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REVIEW

Guillain-Barré syndrome associated with SARS-CoV-2 infection: A systematic review and individual participant data meta-analysis

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Abstract

Several published reports have described a possible association between Guillain-Barré syndrome (GBS) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This systematic review aimed to summarize and meta-analyze the salient features and prognosis of SARS-CoV-2-associated GBS. We searched the PubMed (Medline), Web of Science and Cochrane databases for articles published between 01 January 2020 and 05 August 2020 using SARS-CoV-2 and GBS-related keywords. Data on sociodemographic characteristics, antecedent symptoms, clinical, serological and electrophysiological features, and hospital outcomes were recorded. We included 45 articles from 16 countries reporting 61 patients with SARS-CoV-2-associated GBS. Most (97.7%) articles were from high- and upper-middle-income countries. Forty-two (68.9%) of the patients were male; median (interquartile range) age was 57 (49-70) years. Reverse transcriptase polymerase chain reaction for SARS-CoV-2 was positive in 90.2% of patients. One report of SARS-CoV-2-associated familial GBS was found which affected a father and daughter of a family. Albuminocytological dissociation in cerebrospinal fluid was found in 80.8% of patients. The majority of patients (75.5%) had a demyelinating subtype of GBS. Intravenous immunoglobulin and plasmapheresis were given to 92.7% and 7.3% of patients, respectively. Around two-thirds (65.3%) of patients had a good outcome (GBS-disability score ≤ 2) on discharge from hospital. Two patients died in hospital. SARS-CoV-2-associated GBS mostly resembles the classical presentations of GBS that respond to standard treatments. Extensive surveillance is required in low- and lower-middle-income countries to identify and report similar cases/series. Further large-scale case-control studies are warranted to strengthen the current evidence. PROSPERO Registration Number CRD42020201673.

KEYWORDS

coronavirus disease, COVID-19, GBS, Guillain-Barré syndrome, SARS-CoV-2

Imran Hasan and KM Saif-Ur-Rahman contributed equally to this study.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a worldwide pandemic. Based on data from Johns Hopkins University, as of 8 October 2020, around 36.2 million cases have been detected and more than 1 million patients have died of COVID-19 globally.[1] COVID-19 predominantly affects the respiratory tract and lung parenchyma and patients typically present with a cough, sore throat, fever, fatigue and breathing difficulties.[2] However, there is evidence of neurological involvement in COVID-19[3]; a study from China reported that 36.4% of patients had neurological symptoms, including impaired smell and taste, headaches, dizziness, acute cerebrovascular attacks and encephalopathy.[3] Another study from France reported that 84% of patients with severe COVID-19 presented with neurological complaints.[4]

The postinfectious cellular-immune or antibody-mediated phenomenon Guillain-Barré syndrome (GBS) usually occurs sporadically. However, several studies reported an increased incidence of GBS after various epidemics around the world. For instance, the incidence of GBS increased during the Zika epidemic in French Polynesia.[5] GBS has also been reported after infection with Middle East respiratory syndrome virus.[6] More recently, numerous case report/series and cross-sectional studies have described cases of GBS linked to SARS-CoV-2 infection, which suggests a possible association between GBS and COVID-19. Moreover, several systematic reviews have also reported COVID-19-associated GBS.[7-10] Two initial reviews included a small number of articles (8 and 14) and only narrated the findings.[7,8] Two subsequent reviews reported a comparatively larger number of articles, yet only searched one database (PubMed).[9,10] Until now, no systematic review has conducted an individual participant data (IPD) meta-analysis, performed meta-regression or assessed the quality of the included articles. An IPD meta-analysis of cases may provide better insight into SARS-CoV-2-associated GBS.

The growing number of cases globally and the need for an IPD meta-analysis necessitate further reviews to better understand the presentation, risk factors and outcome of SARS-CoV-2-associated GBS to ensure early diagnosis and better management. The objective of this systematic review was to identify the sociodemographic, clinical, serological and electrophysiological features and prognosis of SARS-CoV-2-associated GBS and perform an IPD meta-analysis.

2 | MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[11,12] A PRISMA-P checklist has been provided as an online supplementary file (Appendix S1). We included studies from all geographical regions describing participants of all age groups, ethnicities and genders. The primary outcomes considered in this review were GBS and its variants, based on the National Institute of Neurological Disorders and Stroke (NINDS)[13] or Brighton[14] criteria, associated with antecedent/concomitant SARS-CoV-2 infection confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) or serological testing (IgM or IgG). We also considered the sociodemographic, clinical, serological and electrophysiological features, risk factors and prognosis of SARS-CoV-2-associated GBS as secondary outcomes. The severity of GBS was measured using the GBS disability score.[15]

We included all original studies that reported GBS related to COVID-19 retrieved from the comprehensive search. Review articles, editorials, opinions, viewpoints, perspectives and comments were excluded. However, letters to editors or comments that reported original case/patient information were included. Only articles published in English were included. In addition, the corresponding author of one article published in Spanish provided an English translation, which was included in this review.

We searched MEDLINE through PubMed, Web of Science and Cochrane library databases using a comprehensive search strategy developed in consultation with an experienced systematic reviewer and search manager. The strategy was adapted to the selected bibliographical databases, in combination with Boolean operators, truncations and database-specific built-in filters. We searched for studies published between 01 January and 05 August 2020, as COVID-19 was first reported in late December, 2019. The search strategy included the terms ("Coronavirus" OR "Coronavirus disease" OR "novel coronavirus" OR "Severe acute respiratory syndrome coronavirus 2" OR "COVID-19" OR "nCoV 2019" OR "SARS-CoV-2") AND ("Guillain-Barré syndrome" OR "GBS" OR "Miller Fisher syndrome" OR "MFS" OR "Miller Fisher-GBS overlap syndrome" OR "MFS-GBS overlap syndrome" OR "acute inflammatory demyelinating polyneuropathy" OR "AIDP" OR "acute motor axonal neuropathy" OR "AMAN" OR "acute motor sensory axonal neuropathy" OR "AMSAN").

We used the EndNote reference management software (Clarivate Analytics, Philadelphia, USA) to compile the articles retrieved from the comprehensive literature search. The search results from the three databases were combined and duplicate articles were removed. The remaining articles were exported to the web-based application "Rayyan QCRI"[16] to facilitate article screening and collaboration between the reviewers. Two reviewers independently screened the titles and abstracts of all retrieved articles to identify eligible studies. Then, the full-text articles of the eligible studies were independently reviewed for final inclusion. Disagreements between the two reviewers were resolved by a third reviewer. Reasons for exclusion were recorded.

Data extraction was conducted using Microsoft Excel (Microsoft Corporation, Washington, USA). Data on the study site/country, sociodemographic characteristics, preceding symptoms, clinical, serological, electrophysiological and cerebrospinal fluid (CSF) features and hospital outcomes were recorded. Data extraction was performed independently by two reviewers. The lead reviewer cross-checked and finalized any discrepancies. Two other reviewers independently assessed the quality of the included studies using the Joanna Briggs Institute Critical Appraisal Checklist for case reports, case series and cross-sectional studies.[17] These tools incorporate an assessment of patient demographic features, diagnostic criteria, reporting of clinical

information and adverse events, reporting of outcomes, and appropriate use of statistical methods. While assessing quality, disagreements between the two reviewers were resolved by a third reviewer.

A narrative synthesis of the findings from the included studies was conducted, focusing on the features and outcome of SARS-CoV-2-associated GBS. Sociodemographic characteristics and clinical, serological and electrophysiological features, including antecedent COVID-19 symptoms, diagnosis of COVID-19, presenting symptoms of GBS, and variants and subtypes of GBS were recorded in tabular format using frequencies and percentages. We aimed to conduct a meta-regression; however, this was not possible as the assumptions were not fulfilled.

3 | RESULTS

Our initial search retrieved a total of 174 articles from the three databases. After removing duplicates, screening the titles/abstracts and

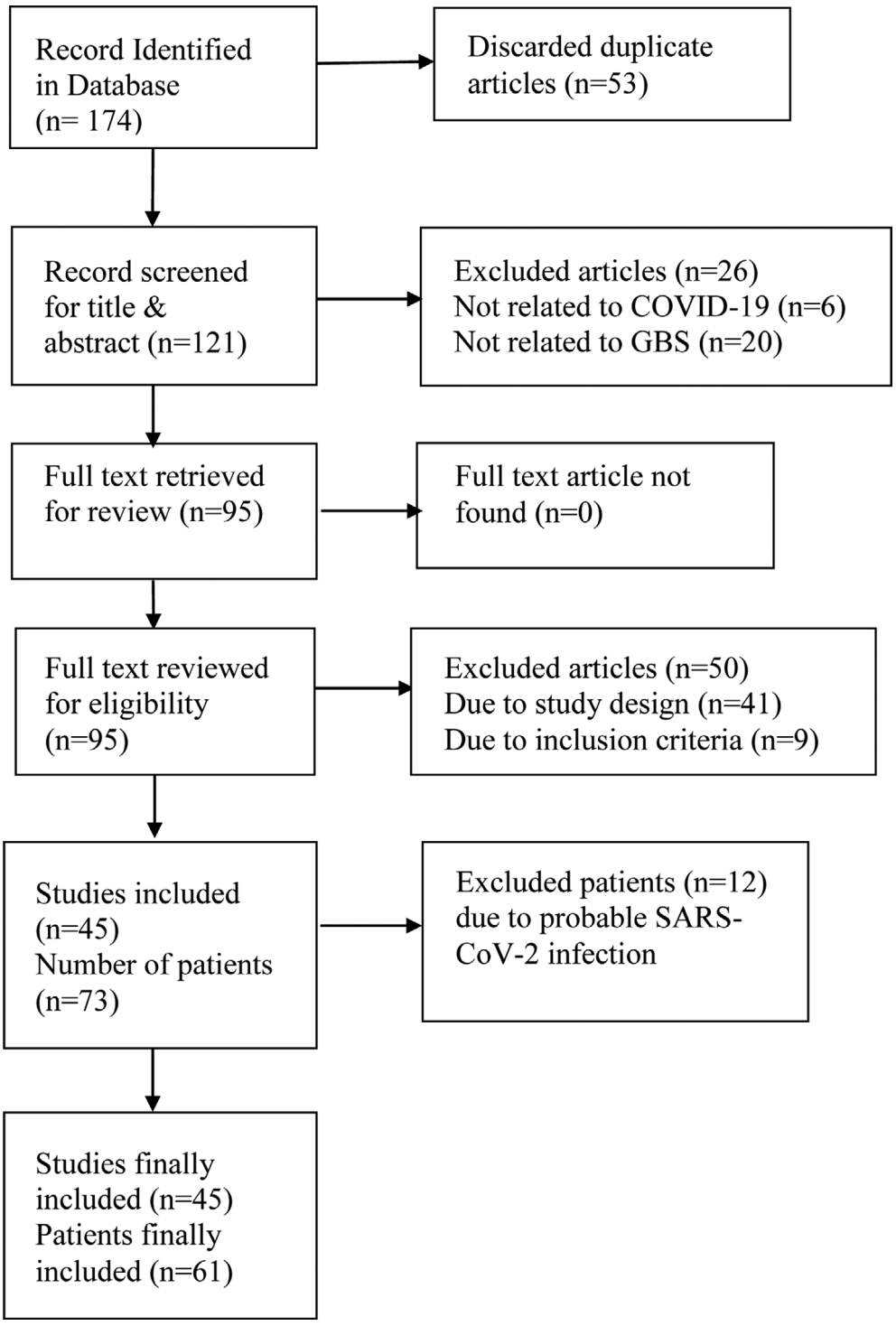

FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram of the systematic review and individual participant data meta-analysis

TABLE 1 Characteristics and quality of the articles included in the systematic review and IPD meta-analysis

Author, Year	Type of article	Country	Number of cases	RT-PCR status	Serological (IgM/IgG) status	EDx subtype	Quality assessment score
Helbok et al., 2020	Case report	Austria	1	Negative	Positive (IgM and IgG)	AIDP	7/8
Frank CHM et al., 2020	Case report	Brazil	1	Positive	Positive (IgM and IgG)	AMAN	6/8
Chan JL et al., 2020	Case report	Canada	1	Positive	Not reported	AIDP	7/8
Zhao H et al., 2020	Case report	China	1	Positive	Not reported	AIDP	7/8
Arnaud S et al., 2020	Case report	France	1	Positive	Not reported	AIDP	6/8
Bigaut K et al., 2020	Case series	France	2	Positive	Not reported	AIDP	7/10
Camdessanche JP et al., 2020	Case report	France	1	Positive	Not reported	AIDP	6/8
Scheidl E et al., 2020	Case report	Germany	1	Positive	Not reported	AIDP	7/8
Farzi MA et al., 2020	Case report	Iran	1	Positive	Not reported	AIDP	7/8
Paybast S et al., 2020	Case series	Iran	2	Positive	Not reported	Mixed (n = 1); Not reported (n = 1)	7/10
Sedaghat Z et al., 2020	Case report	Iran	1	Positive	Not reported	AMSAN	6/8
Agosti E et al., 2020	Case report	Italy	1	Positive	Not reported	AIDP	6/8
Alberti P et al., 2020	Case report	Italy	1	Positive	Not reported	AIDP	7/8
Assini A et al., 2020	Case series	Italy	2	Positive	Not reported	AIDP (n = 1); AMSAN (n = 1)	8/10
Gigli GL., 2020	Case series	Italy	1	Negative	Positive (IgM and IgG)	AIDP	6/10
Manganotti P et al., 2020	Case series	Italy	5	Positive	Not reported	AIDP (n = 3); AMAN (n = 2)	9/10
Manganotti P et al, 2020	Case report	Italy	1	Positive	Not reported	NA	7/8
Ottaviani D et al., 2020	Case report	Italy	1	Positive	Not reported	AIDP	7/8
Padroni M et al., 2020	Case report	Italy	1	Positive	Not reported	AIDP	6/8
Riva N et al., 2020	Case report	Italy	1	Negative	Positive (IgG)	AIDP	6/8
Toscano G et al., 2020	Case series	Italy	5	Positive (n = 4)	Positive (IgG) (n = 2)	AIDP (n = 2); AMSAN (n = 2); AMAN (n = 1)	7/8
El Otmani et al., 2020	Case report	Morocco	1	Positive	Not reported	AMSAN	6/8
Kilinc et al., 2020	Case report	Netherlands	1	Negative	Positive (IgM and IgG)	AIDP	6/8
Khalifa et al., 2020	Case report	Saudi Arabia	1	Positive	Not reported	AIDP	7/8
Esteban M et al., 2020	Case report	Spain	1	Positive	Not reported	AIDP	7/8
Fernández et al., 2020	Case report	Spain	1	Positive	Not reported	AIDP	6/8
García-Manzanedo et al., 2020	Case report	Spain	1	Positive	Not reported	AMSAN	6/8
Gutiérrez-Ortiz C et al., 2020	Case series	Spain	2	Positive	Not reported	NA	9/10
Marta-Enguita J et al., 2020	Case report	Spain	1	Positive	Not reported	NA	7/8
Reyes-Bueno JA et al., 2020	Case report	Spain	1	Negative	Positive (IgG)	AIDP	6/8
Sancho-Saldaña A et al., 2020	Case report	Spain	1	Positive	Not reported	AIDP	6/8
VelayosGalán A et al., 2020	Case report	Spain	1	Positive	Not reported	AIDP	6/8
Coen M et al., 2020	Case report	Switzerland	1	Positive	Positive (IgG)	AIDP	6/8
Lascano AM et al., 2020	Case series	Switzerland	3	Positive	Positive (IgM and IgG) (*n* = 1)	AIDP	9/10
Oguz-Akarsu E et al., 2020	Case report	Turkey	1	Positive	Not reported	AIDP	7/8
Paterson RW, 2020	Cross-sectional	United Kingdom	3	Positive	Not reported	AIDP	6/9
Tiet MY et al., 2020	Case report	United Kingdom	1	Positive	Not reported	AIDP	7/8
Webb S et al., 2020	Case report	United Kingdom	1	Positive	Not reported	AIDP	7/8
Abrams RMC et al., 2020	Case report	United States	1	Positive	Positive (IgM and IgG)	NA	7/8

TABLE 1 (Continued)

Author, Year	Type of article	Country	Number of cases	RT-PCR status	Serological (IgM/IgG) status	EDx subtype	Quality assessment score
Elkhouly et al., 2020	Case report	United States	1	Positive	Not reported	AMAN	
Hutchins et al., 2020	Case report	United States	1	Positive	Not reported	Mixed demyelinating and axonal	8/8
Lantos JE et al., 2020	Case report	United States	1	Positive	Not reported	NA	6/8
Rana S et al., 2020	Case report	United States	1	Positive	Not reported	AIDP	7/8
Su XW et al., 2020	Case report	United States	1	Positive	Not reported	AIDP	7/8
Virani A et al., 2020	Case report	United States	1	Positive	Not reported	NA	7/8

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; EDx, electrophysiological diagnosis; NA, not available.

reading the full texts of eligible articles, we identified 73 patients reported in 45 articles. Seven patients (out of eight) from a case series[18] and five patients (out of eight) from a cross-sectional study[19] were excluded as the diagnoses of probable/possible SARS-CoV-2 infection did not meet our inclusion criteria. Therefore, we finally included 61 patients diagnosed with GBS with laboratory-confirmed preceding/concomitant SARS-CoV-2 infection from 45 articles.[18-62] The PRISMA flow diagram of the included articles is presented in Figure 1.

Thirty-seven of the included articles were case reports, along with seven case series and one cross-sectional study. Most (97.7%) articles were reported from high- and upper-middle-income countries, according to the World Bank country classification. One article was reported from Morocco, a lower-middle-income country in Africa. The majority (64.4%) of articles was reported from European countries; no articles were reported from South Asia, South-East Asia or Australia. Only one article form Italy compared GBS incidence during the peak of pandemic and at the same time-period in the previous years.[18] The study found a 5.4-fold increase in the incidence of GBS during the pandemic.[18]

All case reports included the demographic characteristics, clinical history, presentation, diagnostic tests and treatment of the patients. However, the clinical condition of the patients after treatment and adverse events were not clearly described in the majority of reports. The case series consistently reported the diagnostic (NINDS or Brighton) criteria, demographic characteristics, clinical symptoms, follow-up, and outcome of GBS. However, most case series did not report consecutive and complete inclusion of participants. The single cross-sectional study was considerable regarding the sampling frame, response rate, reporting of clinic-pathological features and outcome. The quality scores of the included articles are shown in Table 1.

Two-thirds (68.9%) of patients were male and the median patient age (IQR) was 57 (49-70) years. Three patients were in the pediatric age group (<18 years).[34,39,52] All three pediatric patients had the classical sensorimotor presentation of GBS; one was a familial case of GBS following SARS-CoV-2 infection, who developed GBS after her father developedCOVID-19-associated GBS.[52] Fifty-seven (96.6%) of the patients had antecedent COVID-19 related symptoms including fever (69.4%), cough (72.8%), anosmia (28.8%), and ageusia (28.8%) (Table 2). The median interval between SARS-CoV-2 symptoms and onset of GBS was 14 days (interquartile range: 9-20 days) with rage of 2 to 33 days. COVID-19 symptoms developed 1 day after the onset of GBS in one patient[19], 8 days after onset of GBS in another patient[62]. The symptoms of COVID-19 were concomitant in one patient[46] and never developed in another patient,[27] although computed tomography of chest showed ground glass opacity. The included studies in this review did not mention the severity of SARS-CoV-2 infection, rather described the symptoms of SARS-CoV-2 infection. Therefore, we were not able to analyze the relationship between severity of SARS-CoV-2 infection and GBS outcome.

SARS-CoV-2 infection was confirmed for 55 (90.2%) patients by RT-PCR analysis of nasopharyngeal or oropharyngeal swabs. IgM and IgG antibodies against SARS-CoV-2 were assessed in six and 12 patients respectively; six patients (100%) and 11 patients (91.7%) were positive for IgM and IgG antibodies, respectively. Six patients tested negative in RT-PCR analysis for SARS-CoV-2, but had positive IgM and/or IgG serology.[18,37,40,50,51,58]

We reassigned the Brighton criteria level for each case based on the description and presentation of the cases/series. Fifty-eight (95.1%) of the patients fulfilled level-1 or level-2 of Brighton criteria, which reinforces the diagnostic certainty of the patients included. The majority of patients had the classical sensorimotor presentation (68.9%) of GBS. The electrophysiological findings were consistent with acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor sensory axonal neuropathy (AMSAN) in 75.5%, 11.3%, and 9.4% of patients, respectively. Fifty-one patients (92.7%) received intravenous immunoglobulin (IVIg) as a treatment for GBS. Twenty-three (41.1%) patients were shifted to intensive care unit (ICU) and 17 (30.4%) patients required mechanical ventilation (Table 2).

Most included articles did not explicitly mention the GBS disability score at hospital discharge. Therefore, we reconstructed the GBS disability scores based on the descriptions of patient outcomes at discharge from hospital. Two-thirds (65.3%) of patients had good outcome (GBS disability score ≤ 2) at discharge from the hospital. The demographic characteristics, clinical, serological, electrophysiological

TABLE 2 Demographic, clinical, laboratory and electrophysiological features of the patients with GBS following SARS-CoV-2 infection

Characteristic	Number (%)
Number of patients	61
Age (years)	
Median (IQR)	57 (49-70)
Range	11-94
Sex	
Male	42 (68.9)
Female	19 (31.1)
Previous comorbidities	18 (29.5)
Antecedent COVID-19 symptoms	57 (96.6)
Asymptomatic	2 (3.4)
Fever	41 (69.4)
Cough	43 (72.8)
Dyspnea	16 (27.1)
Headache	7 (11.8)
Anosmia	17 (28.8)
Ageusia	17 (28.8)
Diagnosis of COVID-19	
RT-PCR positive	55 (90.2)
Serology (IgM) positive	6/6 (100)
Serology (IgG) positive	11/12 (91.7)
Days between antecedent event and onset of weakness	
Median (IQR)	14 (9-20)
Range	2-33
Presenting symptoms of GBS	
Paraparesis	23 (43.4)
Quadriparesis	30 (56.6)
Hyporeflexia	48 (78.7)
Sensory symptoms	18 (29.5)
Pain	9 (14.8)
Facial palsy	18 (29.5)
Bulbar palsy	11 (18.0)
Autonomic dysfunction	9 (14.8)
Variant of GBS	
Classical sensorimotor	42 (68.9)
Pure motor	4 (6.6)
Miller Fisher syndrome	7 (11.5)
EDx subtype of GBS	
Not available	8 (13.1)
AIDP	40 (75.5)
AMAN	6 (11.3)
AMSAN	5 (9.4)
Mixed	2 (3.8)
Cerebrospinal fluid	
Normal	10/52 (19.2)
ACD	42/52 (80.8)
RT-PCR negative	34/34 (100)
Antiganglioside antibodies	
Negative	25/26 (96.1)
Positive (anti-GD1bIgG)	1/26 (3.9)
Brighton criteria for GBS	
Level 1	41 (67.2)
Level 2	17 (27.9)
Level 3	3 (4.9)
GBS specific treatment	
Not reported	6 (9.8)
IVIg	51/55 (92.7)
PE	4/55 (7.3)
IVIg and PE	2/55 (3.6)
Admission to ICU	23/56 (41.1)
Mechanical ventilation	17/56 (30.4)
Hospital outcome	
Not reported	9 (14.7)
Good (GBS-DS ≤2)	34 (65.3)
Poor (GBS-DS 3–5)	16 (30.7)
Death	2 (3.8)

Abbreviations: ACD, albuminocytological dissociation; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; EDx, electrophysiological diagnosis; GBS-DS, Guillain-Barré syndrome disability score; ICU, intensive care unit; IQR, interquartile range; IVIg, intravenous immunoglobulin; PE, plasma exchange; RT-PCR, reverse transcriptase polymerase chain reaction.

and cerebrospinal features of the included patients are summarized in Tables 1 and 2.

4 | DISCUSSION

The objective of this review was to conduct an IPD meta-analysis of cases of GBS related to SARS-CoV-2 infection. Our systematic search led to the retrieval of 61 cases of SARS-CoV-2-associated GBS from 45 articles published between 01 January and 05 August 2020. SARS-CoV-2 infection was confirmed for all patients by either RT-PCR or serology for IgM and/or IgG. The majority of patients had the classical sensorimotor presentation and demyelinating subtype of GBS. Most patients were treated with IVIg or plasmapheresis and two-thirds of patients had favorable outcomes. However, as distinct regional variations in the epidemiology and clinical presentation of GBS exist,[63] these results cannot be generalized in the absence of reports from other geographical regions, especially from Asian countries where the axonal subtype of GBS is more common.[64] The chronology of publication of the case reports/series followed the spread of COVID-19, that is, the first report was from China,[62] followed by reports from Italy[58], Iran[55] and the USA.[60] Several mechanisms that is, neurotropism or aberrant immune responses may be associated with the pathogenesis of GBS after SARS-CoV-2 infection.[65]

Nonetheless, the findings of this IPD meta-analysis largely implicate an immune-mediated mechanism in SARS-CoV-2-associated GBS, rather than GBS being directly induced by the viral infection.

Our systematic search of three databases mainly retrieved articles from high- and upper-middle-income countries, two-thirds of which were from Europe, particularly Italy and Spain. At the time of writing this manuscript, India and Brazil had recorded the second and third highest numbers of COVID-19 cases in the world, yet only one report of SARS-CoV-2-associated GBS had been published from Brazil[34] and none had been published from India.[66] Based on the total number of SARS-CoV-2 infections recorded, fewer cases of SARS-CoV-2-associated GBS have been reported from the USA than Italy. Although no countries have escaped the COVID-19 pandemic, it remains unclear why cases of SARS-CoV-2-associated GBS are under-reported from lower-middle-income and low-income countries. Several hypotheses can be postulated in this regard. First, many patients with SARS-CoV-2-associated GBS in developing countries may not seek healthcare due to cognitive barriers (ie, stigma, superstitions, fear of social isolation and hospital-acquired infections), structural barriers (ie, lack of or insufficient testing facilities, unavailability of one-stop services, prolonged waiting times, lockdowns resulting in inadequate transportation services) and financial barriers (ie, lack of health insurance and high out-of-pocket payments).[67] Second, patients with SARS-CoV-2-associated GBS may test negative for SARS-CoV-2 in RT-PCR. Serology for IgM and IgG antibodies could confirm the diagnosis of COVID-19, but may not be widely available in lower-middle- and low-income countries.[66] Third, most healthcare facilities in lower-middle- and low-income countries do not have adequate human resources, even in the absence of a pandemic,[68] which may have led to physicians working over-time leading to burn out,[69] and consequently under-reporting of such cases.

One study in Italy reported an unusual cluster of eight patients with GBS during the peak (March-April, 2020) of SARS-CoV-2 infection in the Friuli Venezia-Giuliaarea.[18] A 5.4-fold increase in the incidence of GBS was observed during that period. Another study reported an occasional cluster of six patients with GBS in the area around the French-Swiss border;[70] however, this cluster was not included in our review as the patients tested negative for SARS-CoV-2 infection in both RT-PCR and serology. A previous study also reported an increase in the incidence of GBS during the Zika virus outbreak in French Polynesia between 2013 and 2014.[5]

The pathogenesis of SARS-CoV-2-associated GBS remains under debate; several reports suggested a para-infectious eithology,[47,62] while others suggest a classical immune-mediated post-infectious mechanism. Several viral infections such as Zika virus and West Nile virus have been shown to cause para-infectious paralysis.[71,72] However, determination of the pattern of paralysis (para/post-infectious) on the basis of the time interval between SARS-CoV-2 infection and the onset of GBS would be unwise, as COVID-19 can be asymptomatic or paucisymptomatic and the incubation period can be up to 2 weeks.[73] In addition, ground glass opacities observed on chest X-rays or computed tomography or magnetic resonance imaging may persist, even after the acute infection subsides. Of the 61 patients included in this IPD meta-analysis, the cerebrospinal fluid of 34/34 patients was RT-PCR-negative forSARS-CoV-2. Moreover, CSF pleocytosis was not reported in any of these34 cases. These observations support a post-infectious pathogenesis forSARS-CoV-2-associated GBS. Anti-ganglioside antibodies were tested in 26 patients; only one patient was anti-GD1b-IgG antibody-positive.[36] Anti-ganglioside antibodies are frequently associated with the axonal variant of GBS. However, the majority of patients included had a demyelinating subtype of GBS, which gives rise to the hypothesis that SARS-CoV-2 infection predominately leads to the demyelinating subtype of GBS—in contrast to the axonal variant, which is associated with *Campylobacter jejuni* infection.[64]

This systematic review included patients with GBS with a confirmed SARS-CoV-2 infection. In the absence of case-control, cohort or population-based studies, this systematic review and IPD meta-analysis provide a comprehensive outline of the clinical, serological and electrophysiological features and outcome of SARS-CoV-2-associated GBS. Reports from other geographical regions, especially South Asia, are required to confirm the presentation and outcome of SARS-CoV-2-associated GBS. Our systematic review also has several limitations, notably restriction of the search to the PubMed, Web of Science and Cochrane databases, inclusion of articles published only in English, and heterogeneity of included studies.

In conclusion, this IPD meta-analysis indicates that GBS associated with SARS-CoV-2 infection resembles the classical presentation of GBS. The absence of SARS-CoV-2 in cerebrospinal fluid reinforces the hypothesis of a post-infectious immune-mediated mechanism, rather than a para-infectious etiology. Surveillance systems in low- and lower-middle-income countries should be strengthened to enable identification and reporting of GBS cases associated with SARS-CoV-2 infection. Although numerous reports of GBS associated with SARS-CoV-2 infection have been published during the current COVID-19 pandemic, considering the total number of SARS-CoV-2 infection in contrast with the number of reported GBS cases, it is still too early to suggest an association between SARS-CoV-2 infection and GBS. Further large-scale cohort and case-control studies are warranted to describe the pathogenesis of SARS-CoV-2-associated GBS and conclusively prove the causal relationship between GBS and SARS-CoV-2 infection.

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CONFLICT OF INTERESTS

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AUTHORS CONTRIBUTIONS

Imran Hasan and Zhahirul Islam conceptualized the review. KM Saif-Ur-Rahman provided expert opinion during the design of the review. Imran Hasan and KM Saif-Ur-Rahman searched the databases. Shoma Hayat, Rufydha Azam, Israt Jahan, and Nowshin Papri, screened the articles, assessed quality, and extracted data. Imran Hasan, KM Saif-Ur-Rahman, and Zhahirul Islam drafted the manuscript. Imran Hasan and Gulshan Ara analyzed the data. Imran Hasan, KM Saif-Ur-Rahman, Zhahirul Islam, shoma Hayat, Israt Jahan, Nowshin Papri, Rufydha Azam, and Gulshan Ara reviewed and revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

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REFERENCES

1. Coronavirus Resource Center - Johns Hopkins University. Accessed 8 October 2020. https://coronavirus.jhu.edu/map.html.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395 (10223):497-506.
3. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
4. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020;382(23):2268-2270.
5. Cao-Lormeau V-M, Blake A, Mons S, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet*. 2016;387(10027):1531-1539.
6. Kim JE, Heo JH, Kim HO, et al. Neurological complications during treatment of Middle East respiratory syndrome. *J Clin Neurol*. 2017; 13(3):227-233.
7. Carrillo-Larco R, Altez-Fernandez C, Ravaglia S, Vizcarra J. COVID-19 and Guillain-Barre syndrome: a systematic review of case reports. *Wellcome Open Res*. 2020;5(107).
8. De Sanctis P, Doneddu PE, Viganò L, Selmi C, Nobile-Orazio E. Guillain Barré syndrome associated with SARS-CoV-2 infection. A systematic review. *Eur J Neurol*. 2020;27:2361–2370.
9. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol*. 2020.
10. Uncini A, Vallat J-M, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. *J Neurol Neurosurg Psychiatry Res*. 2020;91:1105–1110.
11. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1.
12. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *Br Med J*. 2015;g7647:349.
13. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol*. 1990;27(S1):S21-S24.
14. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré syndrome and fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine*. 2011;29(3): 599-612.
15. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. *Lancet*. 1978;2(8093): 750-753.
16. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.
17. JBI Critical Appraisal Tools. Accessed 27 July 2020. https://joannabriggs.org/critical-appraisal-tools.
18. Gigli GL, Bax F, Marini A, et al. Guillain-Barré syndrome in the COVID-19 era: just an occasional cluster? *J Neurol*. 2020;1-3.
19. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143(10):3104–3120.
20. Abrams RMC, Kim BD, Markantone DM, et al. Severe rapidly progressive Guillain-Barré syndrome in the setting of acute COVID-19 disease. *J Neurovirol*. 2020;26:797-799.
21. Agosti E, Giorgianni A, D'Amore F, Vinacci G, Balbi S, Locatelli D. Is Guillain-Barrè syndrome triggered by SARS-CoV-2? Case report and literature review. *Neurol Sci*. 2020.
22. Alberti P, Beretta S, Piatti M, et al. Guillain-Barré syndrome related to COVID-19 infection. *Neurol Neuroimmunol Neruroinflamm*. 2020;7(4): e741.
23. Arnaud S, Budowski C, Ng Wing Tin S, Degos B. Post SARS-CoV-2 Guillain-Barré syndrome. *Clin Neurophysiol*. 2020;131(7):1652-1654.
24. Assini A, Benedetti L, Di Maio S, Schirinzi E, Del Sette M. New clinical manifestation of COVID-19 related Guillain-Barrè syndrome highly responsive to intravenous immunoglobulins: two Italian cases. *Neurol Sci*. 2020;41(7):1657–1658.
25. Bigaut K, Mallaret M, Baloglu S, et al. Guillain-Barré syndrome related to SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm*. 2020;7 (5):e785
26. Camdessanche JP, Morel J, Pozzetto B, Paul S, Tholance Y, Botelho-Nevers E. COVID-19 may induce Guillain-Barré syndrome. *Rev Neurol*. 2020;176(6):516-518.
27. Chan JL, Ebadi H, Sarna JR. Guillain-Barré syndrome with facial diplegia related to SARS-CoV-2 infection. *Can J Neurol Sci*. 2020;-.
28. Coen M, Jeanson G, Culebras Almeida LA, et al. Guillain-Barré syndrome as a complication of SARS-CoV-2 infection. *Brain Behav Immun*. 2020;87:111-112.
29. El Otmani H, El Moutawakil B, Rafai MA, et al. Covid-19 and Guillain-Barré syndrome: more than a coincidence! *Rev Neurol*. 2020;176(6): 518-519.
30. Elkhouly A, Kaplan AC. Noteworthy neurological manifestations associated with COVID-19 infection. *Cureus*. 2020;12(7):e8992.
31. Esteban Molina A, Mata Martínez M, Sánchez Chueca P, Carrillo López A, Sancho Val I, Sanjuan-Villarreal TA. Guillain-Barré syndrome associated with SARS-CoV-2 infection. *Medicina Intensiva*. 2020; S0210-5691(20):30154–30156.
32. Farzi MA, Ayromlou H, Jahanbakhsh N, Bavil PH, Janzadeh A, Shayan FK. Guillain-Barré syndrome in a patient infected with SARS-CoV-2, a case report. *J Neuroimmunol*. 2020;346:577294.
33. Fernández-Domínguez J, Ameijide-Sanluis E, García-Cabo C, García-Rodríguez R, Mateos V. Miller-fisher-like syndrome related to SARS-CoV-2 infection (COVID 19). *J Neurol*. 2020;267(9):2495-2496.
34. Frank CHM, Almeida TVR, Marques EA, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection in a pediatric patient. *J Trop Pediatr*. 2020.
35. García-Manzanedo S, López de la Oliva Calvo L, Ruiz Álvarez L. Guillain-barré syndrome after covid-19 infection. *Med Clin*. 2020; 155:366.

36. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology*. 2020;95(5):e601.
37. Helbok R, Beer R, Löscher W, et al. Guillain-Barré syndrome in a patient with antibodies against SARS-COV-2. *Eur J Neurol*. 2020;27:1754-1756.
38. Hutchins KL, Jansen JH, Comer AD, et al. COVID-19-associated bifacial weakness with Paresthesia subtype of Guillain-Barré syndrome. *Am J Neuroradiol*. 2020;41(9):1707–1711.
39. Khalifa M, Zakaria F, Ragab Y, et al. Guillain-Barre syndrome associated with SARS-CoV-2 detection and a COVID-19 infection in a child. *J Pediatric Infect Dis Soc*. 2020;9(4):510–513.
40. Kilinc D, van de Pasch S, Doets AY, Jacobs BC, van Vliet J, Garssen MPJ. Guillain-Barré syndrome after SARS-CoV-2 infection. *Eur J Neurol*. 2020;27:1757-1758.
41. Lantos JE, Strauss SB, Lin E. COVID-19-associated miller fisher syndrome: MRI findings. *Am J Neuroradiol*. 2020;41(7):1184-1186.
42. Lascano AM, Epiney JB, Coen M, et al. SARS-CoV-2 and Guillain-Barré syndrome: AIDP variant with favorable outcome. *Eur J Neurol*. 2020;27:1751-1753.
43. Manganotti P, Bellavita G, D'Acunto L, et al. Clinical neurophysiology and cerebrospinal liquor analysis to detect Guillain-Barré syndrome and polyneuritis cranialis in COVID-19 patients: a case series. *J Med Virol*. 2020.
44. Manganotti P, Pesavento V, Buoite Stella A, et al. Miller fisher syndrome diagnosis and treatment in a patient with SARS-CoV-2. *J Neurovirol*. 2020;26:605-606.
45. Marta-Enguita J, Rubio-Baines I, Gastón-Zubimendi I. Fatal Guillain-Barre syndrome after infection with SARS-CoV-2. *Neurologia*. 2020;35(4):265-267.
46. Oguz-Akarsu E, Ozpar R, Mirzayev H, et al. Guillain-Barré syndrome in a patient with minimal symptoms of COVID-19 infection. *Muscle Nerve*. 2020;62(3):E54–E57.
47. Ottaviani D, Boso F, Tranquillini E, et al. Early Guillain-Barré syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital. *Neurol Sci*. 2020;41(6):1351-1354.
48. Padroni M, Mastrangelo V, Asioli GM, et al. Guillain-Barré syndrome following COVID-19: new infection, old complication? *J Neurol*. 2020;267(7):1877-1879.
49. Rana S, Lima AA, Chandra R, et al. Novel coronavirus (COVID-19)-associated Guillain-Barré syndrome: case report. *J Clin Neuromuscul Dis*. 2020;21(4):240-242.
50. Reyes-Bueno JA, García-Trujillo L, Urbaneja P, et al. Miller-fisher syndrome after SARS-CoV-2 infection. *Eur J Neurol*. 2020;27:1759-1761.
51. Riva N, Russo T, Falzone YM, et al. Post-infectious Guillain-Barré syndrome related to SARS-CoV-2 infection: a case report. *J Neurol*. 2020;267(9):2492-2494.
52. Paybast S, Gorji R, Mavandadi S. Guillain-Barré syndrome as a neurological complication of novel COVID-19 infection: a case report and review of the literature. *Neurologist*. 2020;25(4):101-103.
53. Sancho-Saldaña A, Lambea-Gil Á, Liesa JLC, et al. Guillain-Barré syndrome associated with leptomeningeal enhancement following SARS-CoV-2 infection. *Clin Med*. 2020;20:e93-e94.
54. Scheidl E, Canseco DD, Hadji-Naumov A, Bereznai B. Guillain-Barré syndrome during SARS-CoV-2 pandemic: a case report and review of recent literature. *J Peripher Nerv Syst*. 2020;25(2):204-207.
55. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: a case report. *J Clin Neurosci*. 2020;76:233-235.
56. Su XW, Palka SV, Rao RR, Chen FS, Brackney CR, Cambi F. SARS-CoV-2-associated Guillain-Barré syndrome with dysautonomia. *Muscle Nerve*. 2020;62:E48-E49.
57. Tiet MY, AlShaikh N. Guillain-Barré syndrome associated with COVID-19 infection: a case from the UK. *BMJ Case Rep*. 2020;13(7):e236536.
58. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barré syndrome associated with SARS-CoV-2. *New Engl J Med*. 2020;382(26):2574-2576.
59. Velayos Galán A, Del Saz Saucedo P, Peinado Postigo F, Botia Paniagua E. Guillain-Barré syndrome associated with SARS-CoV-2 infection. *Neurologia*. 2020;35(4):268-269.
60. Virani A, Rabold E, Hanson T, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection. *IDCases*. 2020;20:e00771.
61. Webb S, Wallace VC, Martin-Lopez D, Yogarajah M. Guillain-Barré syndrome following COVID-19: a newly emerging post-infectious complication. *BMJ Case Rep*. 2020;13(6):e236182.
62. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol*. 2020;19(5):383-384.
63. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet*. 2016;388(10045):717-727.
64. Islam Z, Jacobs BC, van Belkum A, et al. Axonal variant of Guillain-Barre syndrome associated with campylobacter infection in Bangladesh. *Neurology*. 2010;74(7):581-587.
65. Dalakas MC. Guillain-Barré syndrome: the first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e781.
66. Islam Z, Hasan I, Mohammad QD. Guillain-Barré syndrome in developing countries in the COVID-19 era. *J Neurol Neurosurg Psychiatry*. 2020. https://jnnp.bmj.com/content/91/10/1105.responses.
67. O'Donnell O. Access to health care in developing countries: breaking down demand side barriers. *Cad Saúde Pública*. 2007;23:2820-2834.
68. Fritzen SA. Strategic management of the health workforce in developing countries: what have we learned? *Hum Resour Health*. 2007;5(1):4.
69. Kannampallil TG, Goss CW, Evanoff BA, Strickland JR, McAlister RP, Duncan J. Exposure to COVID-19 patients increases physician trainee stress and burnout. *PLoS One*. 2020;15(8):e0237301.
70. Tatu L, Nono S, Grácio S, Koçer S. Guillain-Barré syndrome in the COVID-19 era: another occasional cluster? *J Neurol*. 2020.
71. Brizzi KT, Lyons JL. Peripheral nervous system manifestations of infectious diseases. *Neurohospitalist*. 2014;4(4):230-240.
72. Uncini A, Shahrizaila N, Kuwabara S. Zika virus infection and Guillain-Barré syndrome: a review focused on clinical and electrophysiological subtypes. *J Neurol Neurosurg Psychiatry*. 2017;88(3):266-271.
73. Qin J, You C, Lin Q, Hu T, Yu S, Zhou XH. Estimation of incubation period distribution of COVID-19 using disease onset forward time: a novel cross-sectional and forward follow-up study. *Science Advances*. 2020;6(33):eabc1202.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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