.5 fold increase in odds of severe COVID-19	2.55 (1.18–5.51)
Zaki et al. (2020)	Systematic Review/Meta Analysis	N/A	CVD	9	674	USA	Further evaluation of relationship of stroke and COVID-19 severity is warranted*	–
Xu et al. (2020)	Systematic Review/Meta Analysis	Up to Aug 10, 2020	CVD	12	10,304	China	Patients with history of CVD were more likely to have adverse and fatal outcomes of COVID019	2.05 (1.34–3.16)
Pranata et al. (2020)	Systematic Review/Meta Analysis	Up to Apr 10, 2020	CVD	16	4448	Indonesia	CVD was associated with increased mortality and severe COVID-19	2.04 (1.43–2.91)
Florez-Perdomo et al. (2020)	Systematic Review/Meta Analysis	Up to May 2020	CVD	7	198	China, Italy	History of CVD was associated with compared to those without	2.78 (1.42–5.46)
Fang et al. (2020)	Systematic Review/Meta Analysis	Up to April 5, 2020	CVD	6	3771	China, Japan, Singapore	History of CVD was significantly associated with higher risk of severe COVID-19 and development of ARDS	2.77 (1.70–4.52)
Figliozzi et al. (2020)	Systematic Review/Meta Analysis	Up to April 24, 2020	CVD	49	602,234	UK, Italy, Greece	History of CVD was associated with the highest risk of adverse COVID-19 outcomes	2.93 (1.64–5.24)
Del Sole et al. (2020)	Systematic Review/Meta Analysis	Up to May 28, 2020	CVD	12	2794	China, Netherlands	Pre-existing CVD was the strongest factor associated with a severe SARS-CoV-2 infection	3.66 (1.73–7.72)
Izcovich et al. (2020)	Systematic Review/Meta Analysis	Up to April 28, 2020	CVD	207	75,607	China, USA, Canada, Spain, France, Turkey, South Korea, Japan, Italy, Germany, India Singapore	History of CVD was a significant prognostic marker for severe COVID-19 course and mortality	2.67 (1.84–3.87)
Yin et al. (2021)	Systematic Review/Meta Analysis	Up to Jan 18, 2021	CVD	41	12,526	China	CVD was the strongest risk factor for COVID-19 exacerbation	3.70 (2.51–5.45)
Cheng et al. (2021)	Systematic Review/Meta Analysis	Up to April 1, 2020	CVD	10	2399	China	History of CVD significantly increased the risk of severe COVID-19 manifestations, ICU admission, and death	3.92 (2.45–6.28)
Patel et al. (2021)	Systematic Review/Meta Analysis	Dec 2019-Apr 2020	CVD	11	4987	USA	Existing CVD was associated with higher risk of ICU admission, mechanical ventilation, and mortality	1.82 (1.25–2.69)
Yu et al. (2021)	Systematic Review/Meta Analysis	Dec 2019–2020	CVD	31		China	History of CVD was associated with compared to those without	3.004 (2.097–4.303)
Harrison et al. (2021)	Systematic Review/Meta Analysis	Jan 1, 2020-Nov 5, 2020	CVD	84		China, Colombia, UK	CVD is a risk factor for higher mortality and severe COVID-19	2.77
Siepmann et al. (2021)	Systematic Review/Meta Analysis	Up to Apr 11, 2020	CVD	11	1805	China	Stroke was associated with a significantly increased risk of severe disease and mortality in COVID-19 patients.	2.39 (1.94–2.94)
Li et al. (2022)	Systematic Review/Meta Analysis	Up to Nov 22, 2021	CVD	47	7,267,055	UK, USA, Denmark, Spain, China, Italy, France, Saudi Arabia, Sweden, Norway, Israel, Lebanon, Netherlands, Brazil, Korea, Russia	Stroke was independently associated with a significantly increased risk for mortality in COVID-19 patients.	1.30 (1.16–1.44)
Huang et al. (2022)	Systematic Review/Meta Analysis	2020-May 2022	CVD	24		China, Bangladesh, Italy, Germany, Colombia, USA, Pakistan, UK	Previous stroke was significantly associated with severe COVID-19, mortality, need for intensive care unit admission, use of mechanical ventilation, and an unfavorable overall outcome	–

2023 were included. Only studies reporting aggregated and summarized data were include to more efficiently assess the wide range of current data.

2.2.1. Data extraction

For each article found during this search, the abstract, methodology, and summarized conclusions were extracted by a 7 person scientific research team composed of adult neurologists, a post-doctoral fellow, medical students, and a graduate research fellow (KT, AB, MP, AS, KH, ZS, SG). Outcomes of interest were the severity and mortality of COVID-19. As per WHO criteria, severe COVID-19 was defined as the presence of oxygen saturation (SpO2) <94% on room air at sea level, arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO2/FiO2) <300 mmHg, a respiratory rate > 30 breaths/min, or lung infiltrates

Table 3
Selected articles assessing relationship between dementia and COVID-19 infection severity.

Authors	Study Design	Data Collection Timeline	Conditions Studied	Total Studies Included	Total Cases	Countries	Conclusions	Potential Confounders
Hariyanto et al. (2021)	Systematic Review/Meta-Analysis	Initiation-10/25/2020	Dementia	24	46,391	USA, UK, China, Egypt, Poland, Indonesia, South Korea	Dementia was associated with higher risk of severe COVID-19 [RR 2.63 (95% CI 1.41–4.90), $p = 0.002$] as well as COVID-19 mortality –[RR 2.62 (95% CI 2.04–3.36), $p < 0.00001$]	Age, comorbidities, nutritional status, daily medications.
Hariyanto et al. (2021)	Systematic Review/Meta-Analysis	1/2019–7/14/2020	Dementia	5	881	Italy, South Korea, China	Dementia was associated with a greater risk of COVID-19 mortality [RR 2.60 (95% CI 1.86–3.65), $p < 0.00001$]	Age, Nutritional Status and Daily medications.
July et al. (2021)	Systematic Review/Meta-Analysis		10	56,577	China, USA	Dementia was associated with increased mortality [Pooled Unadjusted OR: 2.80, 95% CI 1.85–4.24, $P < 0.001$. Adjusted OR: 1.80, 95% CI 1.45–2.24, $P < 0.001$] and this relationship was impacted by age and hypertension.	Age and comorbidities.
Alves et al. (2021)	Systematic Review/Meta-Analysis	Initiation-7/2020	Dementia	5	3327	Italy	Among elderly people (>65) hospitalized with COVID-1, patients with dementia had a higher risk of mortality compared to those without [RR: 3.67, 95% CI 2.43–5.55, $p < 0.001$]	Patient age.
Saragih et al. (2021)	Systematic Review/Meta-Analysis	12/1/2019–11/29/2020	Dementia	15	27,952	Italy, Spain, Belgium, France, Turkey, Japan, South Korea	Older adults with COVID-19 and dementia had a higher mortality rate compared to patients without dementia [odds ratio: 2.96; 95% CI 2.00–4.38, $p = 0.224$]	Patient age.

>50% [3]. Critical COVID-19 infection outcomes were defined as respiratory failure, septic shock, and/or multiple organ dysfunction that may necessitate the requirement of non-invasive supplemental oxygen therapy or intensive care unit (ICU) admission, and/or intubation. Outcomes investigated, study design details, study settings (hospital versus home-based care; country or region of studies), sample size, mean age of participants and number of male and female participants were noted from each article. Examples of outcomes discussed in the selected articles include relative risk, odds ratio, and meta-regressional correlations of severe COVID-19 and mortality in pre-existing disease patients compared to general population studies. Each article included in the analysis was reviewed by at least 2 authors. Potential limitations, biases, and gaps in the existing literature were identified by authors to determine the quality of current evidence.

3. Results

Thirty-nine articles met inclusion criteria, with data assessing >3 million patients from 51 countries representing 5 WHO regions (Americas, Eastern Mediterranean, Europe, South-East Asia, Western Pacific). Per World Bank classification, 26/51 (50.9%) of the countries analyzed were classified as high income, 16/51 (31.3%) classified as upper middle income, and 9/51 (17.6%) classified as lower middle income (See Fig. 1).

4. Relationship between overall pre-existing neurological disease and COVID-19 infection severity

Four reviews analyzing a total of 2,469,753 patients assessed the impact of a broad range of pre-existing neurological conditions on COVID-19 severity (Table 1) [1,4–6]. Conditions analyzed in these studies included stroke/cerebrovascular disease (CVD), dementia, Parkinson's disease (PD), epilepsy, and multiple sclerosis (MS). All studies specifically found that individuals with pre-existing CVD were more likely to have severe COVID-19 disease. This was illustrated by increased risk of ICU admission, development of acute respiratory distress syndrome (ARDS), and overall mortality risk seen among patients [4,5]. Kubota and Kuroda found that 22% of cases with severe COVID-19 had a history of pre-existing neurological disease [6]. Patients with history of either CVD, dementia, PD, epilepsy, or MS composed a majority of these cases. The review completed by Liu et al., which provided the most recent data (up to 7/7/21) and assessed the greatest number of cases, found that pre-existing neurological disorders were significantly associated with increased COVID-19 illness severity and mortality [1]. The additional two reviews showed no significant associations between dementia, epilepsy, or PD, however only a small minority of the studies analyzed in these reviews assessed these conditions (3/22 in Herman et al., 5/69 in Gao et al.). The article search period for these two reviews captured patients seen in the early pandemic period (up to 6/27/20) [4,5].

5. Disease-specific relationships to COVID-19 severity

5.1. Cerebrovascular disease

A total of 17 systematic reviews and meta-analyses addressed the relationship between cerebrovascular disease and COVID-19 infection (Table 2) [7–22]. The included articles highlighted significant and notable associations between cerebrovascular disease and a number of outcomes, including severe COVID-19 and in-hospital mortality. Yu et al. highlighted the average prevalence of CVD among groups of COVID-19 severity and mortality to be 16.27% and 15.15%, respectively [18]. Similarly, a meta-analysis conducted by Del Sole et al. provided a pooled prevalence of cerebrovascular disease of 6.01% among patients with severe COVID-19, which is in stark contrast to a pooled prevalence of 1.19% among patients with non-severe disease [14].

As opposed to the associations observed with disease severity and mortality, the association between cerebrovascular disease among COVID-19 patients and ICU admission was less consistent. Among six records that provided data on the risk of ICU admission with pre-existing cerebrovascular disease, Huang et al. found that five demonstrated a significant association. Similarly, Patel et al. reported that pre-existing cerebrovascular disease was associated with higher risk of ICU admission (OR: 1.82; 95% CI: 1.25–2.69) [17]. However, in an umbrella

Table 4
Selected articles assessing relationship between epilepsy and COVID-19 infection severity.

Authors	Study Design	Data Collection Timeline	Conditions Studied	Total Studies Included	Total Cases	Countries	Conclusions	Potential Confounders
Siahann et al. (2021)	Systematic Review/Meta-Analysis	12/2019–6/30/2021	Epilepsy	13	67,131	USA, Iran, Spain, UK	Epilepsy was associated with increased COVID-19 severity [OR, 1.69; 95% CI: 1.11–2.59; p = 0.010] and COVID-19 mortality [OR, 1.71; 95% CI: 1.14–2.56; $p = 0.010$].	Motor disabilities, obesity, immunosuppression.

Table 5
Selected articles assessing relationship between Parkinson's disease and COVID-19 infection severity.

Authors	Study Design	Data Collection Timeline	Conditions Studied	Total Studies Included	Total Cases	Countries	Pertinent Conclusions	Potential Cofounders
Putri et al. (2021)	Systematic Review/ Meta-Analysis	Initiation of database-12/25/20	PD	12	103,874	USA, Spain	Parkinson's disease was associated with poor in-hospital outcomes [[OR 2.64 (95% CI 1.75–3.99), $p < 0.00001$, I2 = 81%]	Age, hypertension, diabetes
Chambergo-Michilot et al. (2021)	Systematic Review/ Meta-Analysis	11/14/2020–4/1/2021	PD	6	1388	USA, Spain, Italy	PD may predispose individuals to the risk of severe COVID-19 (OR: 11.78, 95% CI: 6.27–22.12, I2: 0%), and increased mortality rate (OR: 11.23, 95% CI: 3.92–32.18, I2: 0%)	Age, obesity, pulmonary disease, comorbidities
El-Qushayri et al. (2022)	Systematic Review/ Meta-Analysis	Initiation of database-3/12/21	PD	13	8649	USA, UK., China, Italy, Spain	Patients with PD and COVID-19 had increased risk of mortality [25.1% (95%CI: 16.37–38.49])and hospital admission [39.89% (95% CI: 27.09–58.73)]	Age, co-morbidities
Khoshnood et al. (2022)	Systematic Review/ Meta-Analysis	Initiation-9/2021	PD	30	90,322	China, USA, Germany, Iran, Brazil, Italy, UK, Spain	PD may predispose cases to the risk of severe COVID-19 requiring hospitalization [pooled prevalence 49% (95%CI: 29–52%) (I2: 93.5%, $P < 0.001$) and higher rate of mortality [12% (95%CI: 10–14%) (I2 = 97.6%, $P < 0.001$).]	Age, comorbidities
Afraie et al. (2022)	Systematic Review/ Meta-Analysis	1/2019–10/20/2021	PD	20	75,701	Turkey, Italy, Germany, Iran, Japan, Morocco, China, Netherlands, India, USA	Rates of mortality and hospitalization were not significantly different between PD patients and the general population.*[RR 0.96 (CI 95% 0.50–1.87; $P = 0.49$)	Age, physical symptoms

review of systematic reviews, Harrison et al. included two reviews that provided data on the risk of ICU admission and cerebrovascular disease and the largest of the two did not find a significant association (RR: 1.9; 95% CI: 0.9–4.0) [19].

5.2. Dementia

Overall, five meta-analyses, scoping reviews, and/or systematic reviews focus on pre-existing dementia and COVID-19 (Table 3) [23–27]. These articles revealed that among older adults with COVID-19, patients with dementia had worse health outcomes including an increased risk of COVID-19 infection, severe COVID-19, and higher rates of mortality compared to those without dementia. Specifically, Saragih et al. revealed a 39% pooled mortality prevalence from COVID-19 in patients with dementia compared to a 20% pooled mortality prevalence from COVID-19 in patients without dementia [27]. One meta-analysis of 5 Italian studies revealed that among elderly people hospitalized with COVID-19, patients with dementia had a greater risk of mortality compared to patients without dementia (RR 3.67 [95% CI 2.43 − 5.55], $p < 0.001$) [26]. Another study revealed a relationship between dementia and increased mortality in patients with COVID-19 (pooled unadjusted OR: 2.80 [95% CI 1.85–4.24], $p < 0.001$ and adjusted OR:1.80, 95% CI 1.45–2.24; $p < 0.001$) [25]. This relationship between dementia and mortality in COVID-19 patients was impacted by age (coefficient − 0.047, $p < 0.001$) and hypertension (coefficient − 0.009, $p = 0.02$) but not significantly impacted by presence of diabetes or sex [25].

5.3. Epilepsy

One meta-analysis analyzed the relationship between epilepsy and COVID-19 outcomes (Table 4) [28]. Thirteen studies were included in the analysis, with a total of 67,131 COVID-19 patients [28]. The average age across studies ranged from 47 to 77.6 years. The study focused on severe COVID-19 and mortality as outcomes. Epilepsy was associated with an increased risk of severe COVID-19 outcomes (OR 1.69; 95% CI 1.11–2.59, $p = 0.01$) and COVID-19 mortality (OR 1.71; 95% CI 1.14–2.56 $p = 0.01$). Meta-regression analysis revealed that the relationship between epilepsy and severe COVID-19 was significantly influenced by male sex and neurodegenerative disease. No statistically significant influence for severe COVID-19 was discovered for age, hypertension, stroke, diabetes, or neoplasm. The relationship between epilepsy and COVID-19 mortality was not influenced by age, sex, hypertension, neurodegenerative disease, diabetes, stroke or neoplasm [28].

5.4. Parkinson's disease (PD)

Five systematic reviews assessed the impact of PD on COVID-19 severity across 279,934 patients with PD (Table 5) [29–33]. Across several of these reviews it was found that the risk of severe COVID-19 in

Table 6
Selected Articles Assessing Relationship Between Multiple Sclerosis and COVID-19 Infection Severity.

Authors	Study Design	Data Collection Timeline	Conditions Studied	Total Studies Included	Total Cases	Countries	Pertinent Conclusions	Potential Cofounders
Sharifian-Dorche (2021)	Systematic Review	1/1/2020–12/3/2020	MS	84	2493	Iran, USA, France, Chile, Italy, Spain, Australia, UK, Germany, Sweden, Norway, Switzerland, Belgium, Mexico, China, Denmark	Overall mortality rate of COVID-19 in people with MS was similar to the general population (1.8% vs. 2.1%). Highest mortality rate was in patients on Rituximab (4.0%) or no therapy (3.6%).	Age, baseline disability, comorbidities
Schiavetti (2021)	Systematic Review/ Meta-analysis	– 7/31/2021	MS	29	5173	Spain, Iran, Austria, USA, Chile, Poland, Italy, Belgium, Brazil, Argentina, Chile, Mexico, Ecuador, France, Denmark, Turkey, Sweden	Patients on anti CD20 therapy had increased risk for severe COVID-19 depending on treatment duration: < six 6 mo [OR = 1.65(95% CI = 0.56–4.90), $p = 0.36$], 6–12 mo [OR = 2.2 (95% CI = 0.91–5.55), $p = 0.08$], > 12 mo [OR = 2.98(95% CI = 1.37–6.46), $p = 0.006$]	Age, comorbidities
Etemadifar (2021)	Systematic Review/ Meta-analysis	– 5/2021	MS	13	4493	USA, Canada, Italy, France, Turkey, Spain, The Netherlands, Argentina, Aruba, Brazil, Chile, Colombia, Ecuador, El Salvador, Honduras, Mexico, Nicaragua, Panama, Paraguay, Rep.Dominicana, Costa Rica, Venezuela, Iran	Increased risk of severe COVID-19 in patients with Progressive MS [OR = 3.74 (95% CI 2.57–5.46), $p < 0.001$] and EDSS >6 [OR = 3.48 (95% CI 1.67–7.24), $p = 0.001$].	Age, comorbidities
Prosperini (2021)	Systematic Review/ Meta-analysis	1/1/2020–7/31/2021	MS	18	5634	Iran, USA, Austria, Brazil, Chile, Czechia, France, Italy, The Netherlands, Poland, Saudi Arabia, Spain, Turkey, Argentina, Aruba, Colombia, Ecuador, El Salvador, Honduras, Mexico, Nicaragua, Panama, Paraguay, Rep. Dominicana, Costa Rica, Venezuela	Mortality rate of patients with MS 1.97% (95% CI 1.61–2.33). Higher mortality rate in progressive disease course ($\beta = 0.15$, $p = 0.027$), and treatment with anti-CD20 agents ($\beta = 0.18$, $p < 0.001$)	Age, comorbidities
Barzegar (2021)	Systematic Review	12/1/2019–12/18/2020	MS	87	4310	USA, France, The Netherlands, UK, Italy, Chile, Iran, Spain, Germany, Poland, Turkey, Belgium, Mexico, Norway, Romania, Brazil	Among patients with MS who got COVID-19, hospitalization rate was 20.7%, mortality rate was 3.0%. The highest hospitalization and mortality rates were in patients with no treatment (42.9% and 8.4%), and anti-CD20 therapies (29.2% and 2.5%)	Age, comorbidities, disability
Hada (2022)	Systematic Review	–5/2/2021	MS	16		Italy, Iran, France, USA, Spain, Denmark, Poland, Turkey	MS patients treated with anti-CD20 therapies may be at increased risk for severe COVID-19	Age, comorbidities, disability
Barzegar (2022)	Systematic Review/ Meta-analysis	12/1/2019–07/26/2021	MS	10	40,551	USA, Spain, Italy, Sweden, Iran, Denmark	No DMTs meaningfully affect risk of acquiring COVID19. Rituximab use increases risk of severe COVID-19 [OR 2.06 (95% CI 0.94–4.52)]	Age, comorbidities, disability

PD patients increased with age [29–31]. Additionally, PD was associated with poor in-hospital outcomes, increased infection severity, and increased risk of mortality in a majority of the reviews. However, one meta-analysis with a large sample size of 75,701 cases did not find a significant correlation between history of PD and COVID-19 hospitalization and mortality rates compared to the general population [33].

5.5. *Multiple sclerosis (MS)*

Seven systematic reviews assessed the impact of MS on COVID-19 severity across 62,654 patients with MS (Table 6) [34–40]. The overall mortality rate from COVID-19 in people with MS was similar to the general population; however, progressive disease course, untreated MS, and the use of rituximab were associated with higher mortality

[34,37,38]. There was an increased risk of severe COVID-19 in patients with progressive disease and higher baseline disability (Expanded Disability Status Score > 6) [36]. Treatment with rituximab was also associated with an increased risk of severe COVID-19 [38,39], though this may be representative of longer average treatment durations on rituximab versus other anti-CD20 therapies [35].

5.6. Headache disorders

No systematic reviews, meta-analyses, or scoping reviews were identified assessing the relationship between preexisting headache disorders and COVID-19 severity. However, it should be noted that in several large scale systematic reviews assessing the impact of various clinical comorbidities to COVID-19 course, headache disorders are rarely included in the defined lists of comorbid conditions analyzed [15,41].

6. Discussion

In this narrative review, we evaluated 39 articles that analyzed the relationship between pre-existing neurological diseases and COVID-19 severity as defined by the severity of clinical course and mortality. The current literature finds a consistent association between pre-existing neurological conditions, specifically CVD, dementia, epilepsy, and PD, and severe COVID-19 clinical course and mortality. The largest number of studies analyzed the impact of CVD on the COVID-19 clinical course with 94% (16/17) of these articles finding that a history of CVD to be a significant prognostic indicator of disease severity and mortality. Only one article found an indeterminate relationship between stroke and COVID-19 severity, however its analysis included only five studies and was published in the early phases of the pandemic [8]. One systematic review assessing 13 articles suggested an association between epilepsy and increased risk of severe COVID-19 and mortality. Five articles found a significant relationship between pre-existing dementia and disease severity and mortality, particularly in older adults. Additionally, 4/5 systematic reviews found a considerable association between underlying PD and COVID-19 severity. No systematic literature was found evaluating the relationship between headache disorders and COVID-19 disease severity or mortality, highlighting a major gap in literature.

Most of the articles included in this analysis did not collect data beyond 2020 (24/39; 62%). This serves as a limitation, as since only six systematic reviews included data from 2022 (15.4%), the systematic evidence may not fully represent the most recent and updated relationship between neurological history and COVID-19 severity especially in the context of novel strains. Additionally, given our selective inclusion of articles presenting aggregated data and utilization of two databases, relevant original studies may be left out of this analysis. Given that several studies from overlapping time periods are included within this analysis, some individual studies within the aggregated data may overlap between publications. Our team did not remove potential duplicate studies within the analysis as this could impact the conclusions presented by the original systematic reviews, however this could impact our overall statistical analysis. Furthermore, the majority of the studies analyze patients from upper middle-high income countries and none include the WHO African region, significantly limiting the evidence base for policy makers and clinicians in underrepresented regions. Almost all the articles included assessed individuals hospitalized with COVID-19 infections, which reflects a more critically ill population and does not account for a broader range of COVID-19 manifestations. It is also important to note that the selection of patients and case definitions differed across the included publications, therefore the conclusions presented in this narrative review are not a standardized reflection of all evidence. An additional consideration that should be made within the context of this review is the impact of disruption of care among patients with pre-existing neurological disease. The negative impact of the global pandemic on these patient's overall health may have potentially also aggravated the course of COVID-19 within this population.

All articles included in our analysis were written in English language. Lastly, although the methodology of several studies included in this review involved elimination of confounding variables, our individual analysis did not adjust for these factors. The current literature reflects that globally prominent pre-existing neurological conditions (CVD, dementia, epilepsy, and PD) have had a significant impact on both COVID-19 severity and mortality throughout the pandemic, however this review underlies the need for additional studies reflecting current COVID-19 variants, including patients in the African region, and addressing a comprehensive range of neurological conditions including headache.

7. Conclusion

Pre-existing neurological conditions including cerebrovascular disease, dementia, and epilepsy have been shown to be an important risk factors for severe COVID-19 clinical course and mortality in the initial phase of the COVID-19 pandemic. The majority of current evidence on this topic does not assess data beyond 2020, therefore additional updated studies are necessary to fully reflect the evolving pandemic and prioritize safety of vulnerable patients with chronic neurological disorders.

Disclaimer

The authors are responsible for the views expressed in this article. Those views do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated. Institutions are listed for author identification only.

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