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Review Article

Guillain Barré Syndrome and its variants as a manifestation of COVID-19: A systematic review of case reports and case series

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ABSTRACT

Background: The COVID-19 pandemic caused by SARS-CoV-2 began in Wuhan, China in December 2019. Reports of COVID-19 with central (CNS) and peripheral nervous (PNS) system manifestations are emerging. In this systematic review, we compared and summarized the demographics, clinical features, Brighton criteria, immunological and laboratory findings with a focus on modified Erasmus GBS Outcome Score (mEGOS) in SARS-CoV-2 patients with GBS and its variants.

Methods: Based on PRISMA guidelines, we searched three databases (PubMed, Scopus, and Google Scholar) for studies on COVID-19 and GBS between December 1, 2019 to July 15, 2020. For descriptive analysis, we studied two groups with: 1) acute inflammatory demyelinating polyradiculoneuropathy (AIDP) variant, and 2) Non-AIDP/Other variants. We compared mEGOS scores for patients in both groups along with other key clinical features.

Results: Of the 50 GBS cases identified from 37 studies, 33 (66%) had acute inflammatory demyelinating polyradiculoneuropathy (AIDP) while 17 (34%) were of other (non-AIDP) variants. There mEGOS scores did not differ between AIDP patients and AMAN/AMSAN patients. Majority of the AIDP (66.7%) and AMAN/AMSAN (57.2%) patients belonged to Brighton level 1 indicating maximum diagnostic certainty.

Conclusion: To our knowledge, this is among the first reviews that includes GBS variants and the clinical prediction tool mEGOS for prognostication in COVID-19 patients. Further research is needed to assess whether IVIG is preferable over plasmapheresis in this population of GBS patients. It would also be crucial to follow these patients over time to identify the long-term disability as well as treatment outcomes.

Abbreviations: nCov, Novel Coronavirus; AIDP, Acute inflammatory demyelinating polyneuropathy; AMSAN, Acute motor-sensory axonal neuropathy; AMAN, Acute motor axonal neuropathy; BFP, Bifacial weakness with paresthesias; BBE, Bickerstaff’s brainstem encephalitis; MFS, Miller-Fisher syndrome; COVID-19, Coronavirus infectious disease-2019; GBS, Guillain-Barre Syndrome; MERS, Middle East Respiratory Syndrome; SARS-CoV-2, Severe Acute Respiratory Distress Syndrome coronavirus 2; IDSA/ATS, Infectious Disease Society of America/American Thoracic Society; HCQ, Hydroxychloroquine; PLEX, plasmapheresis; IVIG, Intravenous immunoglobulin; IL, Interleukin; mEGOS, Modified Erasmus GBS Outcome Score; IGOS, International GBS Outcome Study; EMG, Electromyography; MRI, Magnetic Resonance Imaging; CSF, Cerebrospinal fluid; HIV, Human immunodeficiency virus; RT-PCR, Reverse transcriptase polymerase chain reaction; WHO, World Health Organization; MRC, Medical Research Council Scale for Muscle Strength.

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1. Introduction

The novel coronavirus disease-2019 (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was officially declared a pandemic on March 11, 2020 by the World Health Organization (WHO) due to its rapid spread worldwide [1]. Previous outbreaks of coronaviruses have included the severe acute respiratory syndrome (SARS) in 2002 and the Middle East respiratory syndrome (MERS) in 2012 [1–4]. SARS-CoV-2 novel coronavirus shares several common viral characteristics with SARS-CoV. Importantly, it has an even stronger affinity towards Angiotensin Converting Enzyme 2 (ACE2) receptor found in the human glial cells, neurons, respiratory epithelial and vascular endothelial cells [5–7]. Studies have found that the most frequent neurological manifestations among COVID-19 infected individuals are ischemic stroke, Guillain-Barré Syndrome (GBS) and encephalopathy due to ICU syndrome, cytokine storm with high fevers and ventilator use [8,9]. Similar neurological outcomes have been reported in previous coronavirus epidemics caused by SARS-CoV and MERS-CoV [10–12]. 

GBS is an acute immune mediated polyradiculoneuropathy that affects motor, sensory and autonomic nerves. It presents with a wide range of neurological manifestations, the most serious being rapidly progressive flaccid paralysis [13–16]. The most severe manifestation leads to acute respiratory failure [15–17]. Overlap of respiratory paralysis in GBS and COVID-19 infection makes it critically important for the physicians to diagnose and manage GBS early in all patients of COVID-19, recognizing that respiratory compromise due to GBS may be rapidly progressive but treatable with a high success rate in COVID-19 patients [14,18–20].

The common variants of GBS are: Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) which is a motor sensory demyelinating disorder; and Acute motor axonal neuropathy (AMAN), and Acute motor polyradiculoneuropathy (AIDP) which is a motor sensory demyelinating disorder; and Acute motor axonal neuropathy (AMAN), and Acute motor sensory demyelinating polyradiculoneuropathy (CIP) and critical illness myopathy; 3) Duplicate studies, studies with missing clinical data, review articles and articles unrelated to our study objective were excluded and 179 full-text literatures were reviewed in accordance with our study objective. We included 40 studies for review that met our above-mentioned inclusion criteria, out of which 37 were of COVID-19 and GBS, 2 were of SARS and GBS and 1 was of MERS and GBS. We excluded studies on SARS and MERS from statistical analysis due to low sample size although we briefly describe these cases in Discussion. Therefore 37 studies of COVID-19 and GBS were reviewed for descriptive analysis (Figure-1).

2. Methods

2.1. Study design

We conducted a thorough literature review in July 2020 using the terms “COVID-19 and GBS”, “SARS and GBS” and “MERS and GBS”. We searched PubMed, Google Scholar and Scopus databases for identifying case series and case reports published between December 1, 2019 to July 15, 2020 for COVID-19; January 01, 2002 to December 31, 2004 for SARS; January 1, 2012 to December 31, 2018 for MERS. Two reviewers independently conducted the search to identify the studies matching the keywords used. Studies describing the cases with SARS-CoV-2, SARS and MERS with GBS were included in the study (Fig. 1), while review articles and consensus statements were excluded from the analysis. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the display of inclusions and exclusions [60]. Based on our search criteria, we found 1699 studies from PubMed, Google Scholar and Scopus. Duplicate studies, studies with missing clinical data, review articles and articles unrelated to our study objective were excluded and 179 full-text literatures were reviewed in accordance with our study objective. We included 40 studies for review that met our above-mentioned inclusion criteria, out of which 37 were of COVID-19 and GBS, 2 were of SARS and GBS and 1 was of MERS and GBS. We excluded studies on SARS and MERS from statistical analysis due to low sample size although we briefly describe these cases in Discussion. Therefore 37 studies of COVID-19 and GBS were reviewed for descriptive analysis (Figure-1).

2.2. Inclusion criteria

The inclusion criteria for the published studies included: 1) Patient age ≥ 18 years; 2) COVID-19 diagnosis confirmed by RT-PCR nasopharyngeal or serum antibody test; 3) GBS confirmed through clinical presentation, and diagnostic tests inclusive of EMG and cerebrospinal fluid (CSF) studies.

2.3. Exclusion criteria

The exclusion criteria for the studies include: 1) Patient age < 18 years; 2) COVID-19 patients with diagnosis other than GBS such as myopathy, toxic induced polyneuropathy, critical illness polyneuropathy (CIP) and critical illness myopathy; 3) Duplicate studies which involved repetition of cases 4) Studies in languages other than English; 5) Exclusion of studies with GBS which did not have confirmatory diagnosis of COVID-19.

Furthermore, we excluded a patient from a case series study as the GBS variant was not described [44]. This resulted in a total of 50 cases from 37 studies as the final count for our review.

2.4. Quality assessment

The critical appraisal checklist for case reports provided by the Joanna Briggs Institute (JBI) was used to perform assessment of overall quality of case series and case reports.

2.5. Data acquisition

From the selected studies, we extracted the following variables for our analysis: study type, date of publication, country of case origin, age, gender, clinical presentation of GBS and its variants (including paraparesis/quadruparesis, cranial nerve deficits and diarrhea), diagnostic tests for SARS-CoV-2 infection in including RT-PCR nasopharyngeal and serum antibodies, latency between COVID-19 symptom onset and initial symptoms of GBS, severity of COVID-19 (based on IDSA/ATS criteria...
which includes either vasopressor use due to septic shock or requirement of mechanical ventilation [61], mEGOS scoring scale that we calculated based on clinical data reported in paper, treatments including standard commercially available IVIG, PLEX, chloroquine, hydroxychloroquine (HCQ), azithromycin, IL-6 blockers (tocilizumab), corticosteroids, cerebrospinal fluid (CSF) total protein levels, anti-ganglioside antibodies, imaging findings, EMG/NCS findings, Brighton electrophysiological criteria and mortality outcomes.

2.6. Data analysis

Pooled descriptive analyses were conducted to assess differences among two main types of GBS variants for all patients across the 37 case reports and case series published in 13 different countries. Table 1 shows a detailed breakdown of studies with information on their respective country, type of study (case series/case report), number of patients in the study, age, gender, and type of GBS variant. Of the 50 cases, 12 were from Italy, 8 from the US, 6 each from Iran and Spain, 4 each from France and Switzerland, 3 from Germany, 2 from the UK, and 1 each from Austria, Canada, China, Morocco and Netherlands. Of all the 50 cases, 66% (n = 33) were of AIDP variant, 14% (n = 7) MFS variant, 12% (n = 6) AMSAN variant, 4% (n = 2) BFP variant, and 2% (n = 1) each of AMAN and polyneuritis cranialis variants.

Tables 2 and 3 display the clinical characteristics of GBS and its variants. There was a significant difference in both the groups (AIDP vs. Non AIDP/Other GBS variants) with regards to age, p-value = 0.02 (Table 2). Furthermore, the age difference was not significant (p = 0.08) while comparing three variant groups (AIDP vs AMSAN/AMAN vs Others) (Table 3). There were 35 males and 15 females in the study. Seventy percent of the AIDP patients, 58% AMSAN/AMAN patients and 80% of the other variants were males.

3. Results

A total of 50 patients with COVID-19 diagnosed with GBS were used for analyses from the 37 case reports and case series published in 13 different countries. Table 1 shows a detailed breakdown of studies with information on their respective country, type of study (case series/case report), number of patients in the study, age, gender, and type of GBS variant. Of the 50 cases, 12 were from Italy, 8 from the US, 6 each from Iran and Spain, 4 each from France and Switzerland, 3 from Germany, 2 from the UK, and 1 each from Austria, Canada, China, Morocco and Netherlands. Of all the 50 cases, 66% (n = 33) were of AIDP variant, 14% (n = 7) MFS variant, 12% (n = 6) AMSAN variant, 4% (n = 2) BFP variant, and 2% (n = 1) each of AMAN and polyneuritis cranialis variants.

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We explored the differences between groups with regards to
Among the AIDP group, 29 cases had RT-PCR positive, 3 negative and the study underwent confirmatory testing for diagnosis of COVID-19. The mean mEGOS scores for AIDP patients and compared them with were positive for antiganglioside antibodies. Further, we also explored SARS-CoV2 antibody was positive. Ganglioside antibody tests were re patients tested positive with RT-PCR, one patient tested negative and 6 cases had SARS-CoV2 IgG positive. For the non-AIDP group, 16 pa- laboratory testing for COVID-19 (Table 2). All the patients included in the study underwent confirmatory testing for diagnosis of COVID-19. Among the AIDP group, 29 cases had RT-PCR positive, 3 negative and 6 cases had SARS-CoV2 IgG positive. For the non-AIDP group, 16 patients tested positive with RT-PCR, one patient tested negative and SARS-CoV2 antibody was positive. Ganglioside antibody tests were reported for 28 patients, 17 patients in the AIDP group and 11 in Non-AIDP group. One patient in AIDP and one patient in non-AIDP group were positive for antiganglioside antibodies. Further, we also explored the mean mEGOS scores for AIDP patients and compared them with AMAN/AMAN patients for the probability of walking independently after 6 months of admission. Mean mEGOS score for patients with AIDP variant (6.8 ± 3.8) was lower compared to AMAN/AMAN (8 ± 5.2, p = 0.57 (Table 2).

Table 3 shows the pattern of symptomatology among three groups (AIDP, AMAN, and Others [BFP, MFS, and Polyneuritis Cranialis]). Although non-significant, a greater proportion of AIDP-GBS variant patients reported paraparesis (36.4%) and quadriparaparesis (48.5%) as compared to AIDP/AMAN patients (28.5% paraparesis and 14.3% quadriparaparesis). There was a significantly greater proportion of patients with ascending paralysis in AIDP-GBS variant (90.9%) compared to AIDP/AMAN-GBS variant patients (85.7%) and other variants (30%). Conversely, 48.5%, 12.2% and 6% patients of AIDP-GBS variant had CN VII palsy, CN IX and X palsy, respectively, compared to 42.9%, 14.3% and 14.3% of patients with AIDP/AMAN-variant GBS (Table 3). A total of 6(24%) patients presented with diarrhea in the AIDP sub-group, whereas 4 cases with diarrhea (40%) were reported in other variants; no diarrhea was reported in AIDP/AMAN variants sub-group (Table 3). The mean latency for the AIDP group was 12.5 ± 7.7, for AIDP/AMAN was 11.1 ± 4.9 and for others was 9.2 ± 6.0 (0.34).

CSF protein levels were highest in the AMAN/AMAN (103.1 ± 52.9), and AIDP groups (100.5 ± 61.5) and then other variants (65.7 ± 23.7) but the differences were not significant. Further details of clinical characteristics are described in Table 3. Albuminocytological dissociation was present in 26 out of 31 AIDP patients (84%), 5 out of 6 patients in AMAN/AMAN/AMAN (83%) and 5 out of 7 patients with other variants (71%) (refer Table 3).

In our entire cohort, we found a total of 17 cases in which MRI imaging of brain and cranial nerves was reported. Among them, 6 (35%) had abnormal findings that included cranial nerve CN III, CN VI and CN VII enhancement. Apart from these, one case of leptomeningeal enhancement of brainstem and cervical spine was noted (24). MRI of the lumbosacral spine was also performed in 36% of the cases (18/50), of which 5 (27%) were found to have abnormal spine nerve root enhancement and the remaining 73% (13/18) had normal spine imaging.

Finally, we assessed whether the patients fulfilled the Brighton criteria for diagnosis of GBS. All the patients fulfilled the Brighton Criteria and were further divided into separate levels. Level 1 of Brighton criteria indicates the maximum diagnostic certainty while Level 4 indicates the least diagnostic certainty. We found that 66.7% (22/33) of AIDP patients belonged to Level 1 of the Brighton criteria, 24.2% (8/33) patients belonged to Level 2, 6% (2/33) patients belonged to Level 3 and 3% of the patients (1/33) belonged to Level 4. Among the 7 patients in the AMAN/AMAN group, 4 patients (57.2%) belonged to Level 1 and 3 patients (42.8%) belonged to Level 2. Out of the 10
remaining patients. Out of all the patients who received IVIG, 10 patients which 3 had AIDP and 2 patients had AMAN/AMSAN. In 3 cases (6.8%), patients (22.8%) had prolonged hospitalization at the time of reporting, 5 (32%) had other GBS variants. No data was available for treatment of the COVID-19 infection and GBS (refer Table 4). For COVID-19, this included use of HCQ, antivirals, IL-6R blockers and antibiotics. For GBS, it included use of IVIG and PLEX. Noticeably, a significantly greater probability of being unable to walk independently after 6 months of admission, EMG findings, to summarize our reported findings.

4. Discussion

In current analysis, we identified and reviewed a total of 50 cases of patients belonging to other variants, only 1 patient each (10% each) belonged to Level 1 and 2 respectively and 8 (80%) patients belonged to Level 4 indicating least diagnostic certainty (refer Table 3). We also compared differences in treatments of GBS variant groups administered for both COVID-19 and GBS (refer Table 4). For COVID-19, this included use of HCQ, antivirals, IL-6R blockers and antibiotics. For GBS, it included use of IVIG and PLEX. Notably, a significantly greater proportion of patients with AIDP variant reported HCQ use, compared to patients with other variants (52.9% vs. 21.1%). For other treatments, no significant differences were found between the two groups. In our review, 44 patients received IVIG, out of which 30 (68%) had AIDP and 14 (32%) had other GBS variants. No data was available for treatment of the reporting patients. Out of all the patients who received IVIG, 10 patients (22.9%) had prolonged hospitalization at the time of reporting, 5 of whom still needed ICU care and only 5 had a fatal outcome among which 3 had AIDP and 2 patients had AMAN/AMSAN. In 3 cases (6.8%), outcomes were not reported. Recovery was observed in 31 patients (70.4%), of which, 21 had AIDP and 10 had other variants. However, this data is limited by lack of long term follow up.

Finally, Table 5 shows a detailed breakdown of the studies with respect to Brighton criteria, mEGOS scores and mEGOS score percentage probability of being unable to walk independently after 6 months of admission, EMG findings, to summarize our reported findings.

### Table 2

| Characteristics                  | GBS subtype       | P-value |
|----------------------------------|-------------------|---------|
|                                  | AIDP n (%)        | Non-AIDP/other n (%) |
| Demographics                     |                   |         |
| Number of patients               | 33 (66.0)         | 17 (34.0) |
| Age, years (Mean ± SD)           | 62 ± 9.9          | 52 ± 16.3 |
| Gender                           |                   |         |
| Male                             | 23 (69.7)         | 12 (70.6) |
| Female                           | 10 (30.3)         | 5 (29.4) |
| Laboratory tests                 |                   |         |
| RT-PCR Nasopharyngeal test (SARS-CoV-2) |       | 0.67     |
| Positive                         | 29 (90.6)         | 16 (94.1) |
| Negative                         | 3 (9.7)           | 1 (5.9) |
| Serological SARS-CoV-2 antibody test (confirmatory) |   |         |
| Positive                         | 1 (4.8)           | 1 (9.1) |
| Antiganglioside antibody         |                   | 0.63     |
| GM2 IgM                          |                   |         |
| GD1b-IgG                         |                   |         |
| Mechanical ventilation           |                   | 1.00     |
| Ventilated                       | 20 (62.5)         | 10 (62.5) |
| Not ventilated                   | 12 (37.5)         | 6 (37.5) |
| Outcome                          |                   | 0.74     |
| Survived                         | 27 (90.0)         | 13 (86.7) |
| Dead                             | 3 (10.0)          | 2 (13.3) |
| mEGOS score (Mean ± SD)*         | 6.8 ± 3.8         | 8 ± 5.2  |
|                                   | 0.57               |         |

* p < 0.05 indicates significant

### Table 3

| Characteristics                  | GBS subtype       | P-value |
|----------------------------------|-------------------|---------|
|                                  | AIDP n (%)        | AMAN/AMSAN n (%) | Others n (%) |
| Demographics                     |                   |         |             |
| Number of patients               | 33                 | 7 (14)  | 10 (20)     |
| Age, years (Mean ± SD)**         | 62 ± 9.9           | 58 ± 17.3| 48 ± 17.3  |
| Gender                           |                   |         |             |
| Male                             | 23                 | 4 (57.1) | 8 (80)      |
| Female                           | 10                 | 3 (42.8) | 2 (20)      |
| Clinical presentation            |                   |         |             |
| Ascending paralysis              | 30                 | 6 (85.7) | 3 (30.0)   |
| Paraparesis                      | 12                 | 2 (28.5) | 3 (17.7)   | <0.001** |
| Quadriparesis                    | 16                 | 1 (14.3) | 1 (10.0)   | 0.04     |
| Duration between CoV infection and GBS presentation (Days, Mean ± SD) | | | | |
| Cranial Nerve X palsy            | 2 (6.1)            | 3 (42.8) | 6 (60.0)   | 0.01     |
| Cranial Nerve VI palsy           | 0.00               | 0.00     | 3 (30.0)   | NA       |
| Cranial Nerve VII palsy          | 0.00               | 0.00     | 3 (30.0)   | NA       |
| Cranial Nerve X palsy            | 4 (12.2)           | 1 (14.3) | 1 (10.0)   | NA       |
| Cranial Nerve II palsy           | 2 (6.0)            | 1 (14.3) | 1 (10.0)   | NA       |
| Preceding infection              | 8 (24.2)           | 0 (0.0)  | 4 (40.0)   | 0.16     |
| Duration between CoV infection and GBS presentation (Days, Mean ± SD) | | | | |
| CNS - Cerebrospinal fluid        |                   |         |             |
| Alumino-cytological dissociation |                   |         |             |
| Present                          | 26                 | 5 (83.3) | 5 (71.4)   | 0.74     |
| Absent                           | 5 (16.1)           | 1 (16.7) | 2 (28.5)   |         |
| Brighton criteria                |                   |         |             |
| Total                            | 33                 | 10 (30.3)| 50          |

** p < 0.05 indicates significant.

GBS with COVID-19 from 39 studies identified worldwide through different case series and reports [5,8,15,16,18–26–57]. The cases were categorized into two groups for further statistical analysis, “AIDP” versus “Non-AIDP/Other variants” which included MFS, AMAN, BFP, AMAN and Polyneuritis cranialis; and further into “AMAN/AMSAN” and “other variants” within the non-AIDP group for subanalysis of specific variables where indicated. The novel addition to our review was use of Brighton criteria for strength of diagnosis and employment of mEGOS score for prognosis on the appropriate GBS variants. GBS is a relatively rare disease of the peripheral nervous system (PNS) having an incidence
of 1.6 / 100,000 person-years [17]. Studies in COVID-19 patients have suggested a link between GBS and SARS-CoV-2. A large Italian study of 1200 patients admitted with SARS-CoV-2 reported an incidence of 0.42% for GBS, much higher than that for the general population [8]. Recent studies interestingly found GBS as one of the most frequent neurological manifestations of peripheral nervous system in COVID-19 patients [5,8,15,16,18–26–57].

The most frequent GBS variant in association with COVID-19 in our analysis was AIDP, which is consistent with the literature in general [17] nearly 66% of GBS cases had AIDP. We found significant differences between AIDP vs. Non-AIDP/Other variants in age at onset; the mean age for AIDP was 62 ± 9.9, 58 ± 17.3 for AMAN/AMSAN and 48 ±/− 15.1 for MFP, BPN and Polynuertis cranialis.

A latency period between the onset of the GBS symptoms and onset of COVID-19 has been reported in recent papers [8,14,40]. A prior study by Caress et al. showed an average latency of 11 days from the onset of COVID symptoms to the presentation of GBS [14]. The mean latency between COVID-19 infection and presentation of GBS between AIDP, AMSAN/AMAN and MFP, BPN and Polynuertis cranialis groups analyzed in our review did not vary significantly and ranged between a duration of 11 to 13 days. There are reports of GBS in SARS-CoV-2 positive individuals who were asymptomatic from the point of view of COVID-19 [29,39]. Additionally, Zhao et al. also reported case where the latency period was recorded as 0 days since GBS-like neurological features preceded the diagnosis of COVID-19 [43]. This latency between the onset of COVID-19 manifestations and GBS symptoms provides clues to the pathogenesis of GBS in SARS-CoV-2 infection. The postinfectious mechanism of GBS is supported by the finding of autoantibodies that result from an immune response directed to an epitope of the infectious agent that then cross-reacts with a structurally similar component of peripheral nerve, resulting in delayed immune-mediated damage to the peripheral nerve [21,52]. This has been well demonstrated in several GBS variants as well as GM1 gangliosides IgG Ab with C. jejuni infection [62] and has been postulated with other infectious agents including Mycoplasma pneumoniae, H pylori and several viruses [10,11,13,21–25].

For GBS triggered by SARS-CoV-2, it is hypothesized that the attachment of SARS-CoV-2 to cell surfaces is mediated by the viral spike (S) protein, which binds to angiotensin-converting enzyme 2 Receptor and also to gangliosides containing sialic acid residues, including the GalNAc residue of GM1 [7,14,20]. It has been suggested that cross-reactivity between the viral protein-associated gangliosides and peripheral nerve gangliosides as the result of molecular mimicry. In our review, we identified 28 patients in the entire cohort (56%) for whom ganglioside antibody tests were performed. Serum ganglioside antibodies were found to be positive in 2 cases (7%), one in each group (i.e., AIDP and Non-AIDP/Other variants). GD1b IgG antibodies were positive in the MFS subtype of GBS case whereas GM2 IgM, IgG was positive in AIDP variant [32,57]. Interestingly, a case reported by Lantos and colleagues had equivocal lab values of GM1 antibody [34]. Alternatively, the mechanism of nerve damage may be primarily facilitated by T-cell activation and release of inflammatory mediators by macrophages. A systematic evaluation of associations of ganglioside antibodies in GBS with COVID-19 will be needed before the mechanisms are clarified. A novel para infectious mechanism for GBS mediated by the generalized, hyperinflammatory response that occurs with COVID-19 was suggested by some authors because the acute symptoms overlap with the onset of GBS and autoantibodies were not detected in their cases [5,43]. However, when all of the cases are considered, the clinical, antiganglioside testing and electrodiagnostic patterns are similar to those of typical GBS cases [14,29,50].

RT-PCR nasopharyngeal swab and serological antibody tests are currently standard and recommended for diagnosing SARS-CoV-2 infection [63]. In our review, out of a total cohort of 50 patients, 49 patients (98%) underwent nasopharyngeal RT-PCR test. A positive test was obtained in 45 patients (91%) and the rest 4 (9%) had a negative test result. The remaining 5 cases (10%) were diagnosed with COVID-19 with a confirmatory serum SARS-CoV-2 IgG antibody test [5,8,33,37,55] (Table 2). Interestingly, none of the reported patients had positive PCR for SARS-CoV-2 in the CSF. The absence of evidence of active infection when the patients have clinical GBS infection supports an immune-mediated mechanism is the most likely pathophysiology behind GBS associated with SARS-CoV-2. Whether this immune-mediated process results from molecular mimicry triggered in the peripheral immune system or results from release of PNS antigens by earlier asymptomatic damage by the virus leading to release of PNS into the peripheral immune system which responds by initiating an autoimmune process is not clear [15,16,37]. Indeed, different scenarios in different patients are possible.

In addition to the clinical evaluation, CSF protein elevation is a known critical biomarker which can be a useful tool to identify the disease severity and extent [64]. Additionally, mean CSF total protein levels were highest among patients with AMAN/AMSAN (103.1 ± 52.9) and AIDP-GBS (101 ± 61.6 mg/dl) variants. For our analysis, we considered CSF total protein of > 45 mg/dl as elevated. Albuminocytological dissociation was found in 36 patients (72%), of which 26 had AIDP (72%) and 10 had other variants (28%) (Table 2).

Modified Erasmus GBS Outcome score (mEGOS) is a key prognostic indicator that helps predict the long-term outcomes of patients based on their clinical presentation at day 7 of admission. Therefore, the higher the score, the greater probability of disability to walk independently at 6 months after admission. This score has been shown to be of significant predictive value in multiple cohort studies in GBS patients [65,66]. On further analysis, the mean mEGOS score for both groups of patients (AIDP vs AMSAN/AMAN) were compared, and did not show a significant difference. Mean mEGOS score for patients with AIDP (6.8 ± 3.8) was considerably lower compared to AMAN/AMSAN variants (8 ± 5.2) (Table 5). We also used the Brighton criteria to differentiate the certainty of classification of the reported variants of GBS [59]. The Brighton criteria is an important tool to evaluate patients using different features for confirmation of diagnosis of GBS and classification of its variants, including MFS. It assesses the patient’s clinical presentation, exam findings, and diagnostic testing to help scoring levels 1–4 of diagnostic certainty (level 1 being the highest certainty). The criteria are key is assisting with diagnosis in low to high risk patients, as well as prompt diagnosis early on in the course of disease. It also helps in guiding different treatment options according to the patient’s diagnosis.

All of the cases included in our analysis fulfilled the Brighton Criteria. Majority of the AIDP cases (66.6%) and the AMAN/AMSAN cases (51.7%) belonged to Level 1, marking the highest diagnostic certainty. While the majority of the patients belonging to the other variants (80%) were Level 4 indicating the least diagnostic certainty (Table 3). In our entire cohort, we found a total of 17 cases in which MRI imaging of brain and cranial nerves was reported. Among them, 6 (35%) had abnormal findings that included cranial nerve CN III, CN VI and CN VII enhancement [8,27,29,34,44,47]. Apart from these, one case of leptomeningeal enhancement of brainstem and cervical spine was noted [27]. MRI of the lumbosacral spine was also performed in 36% of the cases (18/50), of which 5 (27%) were found to have abnormal spine nerve root enhancement and the remaining 73% (13/18) had normal
### Table 5

Electromyographic features mEGOS score, Brighton Criteria for COVID-19 and GBS and its variant.

| Author/country             | Time from neurological presentation to EMG | GBS subtypes based on original article | **mEGOS at day 7 of admission** | Percentage ability to walk after 6 months | NCS findings consistent with one of the subtypes of GBS | **Brighton Criteria Level of diagnostic Certainty (1–4)** |
|----------------------------|------------------------------------------|--------------------------------------|-------------------------------|------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|
| Ottaviani D et al. [16] / Italy | 10 days                                | AIDP                                 | 11                           | 56%                                      | Prolonged DL and slowed CV in tibial/peroneal nerves    | 1                                                  |
| Pflefferkorn T et al. [56] / Germany | 2 days                                 | AIDP                                 | No data available             | No data available                      | Reported as demyelinating pattern, no EMG data available | 2                                                  |
| Scheidt E et al. [39] / Germany | 10 days                                 | AIDP                                 | 1                            | 2%                                       | Prolonged distal latency but preserved CV in 1 nerve (peroneal) | 1                                                  |
| Hutchins K.L et al. [47] / USA | 3 days                                  | BFP                                  | No data available             | No data available                      | Slow peroneal and median nerve, prolonged DL and slow CV  | 4                                                  |
| Arnaud S et al. [46] / France | 5 days                                  | AIDP                                 | No data available             | No data available                      | Slow CV in bilateral tibial and peroneal nerves         | 1                                                  |
| Su X.W.et al [49] / USA | 13 days                                 | AIDP                                 | 12                           | 66%                                      | Prolonged DL and slow CV in tibial and peroneal nerves   | 1                                                  |
| Riva N et al. [37] / Italy | 5 days                                  | AIDP                                 | 7                            | 18%                                      | There is conduction block and slow CV in peroneal and median nerves | 2                                                  |
| Omrani H. El. et al. [31] / Morocco | 10 days                                 | AMSAN                                | No data available             | No data available                      | Reported as acute motor and sensory axonal neuropathy pattern, no EMG data available | 1                                                  |
| Camdessananche J.P. et al. [18] / France | 5 days                                  | AIDP                                 | 11                           | 56%                                      | B/L-tibial nerve distally with slow CV and prolonged DL  | 1                                                  |
| Caamano D.S.J. et al. [28] / Spain | NA                                     | BFP                                  | NA                           | NA                                      | EMG data not available                                    | 4                                                  |
| Webb S et al. [42] / U.K. | 3 days                                  | AIDP                                 | 8                            | 25%                                      | Prolonged DL and slow CV in tibial/peroneal nerves       | 1                                                  |
| Asnini A et al. [15] / Italy | NA                                     | MFS                                  | NA                           | NA                                      | Reported as demyelinating pattern, no EMG data available  | 4                                                  |
| Asnini A et al. [15] / Italy | NA                                     | AMSAN                                | No data available             | No data available                      | Reported as acute motor and sensory axonal neuropathy pattern, no EMG data available | 2                                                  |
| Toscano G et al. [8] / Italy | 2 days                                  | AMSAN                                | 11                           | 56%                                      | Reduced amplitudes in tibial/ulnar nerves (ulnar sensory) | 1                                                  |
| Toscano G et al. [8] / Italy | 12 days                                 | AMSAN                                | 0                            | 1%                                       | Tibial nerve with reduced amplitudes and mildly prolonged DL and ulnar sensory reduced amplitude | 1                                                  |
| Toscano G et al. [8] / Italy | 1 day                                   | AMAN                                 | 10                           | 45%                                      | Tibial and ulnar motor nerves reduced amplitudes         | 1                                                  |
| Toscano G et al. [8] / Italy | 2 days                                  | AIDP                                 | No data available             | No data available                      | Prolonged DL and slow CV in tibial nerve, prolonged F wave | 2                                                  |
| Toscano G et al. [8] / Italy | 4 days                                  | AIDP                                 | 11                           | 56%                                      | Prolonged DL and slow CV in tibial nerve                 | 2                                                  |
| Dinkin M et al. [44] / USA | NA                                     | MFS                                  | NA                           | NA                                      | EMG data not available                                    | 4                                                  |
| Dinkin M et al. [44] / USA | NA                                     | N/A                                  | 2                            | 2%                                       | EMG data not available                                    | 4                                                  |
| Gutierrez-Oritz C et al. [32] / Spain | NA                                     | NA                                   | NA                           | NA                                      | EMG data not available                                    | 4                                                  |
| Gutierrez-Oritz C et al. [32] / Spain | NA                                     | Polyneuritis Cranialis               | NA                           | NA                                      | EMG data not available                                    | 4                                                  |
| Sedaghat Z et al. [46] / Iran | 9 days                                  | AMSAN                                | 11                           | 56%                                      | Prolonged CV and reduced amplitude in tibial nerves      | 2                                                  |
| Zhao H et al. [43] / China | 5 days                                  | AIDP                                 | 5                            | 8%                                       | Preserved CV only peroneal nerve has prolonged DL         | 1                                                  |
| Virani A et al. [41] / USA | Not done                                | AIDP                                 | 11                           | 56%                                      | EMG data not available                                    | 3                                                  |
| Alberti P et al. [26] / Italy | NA                                     | AIDP                                 | No data available             | No data available                      | Slow CV and prolonged DL in peroneal nerve               | 1                                                  |
| Padroni M et al. [35] / Italy | 2 days                                  | AIDP                                 | 2                            | 2%                                       | Preserved CV only peroneal nerve has prolonged DL/Equivocal as only findings slow CV at median and ulnar nerve | 1                                                  |
| Coen M et al. [30] / Switzerland | NA                                     | AIDP                                 | No data available             | No data available                      | Reported as demyelinating pattern, no EMG data available | 1                                                  |
| Mozdehipanah H et al. [50] / Iran | 6 days                                  | AIDP                                 | 0                            | 1%                                       | Prolonged DL bilateral tibial and slow CV in tibial       | 1                                                  |
| Mozdehipanah H et al. [50] / Iran | N/A                                    | AMSAN                                | No data available             | No data available                      | Fulfill criteria reduced amplitude intact DL and preserved CV (tibial/peroneal) | 1                                                  |
| Mozdehipanah H et al. [50] / Iran | N/A                                    | AIDP                                 | 8                            | 25%                                      | Fulfill criteria prolong DL and slow CV in median, ulnar, tibial nerve | 1                                                  |
| Tiet M.Y.et al. [51] / U.K. | N/A                                    | AIDP                                 | 10                           | 45%                                      | Fulfill criteria slow CV in median, prolong DL in median, ulnar, tibial nerve | 1                                                  |
| Ebrahimzadeh S.A. et al. [52] / Iran | 7 days                                  | AIDP                                 | 4                            | 6%                                       | Preserved CV                                              | 1                                                  |

(continued on next page)
In our review, we found 44 patients receiving IVIG 30 patients (68%) were in the AIDP group while 14 (32%) were in Non-AIDP/Other variants (Table 4). We further reviewed the number of patients receiving 0.4 g/kg/day x 5 days versus 2 g/kg IVIG administered over 5 days. Information about different IVIG regimens was not available in 14 cases (10 in the AIDP group and 4 in the Non-AIDP group). 14 patients (70%) in the AIDP group received 0.4 g/kg/day divided over 5 days. The other 6 patients (30%) received 2 g/kg IVIG regimen divided over 5 days. On the other hand, in the Non-AIDP/Other variants group, total patients on 0.4 g/kg and 2 g/kg IVIG regimen were 8 (80%) and 2 (20%) respectively. In total, out of 30 patients on IVIG in the entire cohort, 22 patients (73%) were on 0.4 g/kg dosage and 8 (27%) were on 2 g/kg dosage divided over 5 days.

In addition, 7 patients (14%) out of 50 underwent PLEX. Six cases (85%) were in the AIDP group while 1 case (15%) on PLEX was diagnosed with BFP included in the other variants group. Four patients (4/44, 9%) who were on IVIG also received PLEX.

Although IVIG has known association with thromboembolic adverse event, and SARS-COV-2 is associated with a pro-thrombotic state [72], spine imaging [8,27,45,46].

There is still no specific treatment for COVID-19. However, at the time of reporting of some of the cases in this study there was a proposed approval by WHO for the use of HCQ which was later withdrawn, and antivirals like Ritonavir, Lopinavir, some of which were also proven to be ineffective against COVID-19 and IL-6 receptor (R) blockers such as Tocilizumab as needed [67,68]. Dexamethasone has proved useful in severely affected patients likely by inhibiting the destructive excess inflammatory response in these patients [69]. Our analysis also included the treatment given for COVID-19 in both AIDP vs Non-AIDP/other variants group. 38 patients (76%) in the entire cohort received some form treatment including antivirals (13/38, 34%), antibiotics (8/38, 21%), IL-6R blocker (1/38, 2.6%) or hydroxychloroquine (16/38, 42%). Furthermore, 11 patients who received antivirals also received IVIG, 13 patients who got HCQ, and 1 patient who received IL-6 blocker, also received IVIG therapy in combination (Table 4).

Standard management for GBS includes IVIG and PLEX [70,71]. In our review, we found 44 patients receiving IVIG 30 patients (68%) were
none of the SARS-COV-2 GBS patients who received IVIG treatment developed thrombotic complications. Based on our review, we propose further studies to identify the consideration of IVIG and plasma-exchange as potential standardized treatment options for GBS in COVID-19 patients. While PLEX and IVIG have been shown to be equally effective for treatment of GBS, it would be interesting to compare the issue of side effects in this particular population of GBS patients. There is the potential for thrombotic events with IVIG which is prothrombotic and the potential for cardiovascular events with rapid fluid shifts in moderate and severe cases of COVID-19 [72]. The clinical manifestations of GBS are variable, with most cases having a mild clinical course and recovery with a good response to standard treatment with IVIG or PLEX. However, some cases have also had poor or fatal outcomes in GBS as per literature [17]. It is vital to understand the severity and mortality outcomes of COVID-19 associated peripheral nervous systems disorders; especially GBS, as respiratory failure can be a coinciding symptom of GBS and SARS-CoV-2 individually. Approximately 30% of the GBS patients have had poor outcomes secondary to the respiratory insufficiency [17]. In our review, 30 patients out of total 50 cases reviewed had severe COVID-19 (severity is based on the IDSA/ATS guidelines), classified as patients requiring mechanical intubation [61,73]. Out of the 30 severe cases, 20 (67%) were in the AIDP group while 10 (33%) were in the other groups. Information on intubation and mechanical ventilation were available in 48 cases. Information on outcomes were not available for 5 of the cases. (Table 2). Three AIDP and 2 of the other variants were fatal with a overall fatality rate of 11%. Of the patients who died, 3 (60%) were on combination therapy of 0.4 g/kg/day x 5 days IVIG, HCQ and antivirals; 1 (20%) was managed on antibiotics and IVIG (data not available) and the remaining 1 (20%) was treated with 0.4 g/kg/day x 5 days IVIG.

Given the similarities between SARS-CoV-2 and other coronaviruses, we reviewed papers describing neuromuscular complications in patients with MERS-CoV and SARS, two other severe coronaviral infectious outbreaks. We reviewed a total of 30 studies of SARS and found 2 relevant studies. A case series by Tsai L. et al. reviewed the neuromuscular findings in 4 patients with SARS-CoV infection. However, these patients were not included in our analysis as none of the patients could be confirmed to have GBS based on the diagnostic criteria. These patients were diagnosed as having neuropathy or myopathy and no albugminocytological dissociation was noted in their CSF findings [11]. Another excluded SARS-CoV case series by Stainsby B. et al. reported 3 healthcare workers with SARS infection who developed neuropathy and myopathy [12]. We also reviewed a total of 45 studies of MERS and found 1 case series of interest. Kim and colleagues reported 4 patients it was a case series by Geimnitz et al. [16] that described a case of Bickerstaff brainstem encephalitis, a variant of GBS. This patient had ganglioside antibodies and CSF albuminocytological dissociation. While we reviewed this case, it could not be used for extensive comparative analysis due to lack of any other GBS cases in this report on MERS. The other patients were diagnosed with critical illness neuropathy and acute sensory neuropathy [10].

Although there are couple of recent literature published on COVID-19 and GBS, by Uncini et al. and Abu-Rumeileh et al. [73,74]; our review and analysis differ from these studies. Our review focuses on comparison of separate cohorts of different variants of GBS, i.e., AIDP v/s AMSAN/AMAN and others. In addition, we further analyzed the outcomes and severity (according to the ATS guidelines) in all the cases [61].The study by Abu-Rumeileh et al. has a greater number of cases in the discussion and the case reports. The authors of the study did not include pediatric population. Our study also differs from other studies, in terms of analyzing mEGOS scale, the use of the Brighton classification and also comparing these scale and classification between different variants of GBS [58,59]. Additionally, our study also includes a brief review of pathophysiology of COVID-19 and GBS, as well as the pathophysiology of the treatments for GBS and their correlation. Since both these studies are comparatively new and refer to a rapidly emerging pandemic, we did not discuss a comparison as our study is inclusive of the cases used in the prior studies and also focused on comparison of the different GBS variant cohorts.

The diagnosis of GBS in SARS-CoV-2 is especially challenging as symptoms such as shortness of breath and fatigue could be misinterpreted as being secondary to SARS-CoV-2 delaying the evaluation for GBS. Thus, it is highly advisable that physicians should promptly think about neuromuscular cause such as GBS in their differential when encountering SARS-CoV-2 patients even with minor initial clinical findings such as paresthesia, facial numbness or diplopia and ptosis. During this pandemic it is also useful to test for CoV-2 in patients with GBS who do not manifest clinical symptoms and signs of COVID-19 as there were such cases in our review [28,32,44].

Given the higher rates of requiring mechanical ventilation in SARS-CoV-2 associated GBS patients, it is suggested by some that COVID-19 is a trigger for a rapidly progressing neuropathy [42] although some of the need for ventilator support may relate to lung damage from the infection itself. Successful management of GBS is dependent upon a high clinical index of suspicion and early diagnosis. It is important to differentiate GBS from viral myositis in COVID-19 patients complaining of paresthesia and mobility difficulties.

Our study had several strengths. This is among the first studies focused on comparing the clinical presentation, management and outcomes in COVID-19 patients who were diagnosed with GBS, highlighting on differences among the different variants of GBS. Additionally, we also focused on functional scoring of mEGOS GBS scale and Brighton classification.

Our study should be considered in light of several limitations. Cases included in this review were identified through a comprehensive search of databases using a systematic search strategy. However, despite the set criteria, there is a possibility of missing out new upcoming studies because of the evolving nature of the COVID-19 pandemic. However, substantial evidence on other neurological complications and manifestations of COVID-19 is emerging and sets a strong base for conducting this review. Second limitation associated with this systematic review is the concern that a disproportionate amount of atypical cases of GBS and other neurological disorders associated with COVID are more likely to be reported in case reports and series which can introduce a bias. With the rapidly growing evidence of COVID-19 and association with neurological disorders, case reports and series of atypical clinical GBS are more likely to be published and differences in variants and hence common symptomatology and management of GBS may be missed. Finally, because of the emerging nature of the pandemic, there are no suitable contemporary non-COVID-19 case studies from the institutions reporting the COVID-19 associated GBS variants, which would be the appropriate control for comparing the differences in clinical presentations, outcomes and pathophysiology. This can be a future indication from our study warranting further studies.

However, we consider our search comprehensive enough to capture all the relevant case series and reports. Third limitation is the possibility of limited external validity for the systematic review. Although we identified a full spectrum of studies worldwide, the differences in treatment modalities for COVID-19 in different parts of the world, including controversies surrounding HCQ use, the differences in treatments noted in this review should be cautiously interpreted. However, the protocols for GBS are standardized. Additionally, as another limitation, while mEGOS scores can be calculated for days 1 and 7, we considered mEGOS calculation only at day 7 of admission as Medical Research Council Scale for Muscle Strength (MRC) scores (required for mEGOS calculation) were unavailable for majority of cases before day 7. It is also important to note that this score was calculated based on the clinical details reported in the cases included in our study and the score would be inaccurate if some pertinent clinical detail was not reported.

5. Conclusion

In this systematic review, we compared and summarized the clinical
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Declaration of Competing Interest

None.

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