Brain, Behavior, & Immunity - Health 28 (2023) 100578

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

# Guillain–Barré syndrome associated with COVID-19: A systematic review

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ARTICLE INFO

*Keywords:*
Guillain–Barré
Miller-Fisher
COVID-19
SARS-CoV-2
Peripheral nervous system

ABSTRACT

With the outbreak of coronavirus disease 2019 (COVID-19), the whole world was impacted by a pandemic. With the passage of time and knowledge about the dynamics and viral propagation of this disease, the short-, medium- and long-term repercussions are still being discovered. During this period, it has been learned that various manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affect the nervous system. In recent months, a variety of studies and case reports have proposed an association between COVID-19 and Guillain–Barré syndrome (GBS). The present work aims to systematically review the publications available to date to verify the relationship between these two pathologies and the characteristics of post-COVID GBS. There were 156 studies included in this work, resulting in a total of 436 patients. The findings show a mean age of the patients of 61,38 years and a male majority. The GBS symptoms began on average 19 days after the onset of COVID-19 infection. Regarding GBS, the main manifestations found included generalized weakness, reflex reduction, facial paresis/paralysis and hypoesthesia. As expected, the most common result in cerebrospinal fluid (CSF) analysis was albuminocytological dissociation. A pattern of blood analysis findings common to all patients was not observed due to non-standardization of case reports. Regarding electrodiagnostic studies, acute inflammatory demyelinating polyneuropathy (AIDP) appeared as the most common subtype of GBS in this study. There have been reports, to a lesser extent, of acute motor axonal neuropathy (AMAN), acute sensorimotor axonal neuropathy (AMSAN), the pharyngeal-cervical-brachial variant (PCB), and Miller-Fisher syndrome (MFS). The GBS treatment used was mainly intravenous immunoglobulin (IVIG) and plasma exchange (PLEX). Therefore, the present study reports a high prevalence of hospitalization and intensive care units ICU admissions, conjecturing a relationship between the development of GBS and the severity of COVID-19. Despite the severity, most patients showed improvement in GBS symptoms after treatment, and their residual symptoms did not include motor involvement. Therefore, the development of GBS seems to be related to COVID-19 infection, as reported by the present systematic review.

## 1. Introduction

On December 31, 2019, the World Health Organization (WHO) contacted China to clarify reports that were being published regarding a group of viral pneumonias in Wuhan. These pneumonias were attributed to a novel strain of coronavirus known as SARS-CoV-2. In January 2020, the WHO stated that the spread of SARS-CoV-2 WHO was an international public health emergency (Carvalho et al., 2021).

After the surge of COVID-19, the world underwent an unparalleled pandemic. The short-, medium- and long-term repercussions of this disease are still being discovered. An important finding was that SARS-CoV-2 operates through angiotensin-2 converting enzyme (ACE2), which is expressed in type II pneumocytes, vascular endothelium, cardiomyocytes, smooth muscle cells and enterocytes. This enzyme

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https://doi.org/10.1016/j.bbih.2022.100578
Received 2 August 2022; Received in revised form 9 November 2022;
Available online 17 January 2023

operates as a receptor for the virus to get into host cells; therefore, it is believed that the ability of SARS-CoV-2 to infect cells in vitro is dependent on the expression of ACE2 (Carvalho et al., 2021; Hamming et al., 2004).

During this period, there were several manifestations of SARS-CoV-2 regarding the nervous system. Therefore, manifestations related to the central nervous system (CNS), such as stroke, consciousness impairment, headaches and seizures and related to the peripheral nervous system (PNS), such as isolated involvement of cranial nerves and peripheral neuropathies, have emerged as possible effects of this pathology that are not yet utterly understood.

Guillain–Barré syndrome (GBS) is characterized as an immune-mediated postinfectious syndrome that affects peripheral nerves and nerve roots and is estimated to affect 1.1–1.8 per 100,000 people per year (McGrogan et al., 2009). This occurs due to molecular mimicry triggered by previous infection, which results in the formation of anti-ganglioside antibodies that attack proteins present in the axonal membrane. This aggression causes rapidly progressive ascending flaccid paresis, which can affect sensory fibers and cranial nerves. GBS can be divided into the following subtypes: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN), which can be distinguished through electrophysiological studies and the clinical picture (Amoretti et al., 2002). Miller-Fisher syndrome (MFS) is a rarer subtype of GBS, which presents a triad of clinical features of ophthalmoplegia, ataxia, and areflexia. This pathology, if left untreated, can progress to involvement of the cervical and ventilatory muscles, making mechanical ventilation of the patient necessary.

To date, cases of GBS after EBV (Epstein-Barr virus), *Campylobacter jejuni*, and Zika virus infection and after vaccination for polio, hepatitis B, rabies, and influenza have been described (Sejvar et al., 2011). In addition, cases of GBS after vaccination against COVID-19 have also been reported. However, there is a lack of studies on the subject, and it is not possible to draw conclusions about a significant association between vaccination for COVID-19 and GBS (Kanabar and Wilkinson, 2021).

Recently, there have been reports of patients who progressed to GBS subsequent to a COVID-19 infection. This systematic review was written with the evidence available thus far to help understand the association between COVID-19 and GBS in the adult population to provide a greater understanding of clinical symptoms for the recognition and prevention of poor outcomes and residual symptoms.

## 2. Methods

This systematic review was performed in consonance with the methodology stated in the Cochrane Handbook for Systematic Reviewers (Higgins and Thomas, 2019) and presented as suggested by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Page et al., 2021). The protocol was registered at the International Register of Prospective Systematic Reviews under identification number CRD42021292406.

### 2.1. Search strategy

The literature search was performed in PubMed, Scopus and Embase. The keywords used were “covid-19”, “SARS-CoV-2”, “2019-nCoV”, “guillain barre”, and “miller fisher”. The search terms were used as keywords and in combination as MeSH terms to maximize the output from the literature findings.

### 2.2. Study selection

All the studies and data collection were performed by three authors (V.P., V.W.L., G.L.), and disagreements were resolved by consensus and involvement of a fourth, fifth and sixth author (A.M.A., N.B.E., G.Z.) or the senior author (J.C.C). We considered full texts that were designed as a case report, case series or observational study. We restricted our search to studies published in English or Portuguese.

### 2.3. Eligibility criteria

Studies were included if they had data on any aspects of peripheral nervous symptoms compatible with GBS associated with COVID-19 infection. We excluded cases related to the obstetric and pediatric populations (under the age of 18), as well as cases with missing data, a nonconfirmed diagnosis of GBS and non-English/non-Portuguese articles. The design categories comprising the exclusion criteria were reviews, systematic reviews, abstracts, brief communications, letters to the editor, opinions, editorials and posters.

### 2.4. Data extraction

The information extracted was the following: study data (design and location); demographic data (age, sex, ethnicity, comorbidities); clinical data (showing signs and symptoms), laboratory data, nerve conduction study, treatment, disease severity (mild, hospital ward, intensive care units) and clinical outcome (death, residual symptoms, no sequelae).

## 3. Results

### 3.1. Description of the studies

In a first search, performed on May 1, 2021, a total of 1301 articles were found; after excluding duplicates and non-original papers, a total of 869 articles were used for full-text screening. Finally, only 66 studies matched the final inclusion criteria and were included in our study (total patients = 121). A second search was conducted on September 16, 2022, limiting the date to articles published from May 2021 to the date of the search. In this updating search, a total of 1722 were found; after excluding duplicates and non-original papers, a total of 1682 articles were used for full-text screening. Of these, only 90 new studies were included in the review (total patients = 315). Consequently, in total, this review includes a total of 156 studies (total patients = 436). Fig. 1 illustrates the selection process.

Among the 156 included articles, there were 118 case reports, 22 case series, 2 case-control studies, 8 prospective studies and 6 retrospective studies. To evaluate the scientific level of those studies, we used the Oxford Center for Evidence-Based Medicine Classification and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). These data are summarized in Table 1.

### 3.2. Demographic data

This study included case reports, case series, a prospective observational study and a retrospective observational study. Among the 156 articles analyzed, data referring to 436 patients with Guillain–Barré syndrome associated with COVID were found. Of these patients, 67.20% were male and 32.80% female and the mean age of included patients was 61,38 years.

### 3.3. Clinical findings

#### 3.3.1. Comorbidities

Information regarding the past medical history of the 436 included patients was analyzed and the data found are described below. Among general comorbidities reported were the following pathologies: diabetes mellitus type 2 (n = 50), obesity (n = 31), unspecified pulmonary diseases (n = 10), hypothyroidism (n = 7), asthma (n = 5), gastroesophageal reflux disease (n = 4), chronic obstructive pulmonary disease (n = 2), diabetes mellitus type 1 (n = 2), osteoporosis (n = 2), hiatal hernia (n = 2), previous cholecystectomy (n = 2), hepatitis (n = 1), epistaxis (n = 1), previous splenectomy (n = 1), prediabetes (n = 1), liver failure (n

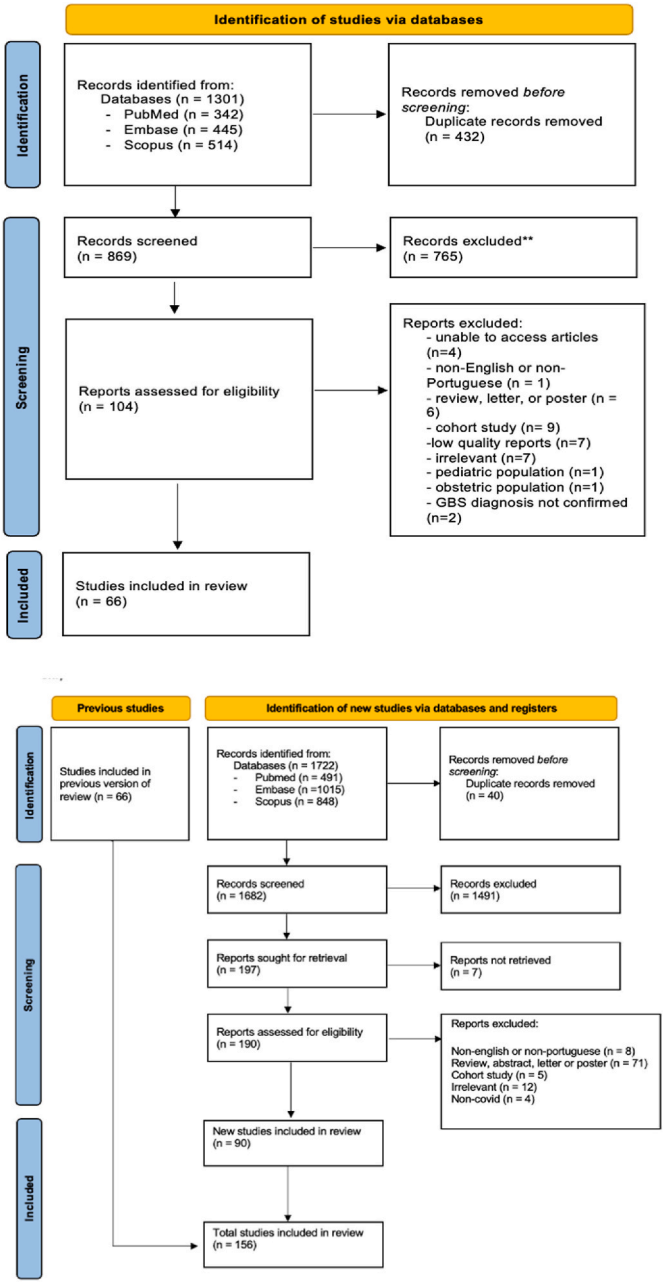


**Fig. 1.** – PRISMA flow diagram of evidence search and study selection.

**Table 1**
Summary of the 156 studies, GRADE and Oxford evidence levels.

| Study Type | Number of studies | GRADE evidence level | Oxford evidence level |
|---|---|---|---|
| Case report | 118 | Very low | 4 |
| Case series | 22 | Very low | 4 |
| Case control | 2 | Very low | 4 |
| Prospective observational study | 8 | Low | 3 |
| Retrospective observational study | 6 | Low | 3 |

= 1) and unspecified colitis (n = 1).

Within cardiovascular comorbidities, hypertension (n = 105) was the most prevalent, followed by dyslipidemia (n = 8), coronary heart disease (n = 3), and previous acute myocardial infarction (n = 3). Atrial fibrillation (n = 2), congestive heart failure (n = 1), aortic aneurysm (n = 1), myocardial infection (n = 1), previous carotid endarterectomy (n = 1) and unspecified cardiovascular diseases (n = 20) were also reported.

Some patients presented previous neurological diseases, including stroke (n = 3), migraine (n = 2), reflex sympathetic dystrophy (n = 2), cervical spondylosis (n = 1), herniated disc (n = 1), lumbar stenosis (n = 1), previous spinal trauma (n = 1), strabismus (n = 1), and unspecified cerebrovascular disease (n = 1). Prior neuropathies were reported in 3 patients (1 Bell's palsy, 1 prior GBS and 1 diabetic polyneuropathy). Autoimmune diseases such as fibromyalgia (n = 3), rheumatoid arthritis (n = 2), psoriasis (n = 1), Crohn's disease (n = 1), and systemic lupus erythematosus (n = 1) affected the patients analyzed as well.

Regarding neoplasms, the most described were breast cancer (n = 4) and leukemia (n = 4), followed by testicular seminoma (n = 2). Other neoplasms such as lung cancer (n = 1), previous thyroid cancer (n = 1), and throat cancer (n = 1) were present in lower numbers. At last, 3 patients were affected by unspecified malignancies.

### 3.3.2. *Symptomatic findings related to COVID-19*

Information regarding previous COVID-19 infection was reported in 365 of the evaluated patients. Among these, fever (n = 217) and cough (n = 184) were the most frequent symptoms reported in the articles during the period of COVID-19 infection, followed by dyspnea (n = 132), myalgia (n = 27), headache (n = 22) and diarrhea (n = 21). Symptoms related to special sensory fibers related to taste and olfaction were reported (64 anosmia/hyposmia; 20 dysosmia, 52 dysgeusia; 20 ageusia). The following symptoms were present: odynophagia (n = 14), fatigue (n = 11), malaise (n = 8), chills (n = 7), rhinorrhea (n = 7), asthenia (n = 7), hemodynamic disorders (n = 7), hyporexia (n = 6), chest pain (n = 5), low back pain (n = 5), sweating (n = 5), nausea (n = 4), vomiting (n = 4), dizziness (n = 4), nasal congestion (n = 3), expectoration (n = 3), arthralgia (n = 3), postural hypotension (n = 2), dysuria (n = 2), abdominal pain (n = 2), dysphagia (n = 1), constipation (n = 1), erectile dysfunction (n = 1), confusion (n = 1), cramps (n = 1) and not specified gastrointestinal symptoms (n = 25). Moreover, in 32 patients, the presence of unspecified respiratory symptoms was described. These data are summarized in Table 2.

### 3.3.3. *Neurological symptoms associated with Guillain–Barré syndrome*

Of the 436 cases evaluated, only 333 reported how many days after the Covid-19 infection the GBS symptoms started. The average number of days for the onset of the neurological condition in these cases was 19 days after the first symptom of Covid-19.

Among the patients evaluated, 293 had information regarding testing of the deep tendon reflexes. Of these, 260 patients had generalized hyporeflexia/areflexia, 24 patients had isolated hyporeflexia/areflexia of the lower limbs, 2 patients had isolated hyporeflexia/areflexia of the upper limbs and 8 patients had normal reflexes. Moreover, generalized hyperreflexia was observed in 1 patient, and associated Babinski sign in this patient and 2 others due to concomitant myelitis (n = 2) and prior encephalitis (n = 1).

Weakness was an extremely prevalent finding among the cases evaluated. Detailed information regarding motor involvement was described in 323 cases. The following patterns were found: generalized weakness, with involvement of both the lower and upper limbs (n = 218); isolated weakness of the lower limbs (n = 49); isolated weakness of the upper limbs (n = 6); single limb weakness (n = 3); hemiparesis (n = 2); limb weakness of unspecified pattern (n = 19) and absence of limb weakness (n = 26). Associated hypotonia (n = 17), cervical weakness (n = 9) and trunk weakness (n = 3) were also reported among these cases.

Respiratory muscle involvement was described in 79 patients of the total cases, need for intubation and mechanical ventilation was reported in 44 of these cases. Also, 54 cases reported ICU admission for unspecified causes, and it was not possible to infer whether it was due to the involvement of ventilatory muscles or other complications related to

**Table 2**
Clinical findings during COVID-19 infection.

| Clinical Findings | Total Number (%) |
|---|---|
| COVID-19 symptoms | 365 (Huang et al., 2020) |
| Fever | 217 (59.45) |
| Cough | 184 (50.41) |
| Dyspnea | 132 (36.16) |
| Myalgia | 27 (7.39) |
| Headache | 22 (6.02) |
| Diarrhea | 21 (5.75) |
| Anosmia/Hyposmia | 64 (17.53) |
| Dysgeusia/Ageusia | 72 (19.72) |
| Dysosmia | 20 (5.47) |
| Odynophagia | 14 (3.83) |
| Fatigue | 11 (3.01) |
| Malaise | 8 (2.19) |
| Chills | 7 (1.91) |
| Rhinorrhea | 7 (1.91) |
| Asthenia | 7 (1.91) |
| Hemodynamic disorders | 7 (1.91) |
| Hyporexia | 6 (1.64) |
| Chest pain | 5 (1.36) |
| Low back pain | 5 (1.36) |
| Sweating | 5 (0.36) |
| Nausea | 4 (1.09) |
| Vomiting | 4 (1.09) |
| Dizziness | 4 (1.09) |
| Nasal congestion | 3 (0.82) |
| Expectoration | 3 (0.82) |
| Arthralgia | 3 (0.82) |
| Postural hypotension | 2 (0.54) |
| Dysuria | 2 (0.54) |
| Abdominal pain | 2 (0.54) |
| Dysphagia | 1 (0.27) |
| Constipation | 1 (0.27) |
| Erectile dysfunction | 1 (0.27) |
| Unspecified gastrointestinal symptoms | 25 (6.84) |
| Unspecified respiratory symptoms | 32 (8.76) |

hospitalization.

In reference of cranial nerves (CN), the following results were found: facial paresis/paralysis (n = 154), bulbar nerve involvement (n = 73), ophthalmoplegia (n = 52); trigeminal hypoesthesia (n = 25) and unspecified cranial nerve involvement (n = 3). In addition, the following symptoms were actively reported in the cases analyzed: diplopia (n = 16); dysphagia (n = 30); dysarthria (n = 15); ptosis (n = 8) dysphonia (n = 5) tongue deviation (n = 2); nystagmus (n = 1); tinnitus (n = 1) and vomiting (n = 1). Gait ataxia has been reported in 51 cases. Dysmetria was observed in 2 patients.

In relation to changes in sensitivity, 181 patients had hypoesthesia. Sixty-four patients reported isolated involvement of the lower limbs, among which 14 reported only distal hypoesthesia. In 62 patients, hypoesthesia with involvement of all four limbs was reported, in 27 of them it was described as glove and boot pattern, with involvement of the distal upper and lower limbs. Hypoesthesia affecting only the upper limbs was reported in only 2 patients, 1 of them with a glove pattern. Hypoesthesia with an unspecified pattern was reported in 52 cases. Paresthesia was found in 116 patients (66 cases affected all four limbs, with 30 of them described as affecting distal extremities only). Isolated lower limb paresthesia was described in 33 cases. In 5 cases only the upper limb was affected, with hand-only disposition in 4 of them. Moreover, paresthesia of unspecified disposition was described in 12 cases. Furthermore, dysesthesias (n = 14), impaired proprioception (n = 12), allodynia (n = 1) and low back pain (n = 18) were reported.

Among the autonomic manifestations, blood pressure abnormalities were a frequent finding. Among the cases analyzed, 30 patients had hypotension, 16 hypertension, 6 blood pressure instability, and 2 postural hypotension. Arrhythmias were reported in 24 cases. Urinary problems were present in 20 cases (17 urinary retention, 3 urinary incontinence) and bowel problems in 12 cases (8 fecal retention/constipation, 3 fecal incontinence, 1 diarrhea). Other abnormalities such as gastroparesis (n = 3), sweating (n = 2), dry mouth (n = 1), erectile dysfunction (n = 1) and unspecified autonomic involvement (n = 13) were also reported.

Concomitant CNS involvement was reported in 35 cases. Among these, 11 patients had decreased level of consciousness, 8 delirium, 6 confusion, 3 myelitis, 2 headache, 2 posterior reversible encephalopathy syndrome, 1 encephalitis, 1 seizures, 1 sensory and auditory hallucinations, 1 acute infarction, 1 cerebral thrombophlebitis, 1 psychomotor agitation, 1 cerebral vasculitis, and 1 acute disseminated encephalomyelitis. These data are summarized in Table 3.

### 3.4. Laboratory findings

Laboratory tests for blood analysis showed cases with leukocytosis (n = 8), lymphopenia (n = 41), neutrophilia (n = 4), thrombocytopenia (n = 8) and unspecified anemia (n = 2). Among the cases which the exams were available, most of them had variations in the inflammatory markers, and the exams that were most commonly altered were CRP (n

**Table 3**
Clinical findings related to Guillain-Barré Syndrome.

| Clinical Findings | Total Number (%) |
|---|---|
| **Guillain-Barré symptoms** | |
| *Reflexes* | 293 (Huang et al., 2020) |
| Generalized hyporeflexia/areflexia | 260 (88.73) |
| Lower limb hyporeflexia/areflexia | 24 (8.19) |
| Upper limb hyporeflexia/areflexia | 2 (0.68) |
| Normoreflexia | 6 (2.04) |
| Generalized hyperreflexia | 1 (0.34) |
| Associated Babinski sign | 3 (1.02) |
| ***Motor impairment*** | **323** (Huang et al., 2020) |
| Generalized weakness | 218 (67.49) |
| Lower limbs weakness | 49 (15.17) |
| Upper limbs weakness | 6 (1.85) |
| Single limb weakness | 3 (0.92) |
| Hemiparesis | 2 (0.61) |
| Absence of limb weakness | 26 (8.04) |
| Limb weakness of unspecified pattern | 19 (5.88) |
| Cervical weakness | 9 (2.78) |
| Trunk weakness | 3 (0.92) |
| ***Cranial Nerve involvement*** | **436** (Huang et al., 2020) |
| Facial paresis/paralysis | 154 (35.32) |
| Bulbar nerve impairment | 73 (16.74) |
| Ophthalmoplegia | 52 (11.92) |
| Trigeminal hypoesthesia | 25 (5.73) |
| Unspecified CNs involvement | 3 (0.68) |
| ***Sensory alterations*** | **436** (Huang et al., 2020) |
| Hypoesthesia | 181 (41.51) |
| Paresthesia | 116 (26.60) |
| Dysesthesia | 14 (3.21) |
| Proprioception disturbance | 12 (2.75) |
| Allodynia | 1 (0.22) |
| Low back pain | 18 (4.12) |
| ***Respiratory muscle involvement*** | **436** (Huang et al., 2020) |
| Neuromuscular respiratory weakness | 79 (18.11) |
| ***Gait disturbance*** | **436** (Huang et al., 2020) |
| Ataxia | 51 (11.69) |
| ***Autonomic dysfunction*** | **436** (Huang et al., 2020) |
| Hypotension | 30 (6.88) |
| Hypertension | 16 (3.66) |
| Blood pressure instability | 6 (1.37) |
| Postural hypotension | 2 (0.45) |
| Arrhythmias | 24 (5.50) |
| Bladder dysfunction | 20 (4.58) |
| Bowel dysfunction | 12 (2.75) |
| Gastroparesis | 3 (0.68) |
| Sweating | 2 (0.45) |
| Dry mouth | 1 (0.22) |
| Erectile dysfunction | 1 (0.22) |
| Unspecified autonomic involvement | 13 (2.98) |

= 23), d-dimers (n = 9), LDH (n = 9), ferritin (n = 5) and CK (n = 9). Only a minority had unaltered inflammatory evidence, three cases found CRP without abnormalities, and one case had CK dosage within reference values. Regarding antibodies, 44 cases reported negative anti-ganglioside antibodies, however these articles didn't specify which antibodies were researched. Only 7 patients presented positive of one or more anti-ganglioside antibodies. One patient had positive serology for recent Campylobacter infection, which could be a confounding factor in relation to the true etiology of GBS. More details of laboratory findings are shown in Table 4.

Regarding the cerebrospinal fluid analysis, 303 cases had detailed results. Among these cases, the most common findings were albuminocytological dissociation (n = 227) and normal CSF analysis (n = 56). We considered as normal CSF analysis the patients who had glycorrhachia levels within normal parameters and did not present albuminocytological dissociation. Furthermore, there was 1 report of a patient that was IgM + for COVID-19 in CSF and 4 reports of patients that were IgG+ and 2 reports of patients that had positive IgG anti-GQ1B in CSF. Table 5 shows CSF findings.

### 3.5. Guillain-Barré and its variants

Guillain Barre variants can be differentiated through electroneuromyography or clinical characteristics. In this research we found reports of 2 patients with confirmed diagnosis of GBS that had a normal electroneuromyography and 55 reports that did not specify the GBS variant after conducting an electroneuromyography study. An AIDP compatible pattern was reported in 201 cases. Axonal damage was described in 84 cases, of which 50 cases were compatible with AMAN and 34 cases with AMSAN. There were also 16 reports of patients who developed MFS, 4 reports of the pharyngeal-cervical-brachial variant (PCB).

Our research also showed some cases with overlap diagnosis between variants of GSB. There were 4 cases with an AIDP and AMSAN diagnosis, 1 case with AMSAN and MFS, 2 cases with AMAN and AMSAN, 2 cases with MFS and an unspecified GBS variant and one case with AIDP and AMAN.

**Table 4**
Laboratory findings.

| Hematology Findings | Total number |
|---|---|
| **Hemogram** | |
| Leukopenia | 6 |
| leukocytosis | 14 |
| Normal leukocytes count | 5 |
| Lymphopenia | 41 |
| Normal lymphocytes count | 3 |
| Neutrophilia | 4 |
| Normal neutrophil count | 1 |
| thrombocytopenia | 8 |
| Normal platelet count | 3 |
| ***Inflammatory tests*** | |
| Elevated CRP | 23 |
| Normal CRP | 3 |
| Elevated d-dimers | 9 |
| Elevated LDH | 9 |
| Elevated ferritin | 5 |
| Elevated IL-6 | 1 |
| Elevated CK | 9 |
| Normal CK | 1 |
| Elevated lactate | 1 |
| ***Antibodies Testing*** | |
| IgG + for anti-GM2 | 1 |
| IgM + for anti-GM2 | 1 |
| IgG + for anti-GD1b | 4 |
| IgM + for anti-GD1b | 1 |
| IgG + for anti-GQ1b | 1 |
| Positive anti-Gal | 1 |
| Positive unspecified Anti-ganglioside | 2 |
| Negative unspecified Anti-ganglioside | 44 |

**Table 5**
CSF findings.

| CSF Findings | Total number |
|---|---|
| Albumin-cytological dissociation | 227 |
| Normal CSF analysis | 56 |
| Elevated protein[a] | 20 |
| IgG + for covid-19 | 4 |
| IgM + for covid-19 | 1 |
| Positive anti-GQ1B antibodies | 2 |

[a] There were 20 cases that were considered as an isolated elevated protein because their reports didn't specify cellularity levels to consider as albumin-cytological dissociation.

### 3.6. Treatment data

Among the 436 patients with GBS or MFS, only 200 had data about their treatment for COVID, and 400 had data about their GBS/MFS treatment. The most used medication for COVID treatment was Hydroxychloroquine (n = 68); antibiotics were used in 101 patients, including azithromycin (n = 10), doxycycline (n = 5) vancomycin (n = 2), amoxicillin-clavulanate (n = 1), amoxicillin (n = 1), meropenem (n = 3), tigecycline (n = 1), ciprofloxacin (n = 1), piperacillin-tazobactam (n = 1), ceftriaxone (n = 7), colistin (n = 1), cefepime (n = 1), clarithromycin (n = 3), linezolid (n = 2), and unspecified antibiotics (n = 62); corticosteroids were used in 73 patients, including dexamethasone (n = 13), methylprednisolone (n = 12), prednisone (n = 1) hydrocortisone (n = 1), and unspecified corticosteroid (n = 46); antivirals were used in 89 patients, including ritonavir/lopinavir (n = 21), remdesivir (n = 34), ritonavir (n = 1), darunavir (n = 5), oseltamivir (n = 5), favipiravir (n = 4), umifenovir (n = 1), ribavirin (n = 1), and unspecified antivirals (n = 17); anticoagulants were used in 80 cases, including enoxaparin and low molecular weight heparins (n = 16), heparin (n = 59), and unspecified anticoagulants (n = 5); other medications were also used, such as interferon beta-1b (n = 1), bamlanivimab (n = 1), tocilizumab (n = 22), acetaminophen (n = 9), meperidine (n = 2), losartan (n = 2), acetylsalicylic acid (n = 1), an unspecified vasopressor (n = 1), an unspecified antiemetic (n = 1), an unspecified antipyretic (n = 2), norepinephrine (n = 1), fluconazole (n = 2), insulin (n = 1), vitamins (n = 4), and unspecified symptomatic treatment (n = 2); one patient was treated with what was called "European Protocol", but it was not described; five patients were not treated for COVID-19. The GBS/MFS treatment used was mostly intravenous immunoglobulin (IVIG) (n = 329) and PLEX (n = 45). Methylprednisolone (n = 3), dexamethasone (n = 2), prednisone (n = 4), gabapentin (n = 3), pregabalin (n = 1), tocilizumab (n = 1), enoxaparin (n = 2), unspecified anticoagulants (n = 3), unspecified steroids (n = 2), vitamins and electrolytes (n = 3), eye drops (n = 1), diclofenac (n = 1), unspecified symptomatic treatment (n = 3) were also used, and 34 patients were not treated.

### 3.7. Outcome data

For the COVID outcome, the 315 patients with available data were separated into 5 groups according to the severity of their infection: asymptomatic (n = 3), mild (n = 82), hospitalized (n = 91), ICU without intubation (n = 43), and ICU with intubation (n = 85). The other 11 patients were admitted to the ICU, but no information was provided about their intubation status.

For the GBS outcome, 295 patients had data available until the end of their respective study follow-up. Of these, 41 had completely recovered, 148 had general or unspecified improvement of the symptoms, 14 had no improvement, and 27 died; 67 patients had residual muscle weakness, 11 had residual cranial nerves symptoms, 9 had residual paresthesia, 5 had residual neuropathic pain, 4 had residual sensory loss, 3 remained areflexic, and 2 had residual dysautonomic symptoms.

## 4. Discussion

This systematic review searched for an association between COVID-19 and GBS in the adult population and demonstrated that there is possibly a correlation between GBS and age and sex, given that the mean age of the analyzed cases was 61,38 years and most of them were men. Regarding COVID-19, the major symptoms presented were fever, cough and dyspnea, and in regard to GBS, the major signs presented were reduction or abolishment of the reflexes, generalized weakness, facial paresis/paralysis, hypoesthesia and paresthesia. There were also some relevant laboratory findings, such as variations in inflammatory markers, in most of the patients. CSF studies showed that albuminocytological dissociation was highly prevalent in the analyzed cases. For electrodiagnostic studies, most cases with available data reported AIDP as the most present variant of GBS in the study. The analysis also demonstrated that the main treatment utilized for COVID-19 infection was hydroxychloroquine and/or antibiotics, and in GBS treatment, the most common option was IVIG. Additionally, it was reported that most of the patients with available information were admitted to the ICU for COVID-19. The outcome of the GBS clinical picture was mainly positive, considering that most of the cases had an improvement in their clinical state after treatment.

### 4.1. Mechanisms of SARS-CoV-2 infection associated with GBS

SARS-CoV-2 has a mechanism of action based on the "key/lock"-type interaction with the angiotensin II converting enzyme (ACE2), which works like an access for the virus into the cell (Li et al., 2003). Xintian and colleagues demonstrated in 2020 that protein S in its RBD binding domain demonstrates high affinity for human ACE2, which gives it a high potential for infection by this pathway (Xu et al., 2020a). Therefore, according to Xu et al. (2020), the large presence and distribution of ACE2 in human tissues may suggest the routes of infection of SARS-CoV-2 (Xu et al., 2020b).

Upon entering the host cell, SARS-CoV-2 begins to prepare for active replication (Tay et al., 2020). With the release of new viral copies, this process causes the infected cell to suffer pyroptosis, and with it, the release of molecular patterns associated with damage occurs (DAMPs) (Tay et al., 2020). This infection process causes the death of lung cells due to the triggering of a local immune response, which starts with the sensitization of macrophages and monocytes that respond to the release of cytokines and through adaptive T and B lymphocytes. Thus, if the process is not efficient, subsequent pyroptosis causes DAMPs and PAMPs to be recognized, and thus, the inflammatory process extends. This process leads to augmented secretion of the proinflammatory cytokines IL-6, IFNγ, MCP1 and IP-10, which further recruits the immune system and thus progresses the inflammatory process (Huang et al., 2020). For this reason, this high degree of cytokine secretion in response to SARS-CoV-2 infection drives the immune system out of control, which can lead to a cytokine storm and sepsis symptoms, which are the cause of death in 28% of infected individuals (Zhang et al., 2020).

According to Yachou et al. (2020), many human viruses (including coronaviruses) have tropism and neuronal invasion properties with the potential to cause other disturbances (Yachou et al., 2020). In addition, regarding the inflammatory aspect of a cytokine storm, Yachou and colleagues also showed that neurological manifestations by COVID-19 arise from inflammatory cascades, that is, from the presence of a cytokine storm (Yachou et al., 2020).

Sedaghat and Karimi (2020) presented a case of a 65-year-old male with symmetrical quadriparesis with progressive and acute weakness of the distal lower extremities. Furthermore, the individual had bilateral facial paresis and RT–qPCR test results were positive for SARS-CoV-2 infection (Sedaghat and Karimi, 2020). Ottaviani et al. (2020) reported the case of a 66-year-old female who was in a viral endemic area and who, for a period of 72 h, had progressive difficulty to walk. In her evaluation, she presented symmetrical and progressive weakness in the lower limbs and paraplegia, as well as distal weakness of the upper limb. Her computed tomography showed bilateral opacity with a “ground glass” appearance, but her first RT–qPCR test was negative for infection (Ottaviani et al., 2020). Nevertheless, Otmani and colleagues reported the case of a 70-year-old female in 2020 who began to experience rapid bilateral weakness and tingling in all extremities within 48 h. In her neurological examination, she demonstrated quadriplegia, hypotonia and bilateral areflexia. In three days of symptoms, she presented dry cough, dyspnea and fever that resolved spontaneously within 48 h, but her computed tomography (CT) scan showed an opaque aspect and “ground glass” findings, and her RT–qPCR test was positive for infection by SARS-CoV-2 (El Otmani et al., 2020). Based on the results, we hypothesize that episodes of SARS-CoV-2 infection and the outcome of GBS are not random. Due to the inflammatory mechanism presented by SARS-CoV-2, it actively contributes to the increase in the inflammatory response and finally to the triggering of a lack of control in the immune system, which can result in neurological illnesses linked to GBS. Fig. 2 illustrates the pathophysiology described above.

### 4.2. Main findings

There are still no biomarkers with good sensitivity and specificity for GBS, so its diagnosis is made through clinical history and physical examination and is assisted by additional tests such as CSF analysis and electrophysiological studies (Leonhard et al., 2019).

Electrodiagnostic studies are not essential to the diagnosis of GBS, but they are of great help, especially for patients with atypical presentations of the disease and to differentiate its subtypes. The most frequent findings in our study were reduction in conduction speed, reduction in muscle action potential amplitude and reduction/absence of sensory action potential amplitude, which is consistent with what is presented in the literature (Leonhard et al., 2019). Regarding the distribution of GBS electrophysiological variants, our analysis showed that COVID-19-associated GBS manifests prevalently with AIDP, as other studies have shown (Abu-Rumeileh et al., 2021). In addition, there were reports, although to a lesser extent, of AMAN, AMSAN, MFS and PCB.

Regarding CSF analysis, our study showed that findings in patients diagnosed with GBS and COVID-19 were similar to findings in non-COVID-19 patients. Our main findings were increased protein with normal cellularity. It is known that an association of increased protein and normal cellularity (determining albuminocytological dissociation) in CSF is a trait of GBS; yet, its isolated presence does not confirm the diagnosis of GBS (van den Berg et al., 2014).

Regarding the analysis of blood samples, our study did not observe a pattern that was common to all patients. Blood count and platelet count results included leukopenia, leukocytosis, lymphopenia, neutrophilia, thrombocytopenia, and normal cell count. Concerning inflammatory tests, most patients had at least one of them that was abnormal, whether CRP, d-dimers, LDH, ferritin or CK. However, there was a minority of cases where inflammatory evidence was within the normal range. This lack of a pattern in the biochemical analysis is common in patients with GBS, as other studies have shown (Abu-Rumeileh et al., 2021; Caress et al., 2020).

Furthermore, most cases were negative for anti-ganglioside antibody testing, and only 7 of our cases tested positive for at least one type of serum anti-ganglioside antibody, the most frequent being anti-GD1b IgG ($n = 4$). Antibody testing can be useful to support a diagnosis. However, it is a test that has limitations because, even if negative, GBS cannot be excluded as a diagnosis and, if positive, it does not confirm the diagnosis of GBS, since anti-ganglioside antibodies can occur in other pathologies. Nevertheless, the presence of anti-GQ1B antibodies appears in up to 90% of patients with MFS. However, in our analysis of the 16 reported cases of MFS, only 2 of them had anti-GQ1B antibody, which represents 12,5% of the MFS reported cases. This may suggest that the development of MFS in COVID and non-COVID patients has different mechanisms, but further studies are needed to prove this hypothesis (Leonhard et al.,

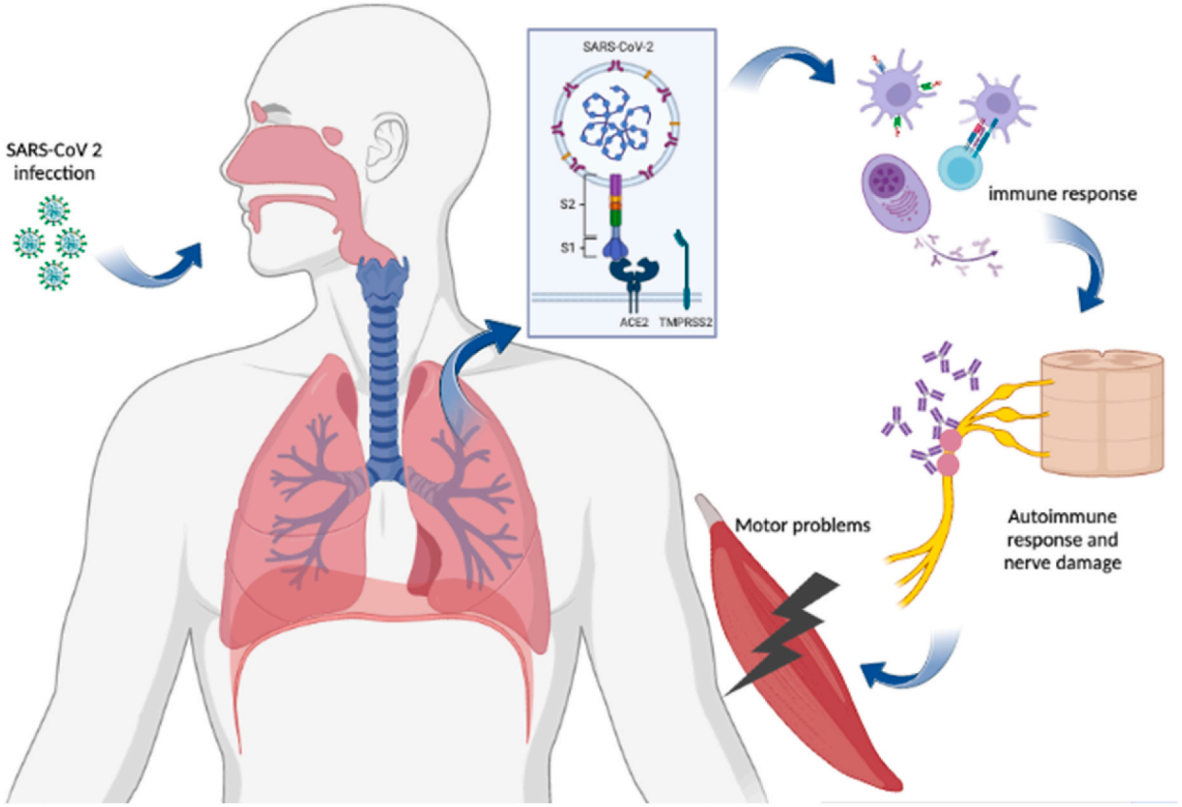


**Fig. 2.** Mechanisms of SARS-CoV-2 infection in GBS.

2019; Abu-Rumeileh et al., 2021; van den Berg et al., 2014).

### 4.3. Clinical features of GBS post-COVID-19

The clinical characteristics of Guillain–Barré after COVID-19 are, in general, similar to those presented by patients who developed this syndrome due to other causes. In this context, the analyzed patients presented decreased strength, predominantly distal, of the limbs with ascending evolution, in addition to paresthesia, tactile and painful hypoesthesia, hyporeflexia or areflexia and cranial nerve alterations (Jasti et al., 2016).

The clinical analysis of the patient, consisting of the search for symptoms through anamnesis added to the detection of signs by physical examination, is the basis of the Guillain–Barré diagnosis. The diagnosis of this pathology is established on criteria proposed by the US National Institute of Neurological Disorders and Stroke (NINDS), which defines the findings as mandatory, strongly associated with the disease and, finally, those that should cause diagnostic doubt when present. The mandatory characteristics for the diagnosis to be made are progressive weakness of the limbs, accompanied by decreased reflexes in the affected limb. Factors supporting the diagnosis involve a progression of up to four weeks, symmetry of motor and sensory deficit, mild sensory involvement, involvement of the cranial nerves (principally VII), onset of recovery four weeks from the stopping of progression, autonomic dysfunction, absence of fever at onset, albuminocytological dissociation in CSF, and slow or blocked nerve conduction for several weeks on electroneuromyography. Among the factors that call into question the diagnosis is a marked asymmetric weakness, initial or persistent visual and/or intestinal dysfunction, high lymphocyte count in CSF and well-demarcated sensory level. Isolated sensory involvement or explanation of the better condition by another neuropathy exclude the diagnosis (van Doorn, 2013).

In our study, the most frequent symptom was limb weakness, which was reported in 297 patients, and the most frequent sign was the reduction or abolition of reflexes, which was present in 286 patients. Sensory alterations were also a highly prevalent finding, especially hypoesthesia. Cranial nerve involvement was also found on neurological examination of the patients evaluated. Corroborating the findings already present in the literature, the facial nerve (VII) was the main affected CN, followed by the bulbar nerves, the III, IV and VI pairs involved in ocular motricity and the V pair. The remaining cranial pairs were affected less frequently.

### 4.4. Relation of GBS variants and other viral diseases

Typical Guillain–Barré syndrome is an acute-onset ascending sensorimotor neuropathy that presents with distal paresthesia or sensory loss, with or followed by muscle weakness that starts in the legs, progressing to the arms and cranial muscles. Reflexes are often decreased or absent at first presentation, and, at nadir, it is present in nearly all patients. However, the disease can have an atypical onset or show as a clinical variant. Variants are defined by the involvement of different sorts of nerve fiber (motor, sensory, motor and sensory, cranial or autonomic), by the nature of the injury (axonal or demyelinating), and by the changes in consciousness. The GBS variants commonly present features from the classic syndrome or show typical aspects from another variant. The most common variant, AIDP, characterized by sensorimotor GBS, is frequently seen combined with autonomic dysfunction and cranial nerve impairment. The AMAN variant presents pure motor GBS, and rarely affects cranial nerves. The AMSAN variant resembles severe AMAN; however, sensory fibers are affected. MFS is a less common variant defined by a triad of clinical features of ophthalmoplegia, ataxia and areflexia. PCB is a rare motor variant that manifests with weakness of the pharyngeal, cervical, and brachial muscles without lower limb weakness (Leonhard et al., 2019; Dimachkie and Barohn, 2013).

Research shows that 2/3 of patients present respiratory or gastrointestinal tract infection symptoms previous to the onset of GBS. The most common pathogens related to GBS are *C. jejuni*, cytomegalovirus,

Epstein–Barr virus, *Mycoplasma pneumoniae*, Zika virus, *Haemophilus influenzae* and influenza A. The most recurring pathogen found prior to GBS development is *C. jejuni*, and it is predominantly related to the AMAN subtype of GBS, yet it is also seen in other variants. On the other hand, our study and other reviews on GBS and COVID-19 have shown that the most common type in COVID-19 patients is the AIDP variant (Leonhard et al., 2019).

During the outbreaks of infectious diseases that trigger GBS, the syndrome can become more prevalent in the population. An example of that was the Zika virus outbreak in French Polynesia, Latin America and the Caribbean between 2013 and 2016. During this period, there was an increase in individuals diagnosed with GBS (Leonhard et al., 2019; van den Berg et al., 2014; Sriwastava et al., 2021). Nonetheless, it has not been proven that there has been an increase in GBS cases after the SARS-CoV-2 pandemic, as occurred in the Zika virus pandemic. In a study conducted across the UK, it was stated that, during the first wave of COVID-19, there was no increased incidence of GBS; thus, COVID-19 couldn't be associated as a cause of GBS in this population. Therefore, more studies are needed to confirm or deny the correlation between COVID-19 and GBS (Keddie et al., 2021).

Studies have shown that there is some evidence to support the hypothesis of the association between GBS and most vaccines as its triggers. An exception was the vaccine for swine influenza used in 1976–77 and older rabies vaccines (Haber et al., 2009). Increases in GBS related to modern influenza vaccines has not been of great prevalence, many robust studies agree in an increase of about one case of GBS per million vaccinations (Lunn et al., 2021). Thus far, there have been reported cases of GBS after a COVID vaccine (Pfizer, Johnson & Johnson, Janssen, AstraZeneca). However, if millions of individuals have been vaccinated and GBS was rarely reported, this does not presuppose a solid connection between COVID-19 vaccines and GBS. Therefore, more research is needed to fully understand the pathogenesis behind GBS following vaccination and to estimate the prevalence of GBS as a possible side effect (Kanabar and Wilkinson, 2021).

### 4.5. Diagnosis and management of GBS

The diagnosis of GBS is initially clinical, based on the presentation of acute progressive and mainly symmetric muscle weakness and the absence or reduction of deep tendon reflexes (Fokke et al., 2014). The clinical diagnosis is accompanied by a CSF study in every patient (Willison et al., 2016). In our study, 297 patients had some level of motor limb impairment, representing approximately 92% of the patients who had the strength analysis described. The reflexes, in turn, were reduced or absent in 97.6% of the post-COVID-19 GBS patients in whom they were tested. Currently, the diagnosis of GBS usually follows the criteria proposed in 1978 by the National Institute of Neurological Disorders and Stroke (NINDS) with a reaffirmation of these criteria in 1990 (Criteria for diagnosis of Guillain, 1978; Asbury and Cornblath, 1990). Moreover, the complete diagnosis of GBS is supported by a CSF study presenting albuminocytological dissociation, which helps exclude other causes of the patient's clinical presentation (Asbury and Cornblath, 1990). In our analysis, 303 patients had detailed results of their CSF studies, with 227 of them showing albuminocytological dissociation. Furthermore, the GBS diagnosis is also reinforced by electrodiagnostic studies of nerve conduction studies (NCS) and electromyography (EMG), which help evaluate the prognosis of the syndrome and differentiate its subtypes (Asbury and Cornblath, 1990). Other tests are also helpful for GBS diagnosis, such as laboratory testing, antibody testing and diagnostic imaging (Kaida et al., 2008; Ogawara et al., 2000; Byun et al., 1998).

The management of GBS is focused mainly on immunotherapy with IVIG or PLEX, with IVIG being more commonly used because of its easier administration and better acceptance from the patient (Hughes et al., 2014; Chevret et al., 2017). Our study showed that from 400 cases with information about their treatment, 329 patients were treated with IVIG and 45 with PLEX. Eleven patients were also treated with glucocorticoids, even though this is not recommended considering that there is no evidence of their benefit to the clinical picture of GBS (Hughes et al., 2016).

This study reported a high prevalence of hospitalization (n = 91) and ICU admissions (n = 139) among the cases with available data, conjecturing a relationship between the development of GBS and COVID-19 severity.

### 4.6. Outcomes

In regard to GBS outcome, most patients with available information had an improvement after treatment in most of their residual symptoms not including motor involvement. However, 27 patients died during the treatment.

### 4.7. Strengths and limitations

The present work is a systematic review that groups together the available literature on the themes of GBS and SARS-CoV-2. Here, the extreme importance of the work was shown by making a compilation of the literature and highlighting the relationship between GBS and viral infection. Based on the search on different platforms, this resulted in a large number of studies (n = 3023), of which after the initial filtering, a significant number of articles reporting common characteristics remained (n = 156). From there, similar characteristics were listed and relevant characteristics about the indicated relationship were analyzed based on preestablished criteria. For this reason, this systematic review demonstrates the rigor with which it was constructed, following the precepts of excellence proposed for a systematic review. As for strengths, we listed the pooling and filtering criteria of the range of proposed studies on the relationship and findings between SARS-CoV-2 and GBS infection. The compilation of studies provided a rigorous view and better inferential potential about the findings. The systematic review provided visualization and an increase in evidence about the aforementioned relationship. Regarding the limitations, the literature presented itself in a distorted way with different types of articles, and based on case reports, large compilation studies were few, which led us to view it as a new description. In our work, we emphasized the importance of an enhanced understanding of the aspects related to the association of the diseases in question, but we recognize that carrying out larger epidemiological studies can contribute to a greater amount of evidence.

## 5. Conclusion

Our study presented a collection of literature related to the link between GBS and SARS-CoV-2 infection. A significant number of studies reported common characteristics between these two conditions. Here, we demonstrated that there is possibly an interrelationship between GBS, age and sex by showing that the mean age of the patients was 61,38 years and that most were male. In addition, we highlighted the major related symptoms for GBS and COVID-19. Regarding GBS, the main manifestations included generalized weakness, reflex reduction, facial paresis/paralysis, hypoesthesia and paresthesia. As expected, the most common feature in CSF analysis was albuminocytological dissociation. Regarding electrodiagnostic results, AIDP was the most frequent subtype of GBS in the present study. The present study reported a high prevalence of hospitalizations and ICU admissions, conjecturing a correlation between the development of GBS and the severity of COVID-19. The results presented in this systematic review can serve as the basis for studies on the influence of SARS-CoV-2 infection on the peripheral nervous system and can be used in clinical practice to assist the medical team in describing clinical GBS findings in patients with COVID-19 manifestations. Recent COVID-19 variants, such as Omicron, whose consequences are still unknown, are occurring worldwide. Thus, in the present scenario, more studies are necessary to investigate the possible permanent neurological impacts due to SARS-CoV-2 infection.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Funding

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001, and by the Conselho Nacional de Desenvolvimento Tecnológico (CNPq). J.C.DaCosta is CNPq researcher.

## Availability of data and materials

The data that support the findings of this study are available from the corresponding author on request.

## Authors' contributions

V.P. and G.Z. designed the manuscript. V.P., V.W.L., G.L.C. and A.M.A. performed the literature search and wrote the original draft. D.R.M., N.B.E. and G.Z. critically revised the manuscript. J.C.C. designed, critically revised, and supervised the study. All authors approved the final version of the manuscript.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Acknowledgements

We would like to thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001, the and Conselho Nacional de Desenvolvimento Tecnológico (CNPq).

## List of abbreviations

| | |
|---|---|
| COVID-19 | Coronavirus disease 2019 |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| GBS | Guillain–Barré Syndrome |
| CSF | Cerebrospinal Fluid |
| AIDP | Acute Inflammatory Demyelinating Polyneuropathy |
| AMAN | Acute Motor Axonal Neuropathy |
| AMSAN | Acute Sensorimotor Axonal Neuropathy |
| MFS | Miller-Fisher Syndrome |
| IVIG | Intravenous Immunoglobulin |
| PLEX | Plasma Exchange |
| WHO | World Health Organization |
| ACE2 | Angiotensin-2 Converting Enzyme |
| CNS | Central Nervous System |
| PNS | Peripheral Nervous System |
| EBV | Epstein-Barr Virus |
| PRISMA | Preferred Reporting Items for Systematic Review and Meta-Analyses |
| ICU | Intensive Care Units |
| GRADE | Grading of Recommendations, Assessment, Development, and Evaluations |
| DM2 | Type 2 Diabetes mellitus |
| GERD | Gastroesophageal Reflux Disease |
| SAH | Systemic Arterial Hypertension |
| CN | Cranial Nerve |
| CRP | C-Reactive Protein |
| CK | Creatine Kinase |
| DAMPs | Molecular Patterns Associated with Damage |
| CT | Computed Tomography |
| NINDS | National Institute of Neurological Disorders and Stroke |

## References

Abu-Rumeileh, S., Abdelhak, A., Foschi, M., Tumani, H., Otto, M., 2021. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases [Internet] J. Neurol. 268 (4), 1133–1170. https://doi.org/10.1007/s00415-020-10124-x. Available from:

Amoretti, M., Amsler, C., Bonomi, G., Bouchta, A., Bowe, P., Carraro, C., et al., 2002. Production and detection of cold antihydrogen atoms [Internet] Nature 419 (6906), 456–459. https://doi.org/10.1038/nature01096. Available from:

Asbury, A.K., Cornblath, D.R., 1990. Assessment of current diagnostic criteria for Guillain-Barré syndrome [Internet] Ann. Neurol. 27 (Suppl. l), S21–S24. https://doi.org/10.1002/ana.410270707. Available from:

Byun, W.M., Park, W.K., Park, B.H., Ahn, S.H., Hwang, M.S., Chang, J.C., 1998. Guillain-Barré syndrome: MR imaging findings of the spine in eight patients [Internet] Radiology 208 (1), 137–141. https://doi.org/10.1148/radiology.208.1.9646804. Available from:

Caress, J.B., Castoro, R.J., Simmons, Z., Scelsa, S.N., Lewis, R.A., Ahlawat, A., et al., 2020. COVID-19–associated Guillain-Barré syndrome: the early pandemic experience [Internet] Muscle Nerve 62 (4), 485–491. https://doi.org/10.1002/mus.27024. Available from:

Carvalho, T., Krammer, F., Iwasaki, A., 2021. The first 12 months of COVID-19: a timeline of immunological insights [Internet] Nat. Rev. Immunol. 21 (4), 245–256. https://doi.org/10.1038/s41577-021-00522-1. Available from:

Chevret, S., Hughes, R.A., Annane, D., 2017. Plasma exchange for Guillain-Barré syndrome [Internet] Cochrane Database Syst. Rev. 2 (3), CD001798. https://doi.org/10.1002/14651858.CD001798.pub3. Available from:

Criteria for diagnosis of Guillain-Barré syndrome [Internet] Ann. Neurol. 3 (6), 1978, 565–566. https://doi.org/10.1002/ana.410030628. Available from:

Dimachkie, M.M., Barohn, R.J., 2013. Guillain-Barré syndrome and variants [Internet] Neurol. Clin. 31 (2), 491–510. https://doi.org/10.1016/j.ncl.2013.01.005. Available from:

El Otmani, H., El Moutawakil, B., Rafai, M.-A., El Benna, N., El Kettani, C., Soussi, M., et al., 2020. Covid-19 and guillain-Barré syndrome: more than a coincidence [Internet] Rev. Neurol. (Paris) 176 (6), 518–519. https://doi.org/10.1016/j.neurol.2020.04.007. Available from:

Fokke, C., van den Berg, B., Drenthen, J., Walgaard, C., van Doorn, P.A., Jacobs, B.C., 2014. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria [Internet] Brain 137 (Pt 1), 33–43. https://doi.org/10.1093/brain/awt285. Available from:

Haber, P., Sejvar, J., Mikaeloff, Y., DeStefano, F., 2009. Vaccines and guillain-Barré syndrome [Internet] Drug Saf. 32 (4), 309–323. https://doi.org/10.2165/00002018-200932040-00005. Available from:

Hamming, I., Timens, W., Bulthuis, M.L.C., Lely, A.T., Navis, G.J., van Goor, H., 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis [Internet] J. Pathol. 203 (2), 631–637. https://doi.org/10.1002/path.1570. Available from:

[Internet]. In: Higgins, J., Thomas, J. (Eds.), 2019. Cochrane Handbook for Systematic Reviews of Interventions, second ed. Standards Information Network [cited 2022 Jan 12]. Available from: https://training.cochrane.org/handbook/current.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [Internet] Lancet 395 (10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5. Available from:

Hughes, R.A.C., Swan, A.V., van Doorn, P.A., 2014. Intravenous immunoglobulin for Guillain-Barré syndrome [Internet] Cochrane Database Syst. Rev. 2019 (9), CD002063. https://doi.org/10.1002/14651858.CD002063.pub6. Available from:

Hughes, R.A., Brassington, R., Gunn, A.A., van Doorn, P.A., 2016. Corticosteroids for guillain-Barré syndrome [Internet] Cochrane Database Syst. Rev. 10 (10), CD001446. https://doi.org/10.1002/14651858.CD001446.pub5. Available from:

Jasti, A.K., Selmi, C., Sarmiento-Monroy, J.C., Vega, D.A., Anaya, J.-M., Gershwin, M.E., 2016. Guillain-Barré syndrome: causes, immunopathogenic mechanisms and treatment [Internet] Expert Rev Clin Immunol 12 (11), 1175–1189. https://doi.org/10.1080/1744666X.2016.1193006. Available from:

Kaida, K., Sonoo, M., Ogawa, G., Kamakura, K., Ueda-Sada, M., Arita, M., et al., 2008. GM1/GalNAc-GD1a complex: a target for pure motor Guillain-Barre syndrome [Internet] Neurology 71 (21), 1683–1690. https://doi.org/10.1212/01.wnl.0000335160.72184.7d. Available from:

Kanabar, G., Wilkinson, P., 2021. Guillain-Barré syndrome presenting with facial diplegia following COVID-19 vaccination in two patients [Internet] BMJ Case Rep. 14 (10). https://doi.org/10.1136/bcr-2021-244527. Available from:

Keddie, S., Pakpoor, J., Mousele, C., Pipis, M., Machado, P.M., Foster, M., et al., 2021. Epidemiological and cohort study finds no association between COVID-19 and

Guillain-Barré syndrome [Internet] Brain 144 (2), 682–693. https://doi.org/10.1093/brain/awaa433. Available from:
Leonhard, S.E., Mandarakas, M.R., Gondim, F.A.A., Bateman, K., Ferreira, M.L.B., Cornblath, D.R., et al., 2019. Diagnosis and management of Guillain–Barré syndrome in ten steps [Internet] Nat. Rev. Neurol. 15 (11), 671–683. https://doi.org/10.1038/s41582-019-0250-9. Available from:
Li, W., Moore, M.J., Vasilieva, N., Sui, J., Wong, S.K., Berne, M.A., et al., 2003. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus [Internet] Nature 426 (6965), 450–454. https://doi.org/10.1038/nature02145. Available from:
Lunn, M.P., Cornblath, D.R., Jacobs, B.C., Querol, L., van Doorn, P.A., Hughes, R.A., et al., 2021. COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations [Internet] Brain 144 (2), 357–360. https://doi.org/10.1093/brain/awaa444. Available from:
McGrogan, A., Madle, G.C., Seaman, H.E., de Vries, C.S., 2009. The epidemiology of Guillain-Barré syndrome worldwide. A systematic literature review [Internet] Neuroepidemiology 32 (2), 150–163. https://doi.org/10.1159/000184748. Available from:
Ogawara, K., Kuwabara, S., Mori, M., Hattori, T., Koga, M., Yuki, N., 2000. Axonal Guillain-Barré syndrome: relation to anti-ganglioside antibodies and Campylobacter jejuni infection in Japan [Internet] Ann. Neurol. 48 (4), 624–631. https://doi.org/10.1002/1531-8249(200010)48:4<624::aid-ana9>3.0.co;2-o. Available from:
Ottaviani, D., Boso, F., Tranquillini, E., Gapeni, I., Pedrotti, G., Cozzio, S., et al., 2020. Early Guillain-Barré syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital [Internet] Neurol. Sci. 41 (6), 1351–1354. https://doi.org/10.1007/s10072-020-04449-8. Available from:
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews [Internet] BMJ 372. https://doi.org/10.1136/bmj.n71. n71. Available from:
Sedaghat, Z., Karimi, N., 2020. Guillain Barre syndrome associated with COVID-19 infection: a case report [Internet] J. Clin. Neurosci. 76, 233–235. https://doi.org/10.1016/j.jocn.2020.04.062. Available from:
Sejvar, J.J., Baughman, A.L., Wise, M., Morgan, O.W., 2011. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis [Internet] Neuroepidemiology 36 (2), 123–133. https://doi.org/10.1159/000324710. Available from:
Sriwastava, S., Kataria, S., Tandon, M., Patel, J., Patel, R., Jowkar, A., et al., 2021. Guillain Barré Syndrome and its variants as a manifestation of COVID-19: a systematic review of case reports and case series [Internet] J. Neurol. Sci. 420 (117263), 117263. https://doi.org/10.1016/j.jns.2020.117263. Available from:
Tay, M.Z., Poh, C.M., Rénia, L., MacAry, P.A., Ng, L.F.P., 2020. The trinity of COVID-19: immunity, inflammation and intervention [Internet] Nat. Rev. Immunol. 20 (6), 363–374. https://doi.org/10.1038/s41577-020-0311-8. Available from:
van den Berg, B., Walgaard, C., Drenthen, J., Fokke, C., Jacobs, B.C., van Doorn, P.A., 2014. Guillain–Barré syndrome: pathogenesis, diagnosis, treatment and prognosis [Internet] Nat. Rev. Neurol. 10 (8), 469–482. https://doi.org/10.1038/nrneurol.2014.121. Available from:
van Doorn, P.A., 2013. Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS) [Internet] Presse Med. 42 (6 Pt 2), e193–e201. https://doi.org/10.1016/j.lpm.2013.02.328. Available from:
Willison, H.J., Jacobs, B.C., van Doorn, P.A., 2016. Guillain-Barré syndrome [Internet] Lancet 388 (10045), 717–727. https://doi.org/10.1016/s0140-6736(16)00339-1. Available from:
Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., et al., 2020a. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission [Internet] Sci. China Life Sci. 63 (3), 457–460. https://doi.org/10.1007/s11427-020-1637-5. Available from:
Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., et al., 2020b. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa [Internet] Int. J. Oral Sci. 12 (1), 8. https://doi.org/10.1038/s41368-020-0074-x. Available from:
Yachou, Y., El Idrissi, A., Belapasov, V., Ait Benali, S., 2020. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients [Internet] Neurol. Sci. 41 (10), 2657–2669. https://doi.org/10.1007/s10072-020-04575-3. Available from:
Zhang, B., Zhou, X., Qiu, Y., Feng, F., Feng, J., Jia, Y., et al., 2020. Clinical characteristics of 82 death cases with COVID-19 [Internet] bioRxiv. https://doi.org/10.1101/2020.02.26.20028191. Available from: