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RESEARCH ARTICLE

Covid-19 with Pre-Existing Neurological Disease

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Abstract

Objective: COVID-19 has varying impact on different groups of people based on age, gender, race and comorbidities. Although the implications of COVID-19 on chronic pulmonary and cardiovascular disease have been extensively studied, the impact on neurological disease remains unclear. We attempt to identify the outcome and challenges of COVID-19 in patients with chronic neurological conditions.

Methods: We conducted a systematic review and meta-analysis of 15 studies and 11,011 patients to compare composite poor outcome and mortality between patients with and without neurological comorbidities. We also analyzed the different clinical presentations and outcome of COVID-19 in different neurological conditions.

Results: We found a markedly higher incidence of composite poor outcome (Odds Ratio: 5.57, 95% CI: 3.81-8.12, P = 0.02) and a higher mortality (Odds Ratio: 6.47, 95% CI: 3.94 - 10.63, P = 0.008) among patients with pre-existing neurological disease, and no significantly different outcomes between patients with cerebrovascular disease and dementia. Linear Meta-regression analysis revealed that the impact of chronic neurological disease on COVID-19 was independent of chronic cardiovascular disease (P=0.406), hypertension (P=0.458), diabetes mellitus (P=0.512), COPD (P=0.281), and advanced age (p=0.066).

Conclusion: Patients with chronic neurological disease seem to develop moderate/severe COVID-19 more frequently, and have an increased mortality rate, independent of other comorbidities. They also show atypical clinical presentation in SARS-CoV-2 infection. Advanced age, cognitive dysfunction, immunosuppression, and respiratory muscle weakness might be responsible for the adverse COVID-19 outcomes in these patients.

1 | INTRODUCTION

COVID-19 was declared a pandemic on March 11, 2020. It emerged from the Hunan SeaFood market in Wuhan China, with just about fifty people initially infected in December 2019. The outbreak has now spread intercontinentally and has been the focus of most current research. Among the questions about treatment, prognosis, and complications lies the question of interaction of COVID-19 with other diseases. It is perceived that COVID-19 infection has varying impacts on different groups of people based on their age, gender, race, comorbidities etc. Among the comorbidities, it is known that diabetes, cardiovascular conditions, COPD, and cancer increase risk of severe illness. Patients with chronic neurological diseases (CND) like stroke, dementia, epilepsy or neuromuscular diseases might also have similar risk of frequent and severe infection. However, there is little substantial evidence and several conflicting reports which make decision-making concerning these conditions difficult. We aim to analyze available data to determine the association between COVID-19 and chronic neurological diseases.

Concerns about the outcomes in patients with neurologic comorbidities have become increasingly evident. These patients are often disabled and have restricted mobility which interfere with the quality of life. Due to the risk of high mortality and morbidity, special considerations are needed in patient management protocols. Immunosuppression therapy in neuroinflammatory conditions has raised concerns in providers and patients as the effect on COVID-19 has not been identified. Neuromuscular disorders also have significant implications on the severity and course of the disease. These patients often suffer from respiratory muscle weakness, theoretically increasing their risk of developing or succumbing to pneumonia. The vulnerability of patients with movement disorders has also been identified as these patients are older and suffer from bulbar symptoms, respiratory dysfunction, and are cognitively impaired. These are just some examples suggesting that the necessity for clear guidelines has surfaced (1).

The purpose of this study is to determine if the outcome of COVID-19 in these patients is any different from the general population. We will attempt to identify challenges these patients and their physicians face, and propose effective, practical management strategies. In order to achieve our goal, we will determine the incidence and presentation of COVID-19 in the patient population under study. We will also ascertain specific complications of the disease course the patients faced. Furthermore, we will consider how the disease affects the current therapeutics and management of these neurologic debilitations. The outcomes and clinical course in terms of severity and mortality of the disease in these patients will be central to determining the best course of action physicians must take to manage COVID-19 patients with underlying neurological disease.

2 | METHODS

The study protocol was designed and registered on PROSPERO International Prospective Register of Systematic Reviews on September 21, 2020 under the title COVID-19 infection with pre-existing neurological disease: a systematic review (PROSPERO ID: CRD42020209734). This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-analysis guidelines (PRISMA).

Search strategy

Seven researchers searched through databases including PubMed, Medline, Google Scholar, Scopus, WHO, and ScienceDirect, to identify relevant articles. The following research key-terms were used to search the databases: “SARS-2”, “COVID-19”, “neurology”, “neurological”, “headache”, “migraine”, “dizziness”, “seizure”, “encephalitis”,

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"myasthenia gravis", and/or "multiple sclerosis." Articles were screened regardless of publication date. Only articles in English with free access were included.

Eligibility criteria

Screening was done by 6 investigators separated into 2 teams. Each team divided the article list and assessed each article using the following inclusion criteria: study method, laboratory-confirmed COVID-19, discussion of patients with pre-existing neurological conditions, and presence of at least one of the following data:

Description of neurological symptoms, complications, or therapeutic challenges caused by COVID-19. Recorded COVID-19 outcomes in the study population.

Study types that were included were case reports, case series, observational cohort, cross-sectional study, and case control. We only included patient data evaluating pre-existing neurological conditions in individuals with a laboratory-confirmed diagnosis of COVID-19. Furthermore, the data assessed were not restricted by age, gender, or ethnicity.

Exclusion criteria included articles that did not involve patients with preexisting neurological comorbidities, systematic reviews, other review articles, commentaries, editorials, and letters to editors. We excluded randomized controlled trials, as we aimed to report on the natural history of the disease in this population. We also excluded studies which reported exclusively on neuropsychiatric conditions.

Risk of Bias Assessment

Two review authors independently evaluated eligible studies for risk of bias using the criteria in the assessment tool provided by the NIH study quality assessment tools and the Cochrane Handbook for Systematic Reviews of Interventions (2).

'Risk of bias' judgments were performed and presented per outcome per study. The two reviewers resolved any disagreements regarding the risk of bias by discussion; in case of further disagreement, they would have consulted a third review author. The following internal validity domains were assessed: Random sequence generation (selection bias), Allocation concealment (selection bias), Incomplete outcome assessment/follow-up (attrition bias), Blinding of participants and personnel (detection bias), Blinding of outcome assessment (detection bias), Significant prognostic factors or follow-up not taken adequately into account (confounding). The risk of bias assessment also included key external validity domains: Poorly defined study group (reporting bias), Poorly defined follow-up (reporting bias), Poorly defined outcome (reporting bias) and Other bias.

For each criterion, the following judgements were used: High Risk of bias, Low Risk of bias, or Unclear Risk of bias (due to either lack of information or uncertainty over the potential of bias).

Data Extraction

Four independent investigators performed data extraction from the studies. The pre-piloted Excel spreadsheet form was used which included basic information about the studies such as the author, publication year, journal, study setting, sample size, study design, duration and the aim of each study. Patient demographics included average age, gender and pre-existing neurological diseases. We separated the comorbidities into specific diseases as seen in Table 1. Our main outcome of interest was composite poor outcome, which is defined as: intensive care unit admission, mechanical ventilation, critical COVID-19, worsening neurological disease, and death. Mortality rate was measured as a secondary outcome.

Statistical Analysis

The meta-analysis was performed using Cochrane's Review Manager (version 5.4). We used the Mantel-Haenszel method to calculate Odds Ratio of dichotomous variables with 95% Confidence Interval. Random effects model was used regardless of heterogeneity. The results are displayed on a forest plot. All P-values in this analysis were two-tailed, and the statistical significance was set at <0.05. Linear regression was performed against age, cardiovascular disease, hypertension, diabetes, and COPD. Funnel plot could not be used to assess publication bias due to the small number of studies (less than 10).

3 | RESULTS

A total of 341 articles were found using the search criteria and with additional bibliographic search of literature reviews. Removal of duplicates resulted in a total of 204 unique articles. Subsequently, the studies were screened by title and abstract, and 154 studies were excluded. Of the remaining 50 studies, 32 articles were excluded after assessing the full-text articles. This resulted in 18 studies remaining to be included in our qualitative analysis. After the Risk of Bias Assessment, 3 studies were excluded due to the high risk of bias (2 case reports and 1 case series). We, therefore, selected 15 studies for our systematic review Figure 1. Only 9 out of the 15 studies were selected for meta-analysis because of the presence of at least two different groups for comparison (ie. patients with neurological diseases vs. patients without neurological diseases).

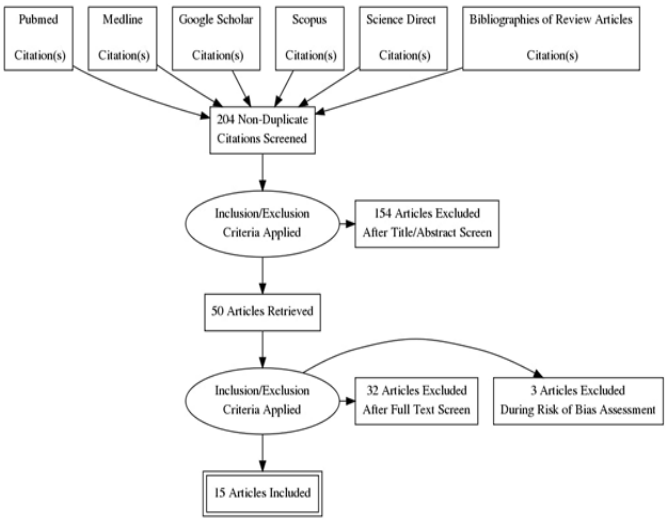


FIGURE 1: PRISMA flowchart

Demographics

A total of 11,011 patients were analyzed in our review, all of whom had been diagnosed with COVID-19 infection using laboratory or radiological diagnostic tests. Data in all the studies was collected between March 2020 and May 2020. The average age of patients was 61.2 years Figure 2, and the male: female ratio was about 1:1 (males: 50.3%). Out of the 15 studies, 11 reported on hospitalized patients only, while 4 studies had data exclusively on non-hospitalized patients. One study presented data on both hospitalized and community patients.

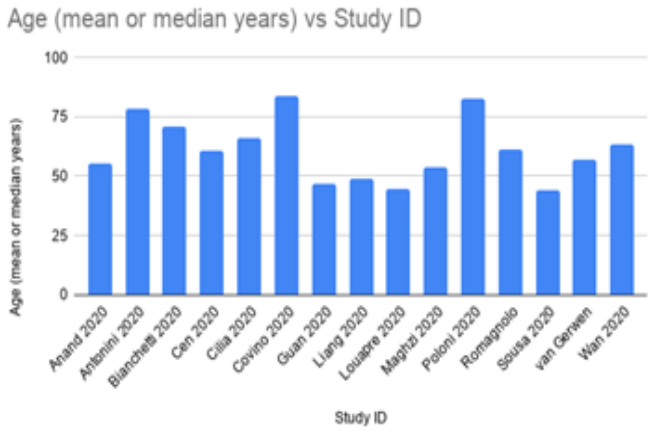
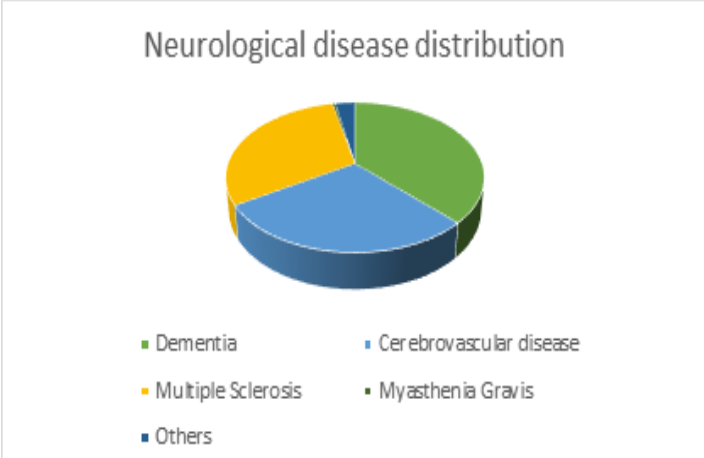


FIGURE 2: Mean age distribution of the studies

Around 10.6% of the study population had neurological comorbidities. However, 6 of the 15 studies were done specifically on patients with neurological comorbidities, creating a selection bias, and so they were not included in the meta-analysis. In the remaining nine studies, the total number of patients was 10,539 (95.71% of the total study population), and 6.6% of those had a neurological condition, with dementia, multiple sclerosis and cerebrovascular disease being the most commonly encountered neurological comorbidities Figure 3. The distribution of neurological disease among hospitalized and non-hospitalized patients was also determined Tables 2 and 3. The results showed a higher percentage of neurological comorbidities among hospitalized patients (9.3% vs 1.3%). Other comorbidities described in the studies are presented in Table 1 and Figure 4.



*Others include migraine/chronic-type headaches/trigeminal neuralgia, epilepsy, peripheral neuropathy.

FIGURE 3: Percentageof neurological diseases in the study sample

Study ID	Study Design	Risk of Bias	Setting	Country	Sample Size	Age (mean or median years)	Male (%)	Neurological comorbidity (%)	Neurological disease	COPD	Asthma	DM	Cardiovascular Disease	HTN	CKD	Liver Disease	Malignancy
Anand 2020	Case series	Unclear	Hospital	USA	5	55.4	40	100%	Myasthenia Gravis	0%	0%	40%	0.00%	60%	0%	20%	0%
Antonini 2020	Case series	Unclear	Hospital	Italy and UK	10	78.3	60	100%	Parkinson's Disease	10%	20%	10%	20%	10%	10%	0%	0%
Bianchetti 2020	Retrospective	Unclear	Hospital	Italy	627	70.7	46.6	13.10%	Dementia	4.30%	4.30%	-	-	-	-	-	-
Cen 2020	Retrospective	Low	Hospital	China	1007	61	49	2.50%	Cerebrovascular disease	4.60%	-	11.80%	6.50%	26.80%	1.40%	0.90%	-
Cilia 2020	Case-Control	Low	Community	Italy	48	65.9	71.4	100 %	Parkinsons Disease	8.30%	-	0.00%	8.30%	33.30%	8.30%	8.30%	16.70%
Covino 2020	Retrospective	Low	Hospital	Italy	69	84	53.6	40.57%	dementia, Cerebrovascular disease	10.10%	-	13.00%	30.40%	59.40%	-	-	4.30%
Guan 2020	Retrospective	Low	Hospital	China	1099	47	58.1	1.40%	Cerebrovascular disease	1.10%	0.00%	7.40%	2.50%	15.00%	0.70%	2.10%	0.90%
Liang 2020	Retrospective	Low	Hospital	China	1590	48.9	56.9	0.10%	Cerebrovascular disease	1.50%	-	8.20%	3.70%	16.90%	1.30%	1.80%	1.10%
Louapre 2020	Retrospective Cohort	Unclear	Hospital	France	347	44.6	28.2	100%	Multiple Sclerosis			4.60%	6.60%	-	-	-	-
Maghzi 2020	Case series	Low	Community	USA	5	53.6	60	100%	Multiple Sclerosis	0%	0%%	0%	0%	20%	0%	0%	0%
Poloni 2020	Retrospective	Unclear	Community	Italy	57	82.8	33.3	100%	Dementia	14.00%	-	19.30%	31.60%	54.40%	-	-	10.50%
Romagnolo 2020	Retrospective	Low	Hospital	Italy	344	61.5	59.3	22.40%	Cerebrovascular disease, dementia, migraine/chronic/eye headaches/trigeminal neralgia, epilepsy, peripheral neuropathy, Parkinson's disease, multiple sclerosis	11.90%	-	12.20%	-	45.90%	5.2	-	14.2
Sousa 2020	Retrospective Cohort	Low	Community	Brazil	2070	44	49.1	1%	not defined	1.45%	1.45%	5.50%	7.30%	-	1.00%	-	-
van Gerwen 2020	Retrospective Cohort	Low	Hospital and community	USA	3703	56.8	55.3	11.18%	CVA, dementia	4.60%	11.60%	28.20%	23.60%	3.76%	9.30%	-	8.40%
Wan 2020	Retrospective	Low	Hospital	China	30	63.4	33.3	17%	Dementia	3.33%	-	-	26.70%	46.67%	-	-	-

Table 1: Demographics of the included studies

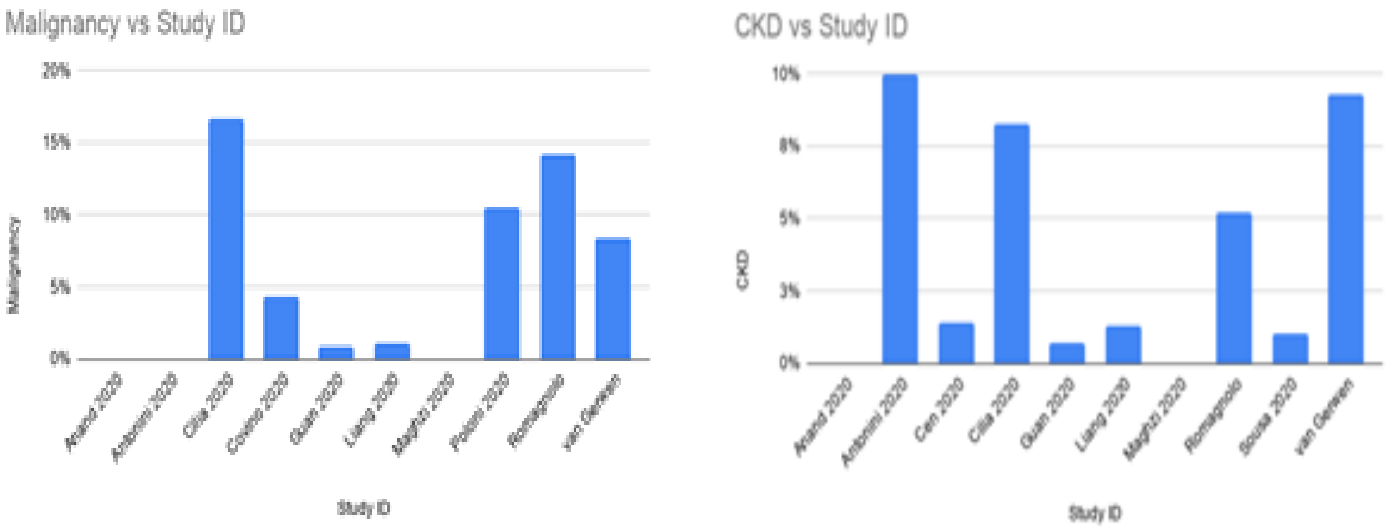
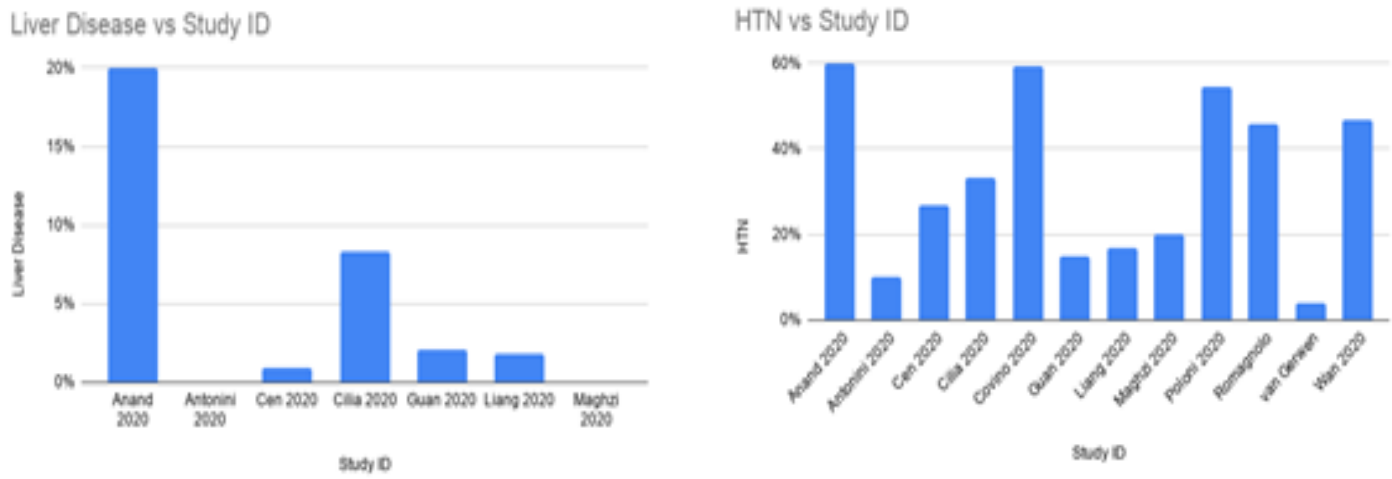
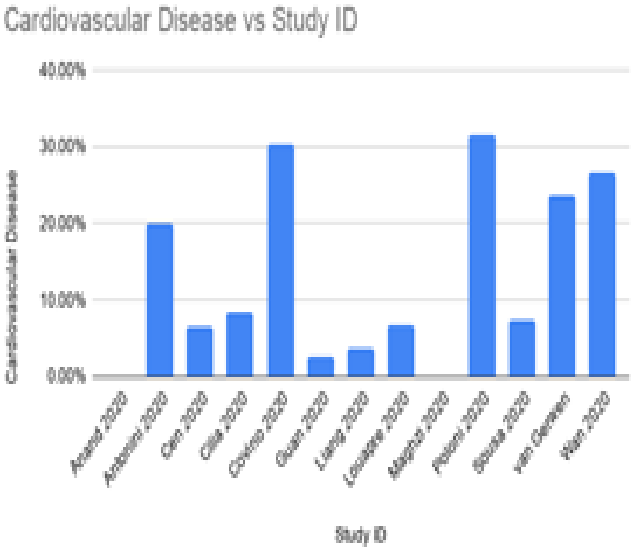
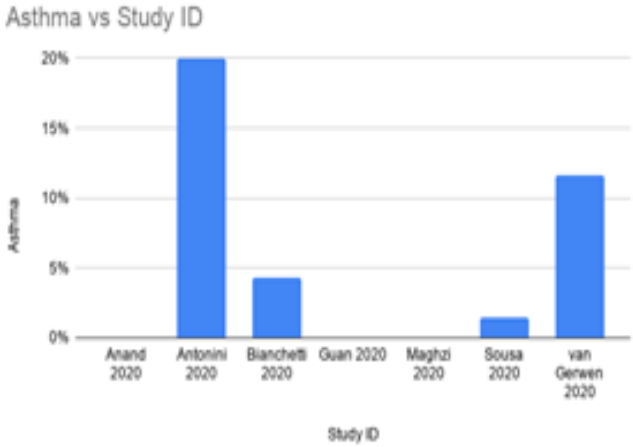
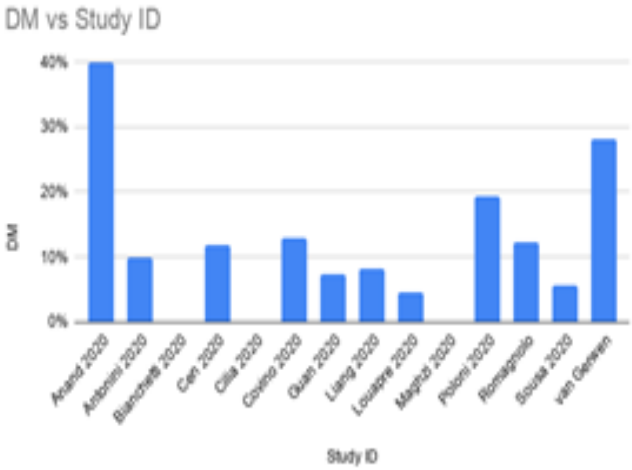


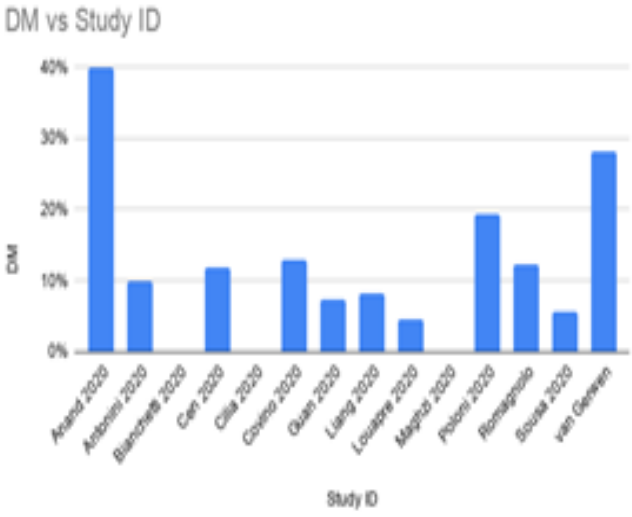
FIGURE 4: Distribution ofcomorbidities in the studies (only studies that had data on a specificcomorbidity were included in each graph)











The symptoms at presentation were not described in all studies. However, from the data available Table 4, the most common symptom at presentation in the population with chronic neurological diseases was fever in 3606/5238 (68.8%), followed by cough in 3373/5238 (64.39%), malaise or fatigue in 1998/5238 (38.14%), shortness of breath in 1195/5218 (22.8%), neurological symptoms (dizziness, anosmia, ageusia or confusion) in 329/2500 (13.16%), and headache in 585/4825 (12.12%).

Quality Assessment

Using the NIH quality assessment scale and the Cochrane Risk of Bias assessment tool, 11 of the 18 studies were determined to be of good quality and low risk of bias. These were all case control or cohort observational studies. Unclear risk of bias was found in 4 studies; however, using the NIH quality assessment tool, they were found to be of either fair or good quality and were, therefore, included in the analysis. There were 3 studies which had a high risk of bias, specifically selection and reporting bias; these were excluded from the final review and analysis Table 1.

Data Analysis

Analysis of the primary outcome among study participants showed a markedly high incidence of composite poor outcome among patients with pre-existing neurological disease compared to patients without (Odds Ratio: 5.57, 95% CI: 3.81-8.12, P = 0.02) Figure 5. Analysis of secondary outcome (mortality) revealed similar results, with the incidence of death being higher among patients with pre-existing

TABLE 2: Distribution of neurological comorbidity inhospitalized patients

Hospital-ized	Bianchetti 2020	Cen 2020	Covino 2020	Guan 2020	Liang 2020	Romag-nolo 2020	Wan 2020	VanGerwen 2020 (hospitalized)	Total
No. of patients	627	1007	69	1099	1590	344	30	2015	6781
No. with neuro dx	82	25	25	15	30	77	5	370	629 (9.3%)
No. with dementia	82	0	8	0	0	25	5	183	303 (4.5%)
No. with CVSD	0	25	20	15	30	30	0	187	307 (4.5%)

TABLE 3: Distribution of neurological comorbidity innon-hospitalized patients

Non-hospitalized	Sousa 2020	Van Gerwen 2020 (non-hospitalized)	Total
No. of patients	2070	1688	3758
No. with neuro dx	16	34	50 (1.3%)
No. with dementia	n/a	19	-
No. with CVSD	n/a	25	-

TABLE 4: Symptoms at presentation in patients with neurological comorbidity

Study	Cough	Headache	Malaise/fatigue	Fever/chills	Dyspnea	Neuro symptoms
Anand 2020	5	0	1	3	1	1
Antonini 2020	8	0	5	6	2	4
Bianchetti 2020	11	0	0	39	36	64
Cilia 2020	9	4	7	10	4	8
Liang 2020	26	8	11	23	12	-
Louapre 2020	266	180	290	260	162	204
Maghzi 2020	2	2	2	4	1	2
Poloni 2020	30	30	30	30	30	21
Wan 2020	18	0	16	19	11	3
Total	375	224	362	394	259	307
Percentage	61.07%	39.74%	58.96%	64.17%	42.18%	50%

neurological disease than those without (Odds Ratio: 6.47, 95% CI: 3.94 - 10.63, P = 0.008) Figure 5. The wide confidence interval is a reflection of the significant heterogeneity (I2=65%), which is likely due to the small number of studies available for analysis. Subgroup analysis of mortality in patients with cerebrovascular disease and dementia showed that there was no statistically significant subgroup difference in the results between these two groups (P=0.41).

Meta-regression analysis revealed that the association of neurological comorbidity in COVID-19 with composite poor outcome was not affected by cardiovascular disease (P=0.406), hypertension (P=0.458), Diabetes Mellitus (P=0.512), and COPD (P=0.281). The association of age with poor outcome in patients with neurological disease was not statistically significant (Correlation coefficient r= -0.0283, 95% CI = -0.059-0.002, p=0.066).Figure 6

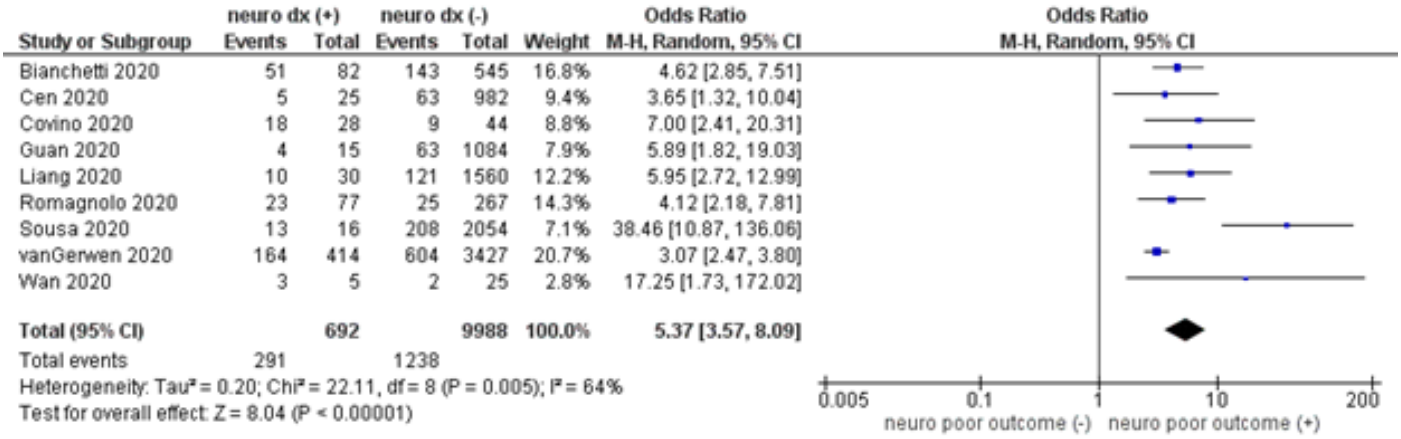


FIGURE 5: Neurological comorbidity and composite poor outcome

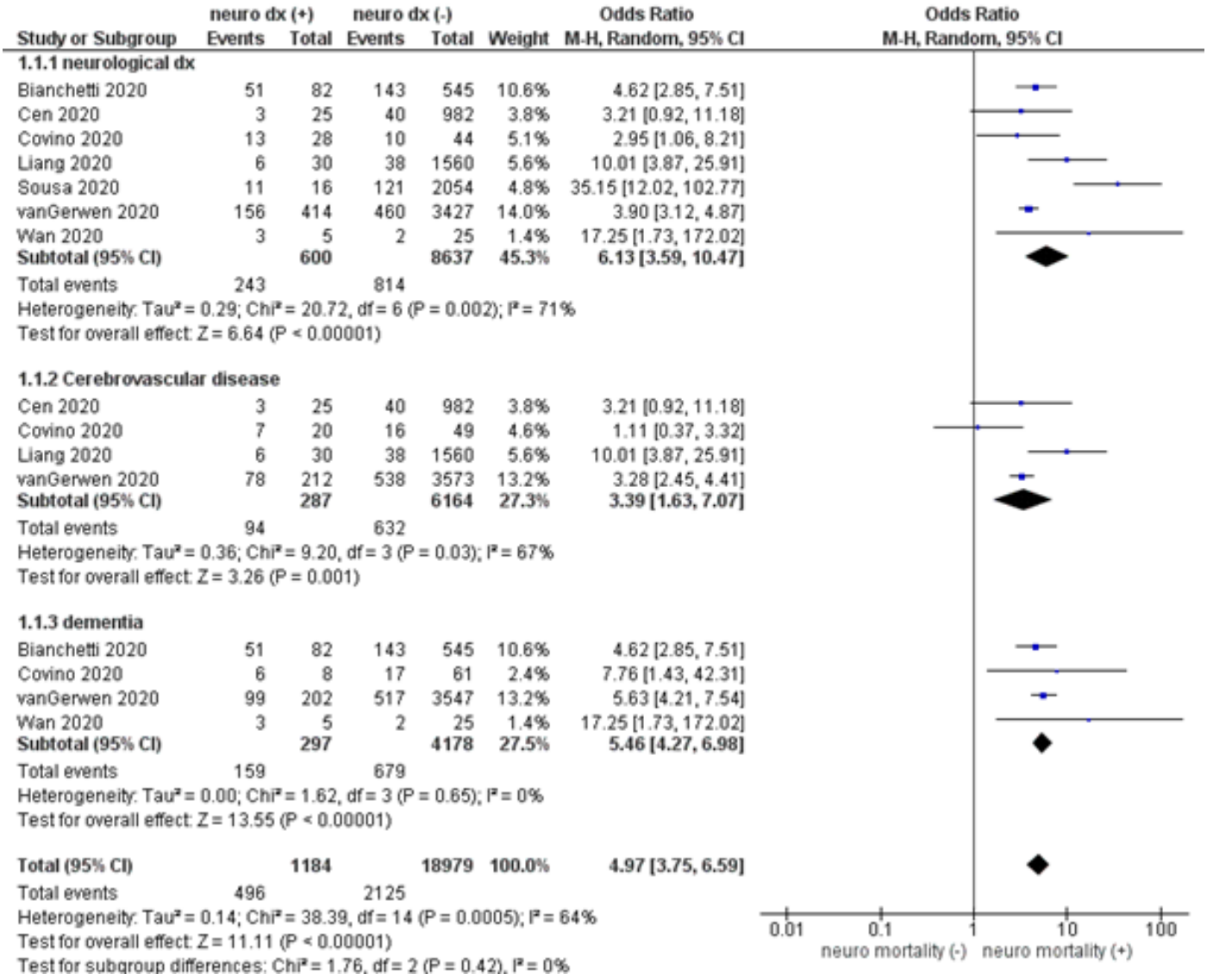


FIGURE 6: Neurological comorbidity and mortalitymeta-analysis

4 | DISCUSSION

COVID-19 is a disease of terrifying outcomes. With over 77 million cases and 1.7 million deaths worldwide, this pandemic has outpaced the yearly influenza 12 times over in number of cases and 3 to 5 times over in mortality (3, 4). The healthcare systems all over the world seem to be buckling under the increasing burden of hospitalizations of SARS-CoV-2 patients (5). As with many other diseases, its impact on communities is skewed by age, gender, race and comorbidities. A study of over 178,000 COVID-19 patients compared mortality of patients between different age and sex groups and showed a mortality rate 8.1 to 62 times higher in patients over 55 years compared with patients under 55 years, and 77% higher in men compared to women (6). Comorbidities, such as diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease and dementia have also been found to contribute to a higher mortality in COVID-19 patients (7).

Existing data suggests that neurological comorbidities predispose to a poor outcome in COVID-19 patients. However, since the more prevalent of these comorbidities including dementia and cerebrovascular diseases are seen predominantly in the older population, age becomes a significant confounding factor. Is the poor outcome due to age alone? Or is it due to the multiple other comorbidities like diabetes, hypertension and cardiovascular disease that often exist in the older population? Do neurological diseases play any independent role in the outcome of COVID-19 patients?

We studied available data on patients with neurological diseases to determine the span of morbidity and mortality caused by COVID-19 across the range of neurological comorbidities. We also tried to determine if there were any peculiarities in their clinical presentation that might help determine the outcome of these patients. Our analysis revealed that neurological comorbidity is present in about 6.44% of older COVID-19 patients, far less common than hypertension (23.91%) and diabetes (14.61%) but more prevalent than COPD (3.11%). Current literature varies on the prevalence of comorbidities in COVID-19 patients. A systematic review of 22,753 COVID-19 patients showed similar statistics with hypertension seen in 27.4%, diabetes in 17.4%, cardiovascular disease in 8.9%, COPD in 7.5% of patients, and neurological diseases not separately reported (8). Other studies report either higher or lower prevalence which understandably varies with age, ethnicity, geography, and hospitalization (9, 10). There is currently not enough data to establish the prevalence of pre-existing neurological disease in COVID-19 patients. However, a scoping review of hospitalized patients with SARS-CoV-2 showed that 8% of them had a neurological comorbidity (11), which is slightly less than our results Figure 3 .

With regards to clinical presentation, our analysis showed that patients with pre-existing neurological disease have a higher incidence of shortness of breath (42.18%) and neurological symptoms (50%) than the general population (12), but similar or slightly decreased incidence of fever, cough, and fatigue - the three most commonly reported symptoms of COVID-19. Shortness of breath is an independent predictor of poor outcome in COVID-19 patients, especially in the older population (13). In our study population, the high incidence of dyspnea substantiates the increased mortality and severity of infection that was seen in our analysis. We attempt to explain the predisposition to this symptom in the context of neurological diseases in the section below.

The neurological symptoms at presentation most commonly reported in patients with chronic neurological diseases were anosmia/ageusia (25.70%) followed by delirium (12.86%), dizziness (9.61%), worsening motor function (7.82%), and behavioral symptoms (1.63%). Anosmia and ageusia, while the most common of the presenting neurological symptoms in our studies were still less commonly reported than in other studies. A review of cross-sectional studies showed that there is an inter-racial variation with more Europeans and Americans, but rarely Chinese experiencing this symptom (14). This might explain the results in our study population which contains a large fraction of Chinese. Another review by Agyeman *et al.* reported lower prevalence of anosmia (coefficient = -0.076; p = 0.02) and ageusia (coefficient = - 0.073; P =0.03) in COVID-19 with increasing age (15).

The impact of chronic neurological disease on COVID-19 mortality and morbidity has not been

established. Our analysis of 9 studies and 10,539 patients showed higher incidence of both composite poor outcome and mortality in patients with chronic neurological disease. This association is not affected by the presence of other comorbidities and therefore, neurological comorbidity can be considered an independent predictor of poor outcome and mortality. In contrast, a retrospective study by Garcia-Azorin *et al.* on 576 patients concluded that neurological comorbidity is an independent predictor of death (HR 2.129, 95% CI: 1.382–3.280), but not severe COVID-19 (OR: 1.75, 95% CI: 0.970–3.158) (16). Larger studies with comparably sized cohorts might be required to resolve this question.

The neurological diseases reported in our studies are dementia, cerebrovascular disease, multiple sclerosis, and myasthenia gravis. We explain the mechanism of association of COVID-19 with these chronic diseases, as follows:

Dementia

One of the most common causes of mortality in dementia patients is lower respiratory tract infection, specifically pneumonia. Several anatomical, functional and social factors contribute to a higher predisposition in these patients. Alzheimer's disease, the most common cause of dementia, is known to accelerate age-related respiratory muscle weakness, which reduces effective ventilation, effective clearance of airway secretions and makes them susceptible to more frequent and severe respiratory infection. Other factors, like pseudobulbar dysphagia, reduced gag reflex, episodes of reduced consciousness, poor oral hygiene, medications used in the treatment of dementia, such as anticholinergics, insertion of orogastric or nasogastric tubes also make patients susceptible to frequent respiratory infections. Patients with dementia, due to their advanced age, are at increased risk of severe pneumonia. High susceptibility to infection and a weakened immune system predisposes to a poor outcome in those patients. In Alzheimer's disease, the Apo-e4e4 gene has been found to carry a higher risk of severe COVID-19, independent of other comorbidities (17). Additionally, COVID-19 has been shown to worsen functional status in dementia patients. This was seen in our study population, as a significant number of patients presented with delirium, hallucinations, loss of motor functioning, and behavioral changes Table 3. Experts explain the pathophysiology to be infiltration of SARS-Cov-2 virus through the blood-brain barrier and impact on dopaminergic neurons which are known to carry ACE2 receptors (18).

Cerebrovascular Disease

Post-stroke immunosuppression is a growing concept. It has been seen that the increased risk of infection after stroke is a result of the systemic immunosuppression which occurs in response to brain injury. Systemic immunosuppression is an adaptive response which is aimed to limit the inflammatory damage to the brain after a stroke. However, this response, manifested as lymphopenia, decreased levels of inflammatory cytokines, monocyte and lymphocyte dysfunction, and atrophy of secondary lymphoid organs, leaves the body at risk for frequent and severe infections (19). Hence, post-stroke infections appear to have an incidence rate of 30% and a mortality rate of 20% in stroke survivors. This immunosuppression appears to persist for a few months after stroke (20), and might be responsible for the increased incidence and mortality of COVID-19 in this time frame. Other long-term factors predisposing to infection that might persist for months to years include disability, lack of physical activity, depression, dysphagia and tube feeding.

Multiple Sclerosis (MS)

While MS has not been associated with an increased risk of developing COVID-19 compared to the general population, the immunosuppressive therapies used pose a potential challenge on the management of the infection and on the response to COVID-19 vaccinations. There is a potential risk of cell-depleting disease-modifying therapy (DMT) like ocrelizumab affecting immune response to COVID-19 infection or vaccination. Hence, experts recommend non-cell-depleting DMTs be used instead (21). Several case reports have also suggested an increased frequency of relapses in MS patients during or after a COVID-19 infection. Suggested mechanisms include the Oligodendrocyte Progenitor Cells (OPCs) which are critical for the differentiation and remyelination of neurons affected by MS. OPCs carry ACE2 receptors and are susceptible to SARS-CoV-2 infec-

tion (22). The systemic inflammation and cytokine storm of COVID-19 can also lead to neuroinflammation and worsening of MS. Interestingly, there appears to be racial differences in the outcome of COVID-19 in MS patients. Data from the COViMS registry, presented at the MS Virtual 2020 summit, suggests a worse composite outcome of mortality or ICU admission in Black MS patients compared to White MS patients, independent of age, sex, comorbidities, MS characteristics or smoking (OR 3.7, 95% 1.6-8.2; *P*=0.002) (23). This underscores the need for further studies on MS patients before dismissing any significant association between MS and COVID-19.

Myasthenia Gravis (MG)

Current data does not establish any increased risk of developing COVID-19 in these patients. However, exacerbation of MG and poor outcome of COVID-19 in MG patients has been reported several times (24–26). It is well established that MG crises are often precipitated by infections (40-70% of cases), and it is known that the crises are characterized by high levels of inflammatory cytokines (27). Infections, and severe COVID-19 in particular, are also associated with increased serum inflammatory mediators which can understandably precipitate MG crises. It is also believed that the immunosuppressive therapy MG patients are often taking makes them susceptible to a severe SARS-CoV-2 infection. Conversely, it has been proposed that immunosuppressive therapy actually counters the severe inflammatory reaction, cytokine storm, of COVID-19 infection and is, therefore, protective. Comprehensive data on MG patients, such as that collected in the CARE-MG registry, will be essential for making recommendations for MG patients with regards to COVID-19.

Implications of results

There is an intricate relationship between the immune system and nervous system, and it becomes evident when we observe the course of COVID-19 in patients with chronic neurological diseases. Patients with dementia or cerebrovascular disease may be at an increased risk of severe infection due to a weakened immune system or poor respiratory system function. Atypical presentations of COVID-19 in dementia or myasthenia gravis may be missed. Delirium, MS exacerbations or myasthenic crisis should alert the physician to possible COVID-19. Management of the chronic neurological disease might also require adjustments, such as in the use of anticholinergics in Parkinson disease, or cell-depleting DMTs in MS. In effect, caregivers, both at hospital and home, need to be aware of the implications of having a chronic neurological disease during this pandemic.

Limitations

This analysis is simply able to summarize available data and generate hypotheses for future research (28). As has been mentioned multiple times in our paper, our analysis has been limited by the literature available at the time this review was performed. Moreover, COVID-19 has only been discovered at the end of 2019, and became a pandemic in March 2020 thus we are only starting to learn about the disease and how it affects special populations, such as those patients with neurological diseases. The few studies we have done an analysis on could not substantially conclude for this population. We were also limited by a language barrier, since only articles written in English were included. Many of the articles we found also did not meet our inclusion criteria. Although great efforts were made to check the quality of the research, there is still heterogeneity in our pooled studies and a risk for including poor quality research (29). The heterogeneity in the studies also limited the number of details that could be extracted from the studies, possibly affecting our analysis. The research did not include neuropsychiatric diseases, although important to analyze as well, would have its own set of outcome measurements that will deviate to our current population, and further increasing heterogeneity.

5 | CONCLUSION

Chronic neurological diseases have a significant impact on COVID-19 in the presentation, morbidity and mortality of patients, independently of other comorbidities or age. COVID-19 patients with neurological comorbidities have markedly higher rates of composite poor outcome and mortality. They are also likely to have atypical symptoms at presentation, specifically exacerbation of their neurological comorbidities. The limited data available suggests that

this group of people requires special attention in the diagnosis and management of COVID-19. Further research will be critical in substantiating the current evidence.

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