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Review

COVID-19 infection complicated by Guillain-Barre syndrome: A systematic review of clinical features, pathogenic mechanisms, and respiratory failure

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Abstract

Introduction: The World Health Organization (WHO) declared a pandemic in March 2020 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Given the neurotropism feature of the coronavirus and growing number of coronavirus disease 2019 (COVID-19) associated neurological disorders, including Guillain Barre syndrome (GBS), we conducted a systematic review to thoroughly describe the clinical features, diagnostic workup, and clinical outcome of COVID-19 associated GBS in 78 cases.

Methods: We identified case reports and case series of COVID-19 associated GBS by conducting a search in the PubMed/MEDLINE and EMBASE databases. We assessed the quality of studies using an appraisal checklist presented by Cochrane Murad et al. Extracted data included demographic characteristics, clinical presentation, diagnostic workup, and outcome.

Results: The systematic search yielded a total of 60 articles reporting 78 patients with a diagnosis of COVID-19 associated GBS. The patients were mainly male (65.3%) with an average age of 57 years. The ascending symmetrical paresis was the most common presentation (79.4%), with demyelinating pattern in 54 patients (79.4%). CSF analysis showed albuminocytologic dissociation in 48 patients (75%). The mortality of COVID-19 associated GBS was estimated as 6.4% attributable to progressive respiratory failure.

Conclusion: Given the associated morbidities such as respiratory failure in patients with COVID-19 related GBS, its timely detection is crucial to prevent poor clinical outcomes. On the other hand, clinicians must be vigilant to identify the clinical findings of SARS-CoV-2 infection in newly diagnosed GBS patients, as this might be a neurological complication of the subclinical viral infection.

Introduction

The World Health Organization (WHO) declared a pandemic in March 2020[1] caused by a rapidly spreading, novel infectious pathogen, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Human coronaviruses have been responsible for significant outbreaks of lethal pneumonia in the 21st century. These viruses include SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and the current SARS-CoV-2.[2] The coronavirus disease 2019 (COVID-19) presentation varies widely and includes asymptomatic infection, gastrointestinal involvement, with mainly respiratory tract infection, and respiratory failure in extreme cases.[3] Besides the systemic and respiratory symptoms, recent studies have indicated that COVID-19 infection could be complicated by central and peripheral nervous system (PNS) involvement.[4]

The development of neurological disorders, including seizure, neuropathy, myopathy, and cerebrovascular disease in the MERS-CoV and SARS-CoV, suggests the neurotropism feature of SARS-CoV-2.[2] In a report from Wuhan, China, more than a third of the hospitalized COVID-19 patients had signs and symptoms related to the nervous system involvement. The commonly reported

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neurological symptoms included hypogeusia, hyposmia, and myalgia with markedly increased serum creatine kinase (CK) levels.[4]

Guillain-Barré syndrome (GBS) is one of the neurological complications reported from different parts of the world in this pandemic. GBS is an acute immune-mediated PNS disorder, usually triggered by a previous infection. GBS outbreaks have been linked with viral epidemics or pandemics, such as the Zika virus (ZIKV)[5] and MERS-CoV.[2,6] The incidence of GBS is estimated to be 0.8–1.9 per 100 000 people per year, increasing with age and more often seen in male patients.[7]

GBS mainly manifests with progressive, ascending, symmetrical limb weakness typically starting distally and moving proximally with or without cranial nerve involvement.[8] The electrophysiological studies can aid in diagnosis of GBS and differentiate between its variants, namely: 1) acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common pattern with favourable prognosis, 2) acute motor axonal neuropathy (AMAN), 3) acute motor sensory axonal neuropathy (AMSAN), and 4) Miller Fisher syndrome (MFS).[9] The typical finding of GBS in cerebrospinal fluid (CSF) analysis— albuminocytologic dissociation (increased CSF protein level without an elevation in white blood cells)—confirms the diagnosis.[8]

This paper aims to review the most important demographic characteristics, clinical manifestations, and diagnostic workup findings of COVID-19 associated GBS. This review also aims to explain the potential mechanisms for PNS involvement in COVID-19 patients and understanding the leading cause of respiratory failure in COVID-19 associated GBS patients.

Methods

Search strategy and selection criteria

This systematic review followed the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We performed a comprehensive literature search in MEDLINE/PubMed and EMBASE databases to identify studies from inception to August 15, 2020. Besides, we manually identified reference lists of all publications meeting the inclusion criteria, to identify any further studies that were not found with the electronic search. We included case reports and case series of COVID-19 associated GBS if the authors established the diagnosis of COVID-19 and GBS or its subtypes such as MFS, based on the standard clinical criteria in use.[8,10] An appraisal checklist presented by Cochrane Murad et al. was used to assess the quality of case reports and case series.[11]

The keywords used in the search strategy were as follows: "Guillain-Barre Syndrome", "GBS," "Miller Fisher syndrome," "polyradiculopathy," "COVID-19," "Coronavirus", "2019 nCoV", and "SARS-COV-2". The detailed search strategy is available in Table S1 of Supplementary file 1. We excluded editorials, letters or commentaries, animal studies, and meeting papers. We did not restrict our search to any language, year of publication, publication status or any other study characteristics.

Data extraction

Database search, article screening, appraisal, and study selection were performed using a standardized approach. The authors selected the studies based on the title, followed by the abstract and finally reviewed the full text in a third screening. If there was a disagreement, the reviewers met for a discussion until an agreement was reached. In case of duplicates or multiple reports of a case, the most complete dataset combined across all known publications was used. Data extracted from each study included baseline characteristics (age, gender, past medical history), clinical presentation (sign, symptom, physical examination), diagnostic workup (laboratory tests, imaging), treatment, and clinical outcome. A flow diagram depicting the process of the literature search is provided in Figure 1.

Results

The systematic search yielded 300 papers. After removing the duplicates and full-text assessment, a total of 60 case reports and case series, reporting 78 patients with diagnosed COVID-19 associated GBS were included in this review. Appraisal of the majority of the case reports/case series revealed a good quality; however, 6 cases (7.6%)[12-17] appeared to have moderate quality, mainly due to the presence of both causality and reporting biases. Regarding the ascertainment domain, 3 out of 60 cases[16,18,19] provided an inadequate ascertainment of either exposure (due to positive laboratory tests for pathogens other than COVID-19) or outcome (no definite diagnosis of GBS). Concerning reporting domain, 7 cases (8.9%) did not satisfy the reporting bias as they did not provide enough reproducible details to let clinicians make inferences related to their own practice.[12-17] None of the studies in this review fully satisfied the causality domain because the follow-up was not long enough to report the final COVID-19 or GBS related clinical outcomes.

Demographics and past medical history

The patient population aged variably across the studies with the mean age of 57, ranging from 11 to 84. Male patients dominated the population, representing 65.3% of the cases. The past medical history was reported in 47 out of 78 cases (60.2%). Hypertension was the most prevalent medical condition (15 patients, 31.9%); followed by 12.7% for diabetes mellitus; 8.5% for each of dyslipidemia and cancer; 6.3% for each of rheumatoid arthritis (RA) and obesity; 4.2% for each of hypothyroidism, aneurysm, chronic obstructive pulmonary disease (COPD), and asthma; 2.12% for each of other medical conditions such as coronary artery disease, psoriasis, alcoholism, restless leg syndrome (RLS), reflex sympathetic dystrophy (RSD),

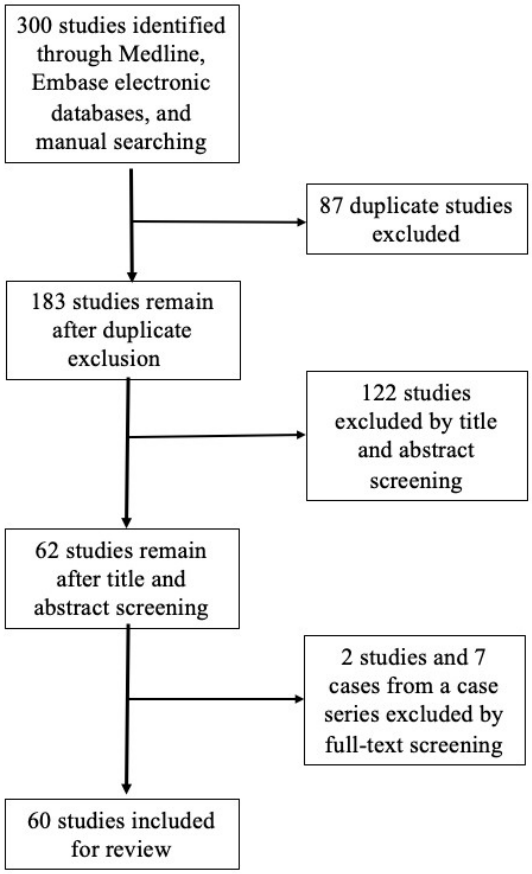

Figure 1. PRISMA flow diagram for search strategy

gastroesophageal reflux disease (GERD), hiatal hernia, and benign prostatic hyperplasia (BPH).

Clinical manifestations

The presentation of GBS during the course of SARS-CoV-2 was remarkably different between the studies. In the majority of patients, GBS-related neurologic manifestations emerged following respiratory or gastrointestinal symptoms (71 patients, 91%); the intermission between the onset of non-neurologic COVID symptoms and neurological symptoms ranged from 0 to 33 days (average: 14 days). Among these patients, 2 cases (2.5%) developed COVID-19 and GBS symptoms at the same time[20,21] and neurologic presentations preceded the respiratory symptoms in 2 patients (2.5%).[22,23] Four out of 78 patients (5.1%) with neurologic symptoms were asymptomatic for COVID-19 infection, but the diagnosis of SARS-CoV-2 was made with laboratory tests.[24-27] Neurologic presentations preceded the respiratory symptoms in 2 patients (2.5%).[22,23] Clinical GBS variants, including MFS and polyneuritis cranialis were evident in 9 (11.5%)[14,20,28-33] and 2 patients (1.2%),[29,34] respectively.

Ascending symmetrical paresis was the most common presentation (62 patients, 79.4%). 33 patients had tetraparesis (53.2%), and 29 patients had paraparesis (46.7%). In 63 patients (80.7%), muscle weakness was accompanied by one or more of sensory deficit symptoms, such as paresthesia, hypoesthesia, or posterior cord syndrome (reduced vibration or reduced light touch sensation). Another common presentation was facial nerve palsy (CN VII) (35 patients, 44.8%), with bilateral involvement in 26 patients (74%). Bulbar symptoms, including dysphagia and dysphonia, were observed in 16 (20.5%) and 2 patients (2.5%), respectively. 14 out of 78 patients (17.9%) with COVID-19 associated GBS developed autonomic dysfunction such as bladder dysfunction (7 patients, 50%), gastrointestinal dysfunction (4 patients, 28.5%), unstable blood pressure (3 patients, 21.4%), and resting tachycardia (2 patients, 14.2%). Ophthalmoplegia presentations such as diplopia, blurry vision, and nystagmus were reported in 11 patients overall (14.1%). The most common physical examination findings were areflexia/hyporeflexia (74 patients, 94.8%) and reduced MRC score (42 patients, 53.8%). Ataxia was reported in 20 patients (25.6%).

SARS-CoV-2 laboratory and imaging tests results

Blood laboratory tests were reported in 67 patients (85.8%). Lymphopenia was the most frequent abnormality in complete blood count (CBC) analysis (23 patients, 34.3%); followed by 13.4 % for leukocytosis (9 patients); 8.9% for thrombocytopenia (6 patients); 5.9% for each of

leukopenia and thrombocytosis; and 31.3% for normal white blood cell count (WBC) (21 patients).

Among the inflammatory markers, raised C-reactive protein (CRP) and lactate dehydrogenase (LDH) were observed in 24 patients (35.8%) and 11 (14.1%) patients, respectively. Other elevated inflammatory markers were seen in 7 patients (10.4%) for ferritin; 6 patients (8.9%) for each of erythrocyte sedimentation rate (ESR) and D-dimer; less than 5 patients (<7.4%) for each of fibrinogen, CK, creatine phosphokinase (CPK), and Interleukin 6 (IL-6).

SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab was performed in 76 out of 78 patients (97.4%), with only 5 patients (6.5%) having a negative result. Out of all the 49 reported PCR tests for SARS-CoV-2 in fecal, serum, and CSF samples, only 1 case was reported as positive, which was in the fecal sample.[35] Serology for SARS-CoV-2 in serum, was performed in 14 patients (17.9%) and was positive in all of them. The detectable antibodies included IgG (12 patients, 92.3%), IgM (5 patients, 38.4%), and IgA (3 patients; 2.3%). Serology for SARS-CoV-2 in CSF of 9 patients (11.5%) revealed detectable antibodies in 2 cases (22.2.%).[36,37]

To evaluate respiratory system involvement, chest CT scan was ordered in 44 patients (56.4%), 34 (77.2%) of which demonstrated SARS-CoV-2 typical findings, such as ground-glass opacities and interstitial pneumonia.

GBS tests results

Blood laboratory tests

To support the GBS diagnosis, the anti-gangliosides antibodies (anti GD1b-IgG, Asialo-GM1, and GM2-IgG/IgM antibodies) were measured in 40 patients (51.2%), and only 4 patients (10%) were positive for either of them.[13-15,38]

Multiplex PCR in serum and CSF to detect the GBS triggering pathogens was performed in 18 patients (23%), being negative in all of them. Pathogens included human immunodeficiency virus (HIV), human herpesvirus-6 (HHV-6), Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), enterovirus, varicella-zoster virus (VZV), human parechovirus (HpeV), Japanese B virus, dengue viruses (DENV), respiratory syncytial virus (RSV), influenza virus, and Mycobacterium tuberculosis.

Multiplex serology in serum and CSF for infectious pathogens was performed in 24 patients (30.7%), and 3 patients (12.5%) had detectable antibodies for HSV, mycoplasma pneumonia, and rhinovirus.[18,19,39] The pathogens tested for included, Borrelia burgdorferi, tick-borne encephalitis (TBE), HIV, EBV, CMV, VZV, influenza virus, Campylobacter jejuni, syphilis, hepatitis E, hepatitis B, hepatitis C, mycoplasma pneumoniae, Lyme disease, West Nile virus (WNV), and rhinovirus.

Serology panel for autoimmune antibodies, including antinuclear antibodies (ANA), cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), anti-DNA, aquaporin-4, myelin oligodendrocyte glycoprotein was performed in 11 patients (17%), all of which were reported as negative.

Cerebrospinal fluid (CSF) analysis

To confirm the presence of GBS, CSF analysis was performed in 64 patients (82%). The analysis showed albuminocytologic dissociation—defined as high CSF protein without an elevation in WBC[8]—in 48 patients (75%). Protein and WBCs were normal in 11(17%) and 9 (14%) cases, each were increased in 4 patients (6.25%). Increased CSF IgG/albumin ratio with increased CSF and serum oligoclonal bands was reported in 2 patients (3.1%). Gram staining and culture on CSF were performed in 9 cases (14%) and were negative in all of them.

Neurophysiological studies

Nerve conduction studies were performed in 68 patients (87%). AIDP was the most prevalent GBS pattern (54 patients, 79.4%) followed by AMSAN (5 patients, 7.3%), AMAN pattern (4 patients, 5.8%), Miller Fisher subtype (MFS) (4 patients, 5.8%), and mixed pattern of AIDP and AMAN (3 patients, 4.4%).

Neuroimaging

Neuroimaging was performed and reported in 49 out of 78 patients (62.8%). Thirty-three patients (67.3%) underwent spinal MRI, 20 of which had normal findings (60%). Nerve root enhancement at different spinal levels was the most prevalent abnormal finding (10 patients; 30.3%), followed by meningeal enhancement (3 patients; 9.09%). One patient revealed evidence of transverse myelitis in the spinal MRI.[40]

Among 32 reported brain MRI and CT scans, 6 patients (18.7%) showed cranial nerve enhancement, including facial nerve (CN VII) (4 patients, 66.6%),[18,24,41,42] oculomotor (CN III) (2 patients, 33.3%),[14,41] abducens (CN VI) (2 patients, 33.3%),[18,41] trigeminal (CNV), and vestibulocochlear nerve (CN VIII) (1 patient, 16.6%).[41] Leukoencephalopathy was observed in one patient only (3.12%).[23]

Treatment and outcome

Treatment for GBS was started in 67 patients (85.8%), among which 55 patients (82%) received a 5-day course of intravenous immunoglobulin (IVIG), 8 patients (11.9%) underwent plasma exchange, 4 patients (5.9 %) were on plasmapheresis (combined treatment with IVIG in 2 of these patients), and 3 patients (4.4%) received corticosteroid therapy.

The various possible clinical outcomes, reported in a total of 72 patients (92.3%), were clinical improvement

in 57 patients (79.16%), with complete recovery in 7 of them (12.2%). Respiratory failure occurred in 28 patients (38.8%), 18 (64.2%) of which were most likely due to GBS rather than SARS-CoV-2.[15,19,23,37-39,41-50] The mortality of COVID-19 associated GBS was estimated to be 6.4% (5 patients) and 1 patient (1.38%) expired due to self-extubation. COVID-19 associated GBS mortality was attributable to progressive respiratory failure; thus we speculate that GBS associated neuromuscular paralysis was the most likely mechanism for respiratory failure. The results are summarized in Table S2 of Supplementary file 1.[12-71]

Discussion

Demographic and clinical characteristics of patients with COVID-19 associated GBS

Demographic characteristics, clinical presentation, NCV findings, and the outcome of patients with GBS induced by SARS-CoV-2 are similar to GBS triggered by other microorganisms. Male and middle-aged or elderly patients represent the main populations affected by COVID-19 associated GBS, as with GBS triggered by other pathogens.[72] There is a lack of evidence on the incidence of GBS in COVID-19 patients, but a study on hospitalized COVID-19 patients reported PNS involvement in 8.9% of the patients.[4] Interestingly, the familial occurrence of COVID-19 associated GBS was reported in a family from Iran (father and daughter)[73]; this is a rare phenomenon reported in 20 families worldwide.[74] Although the exact genetic basis is not clear, the human leucocytic antigen has been suggested as a potential gene, increasing genetic susceptibility.[74] Another rare occurrence, a coincidence of COVID-19 associated GBS and acute necrotizing myelitis has been reported.[40] Given the evidence of increased immune-mediated responses and inflammatory markers in COVID-19 patients, the coincidence of different immune-mediated diseases triggered by SARS-CoV-2 is possible. Hence, besides the features of GBS, the concurrence of acute transverse myelitis should be suspected when fever, significant asymmetrical paresis, a well-demarcated sensory level, and urinary retention is evident at the beginning.[75]

Patients, who had SARS-CoV-2 presented with GBS after an average duration of 14 days following the respiratory or gastrointestinal manifestations of SARS-CoV-2. Several patients with COVID-19 associated GBS only presented with neurological symptoms.[24-27] Similar findings were noted in a retrospective study on the neurological manifestations of hospitalized patients from China,[4] indicating the importance of physician's role in identifying the unusual initial presentation of COVID-19 with neurological symptoms, as suggested by Farzi et al[62] and Mao et al.[4] This will reduce the failure or delay in SARS-CoV-2 diagnosis in this group of patients, leading to timelier treatment, better prognosis, and lesser transmission to other people.

The clinical pattern of COVID-19 associated GBS was variable, but most patients revealed progressive ascending flaccid paresis and sensory deficits with a demyelinating electrophysiological pattern. This is in contrast to initial reports suggesting the axonal variant as the most frequent subtype.[76]

In general, COVID-19 associated GBS outcome was found to be quite favorable; as seen by clinical improvement in 79.16% of the patients with complete recovery in 12.2% of them. 38.8% of total patients had to be mechanically ventilated due to respiratory failure [15-17,19,23,34,37-39,41-50,52-54]; and eventually, 5 of them (6.4%) expired.[16,17,49,50,53] Most patients received immunoglobulin therapy as the treatment of choice and a favorable response was observed in most of them (87%). However, given the incomplete documentation of diagnostic workup and results with lack of information regarding the patients' follow-up, we do not have enough evidence to discuss the prognostic value of the clinical and diagnostic data

Mechanism of peripheral nervous system involvement; direct invasion or indirect injury?

GBS typically presents as a post-infectious disorder, mostly after a latency phase following respiratory or gastrointestinal infections.[77] That being said, a para-infectious pattern, i.e., occurring during or soon after the viral infection, has also been reported in the literature, as described with ZIKV infection.[5] Well-known preceding organisms include bacteria such as Campylobacter jejuni and viruses such as CMV, EBV, ZIKV, and MERS-CoV outbreak reported in 2012.[2,5,77] Three patients with COVID-19 associated GBS had concomitant infection with rhinovirus, mycoplasma pneumoniae, and HSV.[18,19,39] We speculate that rhinovirus is not the possible GBS triggering factors due to the lack of evidence regarding its association with GBS. Given the possibility of other coinfections with SARS-CoV-2, physicians should rule out other preceding infections through PCR and serology testing.

The underlying mechanism for the development of GBS and PNS damage in patients with SARS-CoV-2 is not fully understood; however, we assume a relationship between these two pathologies due to the development of GBS on the average 14 days after the initial SARS-CoV-2 respiratory or gastrointestinal manifestations. The GBS course identified in this review followed a mixed pattern of para-infectious and post-infectious profile, with post-infectious being the dominant course. The occurrence of GBS before or together with clinical manifestation of SARS-CoV-2 in some patients[21-23] suggests the possible role of subclinical SARS-CoV-2 infection in inducing hyperactive immune responses leading to GBS. On the other hand, physicians should be aware that GBS might occur more than 2 weeks later than the SARS-CoV-2

infection. Hence, they should consider different clinical scenarios as the timely diagnosis and treatment of GBS could improve clinical outcomes.

We speculate that the main mechanism, responsible for the development of GBS in these patients, involves an interplay between the inflammatory cascade and immune-mediated pathway (molecular mimicry) rather than direct viral invasion to the PNS. The molecular similarity between the structures on the surface of the SARS-CoV-2 pathogen, such as human ganglioside-like lipooligosaccharide and the ganglioside molecules located on the peripheral nerve myelin sheath might lead to a cross-reaction of the antibodies, causing damage the peripheral nerves.[78] The reasons supporting immune-mediated pathway are as follows: 1) the presence of SARS-CoV-2 antibodies in the serum and CSF of COVID-19 associated GBS patients and the absence of SARS-CoV-2 virus in the CSF of the patients, suggesting the absence of direct neural invasion by SARS-CoV-2; 2) the presence of antiganglioside antibodies in the serum; 3) the increased level of inflammatory markers such as cytokines, CRP, and ferritin, which leads to activation of neuroinflammatory cascades; and 4) favorable response to IVIG therapy indicating the possible role of the immune-mediated pathway. Furthermore, the ability of SARS-CoV-2 to prompt the inflammatory cascade following leukocyte activation and cytokine release can lead to tissue damage in different organs such as the nervous system and, thus, can induce immune-mediated radiculopathy.[79]

There can be other possible mechanisms for development of GBS in COVID-19 patients. Although our results did not give enough evidence to support this hypothesis; the hypothesis of the direct neural invasion by SARS-CoV-2 is still likely due to the affinity of the S (spike) protein of SARS-CoV-2 to ganglioside-bound sialic acids,[80] which are mostly found in the nervous system, making gangliosides as an initial attachment factor for coronavirus. A different molecular mimicry phenomenon than the one mentioned above, is also possible, as seen by the detection of antiganglioside antibodies only in 4 patients.

The mechanism of respiratory failure

GBS is the most common cause of neuromuscular respiratory failure affecting about 30% of the patient population.[81] In line with the literature, 35.8% of the patients with COVID-19 associated GBS developed respiratory failure requiring mechanical ventilation. We speculate that in 64.2% of patients with COVID-19 associated GBS, GBS associated neuromuscular paralysis was the most likely mechanism for respiratory failure.[15,19,37-39,41-50] This hypothesis could be explained by 1) deterioration of the other neuromuscular symptoms before or at the same time with the onset of respiratory failure such as developing dysautonomia, dysphagia, facial palsy, or limb weakness progression, indicating the worsened neuromuscular status, and 2) concomitant clinical improvement of respiratory function and muscle strength following treatment.

However, we cannot completely overlook the possible role of SARS-CoV-2 in the development of respiratory failure in these patients due to the presence of lung involvement as well as the new evidence of respiratory center suppression due to medulla oblongata involvement by the coronavirus.[82] It is important to note that the occurrence of neuromuscular paralysis in GBS could worsen the course of respiratory failure in SARS-CoV-2 patients. Therefore, physicians must consider GBS as a possible diagnosis in case of a respiratory exacerbation or inability to wean from mechanical ventilator in patients with neurological symptoms. In this review, 82% of patients with respiratory failure had at least one of the potential risk factors for developing respiratory failure, including bulbar weakness, dysautonomia, and reduced MRC sum score.[81] Considering ventilated patients' poor outcomes, physicians need to consider these factors before the patients develop respiratory distress symptoms.

Limitations

There are some limitations to the current study. First, the COVID-19 diagnostic workup was not consistent among studies. In most cases, SARS-CoV-2 was diagnosed by PCR in the nasopharyngeal swab and in some others, by lung CT-Scan, which is inferior to RT-PCR for the initial detection of COVID-19. Second, some of the included studies did not precisely report the time interval between respiratory and neurologic symptoms. The third limitation would be, that in most studies, no screening viral and bacterial panel tests were performed to rule out concomitant infection by other microorganisms associated with GBS. Fourth, as mentioned above, there is not enough evidence regarding the short-term and long-term prognosis of COVID-19 associated GBS due to inappropriate documentation of diagnostic workup and the patients' follow-up.

Conclusion

This systematic review contributes to improving physicians' knowledge regarding the probability of association between SARS-CoV-2 infection and GBS in the current pandemic setting, and the possible mechanisms. The timely detection of GBS is crucial to prevent poor clinical outcomes, considering the associated morbidities such as respiratory failure, which may add to the severity of the known impact of SARS-CoV-2 on the respiratory system. On the other hand, clinicians must be vigilant to identify the clinical findings of SARS-CoV-2 infection in newly diagnosed GBS patients, as this might be a neurological complication of the subclinical viral infection.

Conflict of Interest

Authors declare no conflict of interest in this study.

Ethical Approval
Not applicable

Authors' Contribution
MaK, PD, NM and MoK performed the literature review and prepared the draft. SS, SM, and HN confirmed the accuracy of extracted information. RB, GC, and GM provided critical revisions to the draft.

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Supplementary materials
Supplementary file 1 contains Tables S1 and S2.

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