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Evaluation and Comparison of Treatment Response and In-Hospital Prognosis of COVID-19-Related Guillain-Barre Syndrome with Non-COVID-19 Patients

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Abstract

Background: The coronavirus disease 2019 (COVID-19) outbreak has caused significant health and social impacts worldwide. Severe acute respiratory syndrome coronavirus 2, the virus responsible for COVID-19, can lead to neurological symptoms, including Guillain-Barré syndrome (GBS). This study aimed to compare the clinical manifestations, electrophysiological characteristics, degree of disability, and treatment outcomes of GBS patients with COVID-19 (COVID-19-related GBS) with GBS patients without COVID-19.

Methods: This retrospective cross-sectional multicenter study investigated the clinical characteristics and outcomes of GBS patients with a history of COVID-19. A total of 60 patients with GBS and a history of COVID-19 were included in the COVID-19 group, while 56 patients with GBS without COVID-19 were included in the control group. Demographic, clinical, therapeutic, and prognostic data were compared between the 2 groups.

Results: The COVID-19 patients were older (56.2 ± 16.8 vs 47.46 ± 19.25; $P = 0.01$), and there was no sex difference between the 2 groups. The most frequent electrophysiological type was acute inflammatory demyelinating polyradiculoneuropathy (55% and 41%) in both groups. Although almost half of the patients in both groups were admitted to the intensive care unit (ICU), the group of COVID-19 patients required mechanical ventilation more (16.6% vs 0%; $P < 0.001$). Also, the COVID-19 group had more length of ICU stay ($P < 0.001$). Although some electrophysiological differences were found (acute motor axonal neuropathy was more frequent in the non-COVID-19 group), The analysis did not show any difference in the response to treatment scores based on Phenotype, type of treatment, or electrophysiological pattern between the 2 groups of patients.

Conclusion: GBS in COVID-19 patients may have different manifestations and electrophysiological patterns, but the response to treatment and in-hospital prognosis were not different compared with GBS in non-COVID-19 patients.

Keywords: Guillain-Barré Syndrome, COVID-19, Prognosis

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Introduction

In late 2019, the outbreak of coronavirus disease 2019 (COVID-19) occurred in Wuhan, China, resulting in widespread impacts on healthcare and various aspects of daily life. The specific virus responsible for this disease is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is known that SARS-CoV-2 can lead to neurological symptoms such as headaches, dizziness, hypogeusia, and hyposmia (1).

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↑What is "already known" in this topic:
Guillain-Barre Syndrome (GBS), the most common cause of sudden muscle weakness, has different presentations and electrophysiological types with specific treatment methods and prognoses. During the coronavirus disease 2019 (COVID-19) pandemic, treatment methods and prognoses for many diseases were affected.

→What this article adds:
This study discussed presentations of treatment strategies used in GBS associated with COVID-19 and compared the symptoms, mortality, and response to treatment of these patients with patients with GBS without COVID-19.

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Guillain-Barré Syndrome (GBS) is the most common cause of sudden muscle weakness or paralysis. GBS can be classified into 4 main subtypes: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), axonal subtypes like acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome. Also, GBS can be classified based on phenotype: Classic, Paraparesia, and Miller Fisher. These subtypes may vary in prevalence across different geographical regions (2).

GBS has been associated with various infectious agents, including Campylobacter jejuni (C. jejuni), cytomegalovirus (CMV), hepatitis E virus, Mycoplasma pneumonia, Epstein-Barr virus (EBV), and Zika virus. In January 2020, the first case of GBS related to SARS-CoV-2 infection was reported in China (3).

During 5 epidemiologic peaks of COVID-19 and the crowding of COVID-19 patients in hospitals, we were faced with a new group of patients, with COVID-19-related GBS (4).

Therefore, we designed this study to compare the manifestations, electrophysiological characteristics, degree of disability, and treatment outcomes in the population of patients with GBS without COVID-19 to create a more appropriate understanding of the course of the disease and in-hospital prognosis.

Methods

This retrospective multicenter cross-sectional study was conducted in Isfahan, Iran. All GBS patients with a history of COVID-19 presenting to Al-Zahra and Kashani hospitals from September 2020 to September 2022 were checked for inclusion in the study. Patients with a history of symptomatic COVID-19 during the past 4 weeks, proven by nasopharyngeal swab polymerase chain reaction (PCR) or characteristic lung high-resolution computed tomography (HRCT), who developed neurological symptoms and had a definite diagnosis of GBS, according to Brighton (5) and Rajabally's electrophysiological criteria (6), were included in the COVID-19 group (n = 60). All patients with a definite diagnosis of GBS presented to Al-Zahra Hospital from March 2019 to September 2022 without a probable or definite recent diagnosis of COVID-19, formed the group of patients without COVID-19 (n = 56). We excluded patients with GBS-mimicking conditions such as toxic neuropathy, critical illness myopathy, acute vasculitis, or other acute muscle diseases. Demographic, clinical, therapeutic, and prognostic indexes—including age, sex, comorbidities, clinical presentation, electrodiagnostic features, length of hospital stay, length of intensive care unit (ICU) admission, need for mechanical ventilation, disability score before and after treatment, response to treatment score (defined as the difference in disability score before and after treatment), and mortality—were recorded through patient's files.

Disability scores were graded by evaluating the patient's ability to walk (without assistance or with assistance) and by the need for assisted ventilation, as follows:

0: Healthy state
1: Slight symptoms and able to run
2: Able to walk ≥10 meters without assistance but unable to run
3: Able to walk 10 meters outdoors with assistance
4: In bed or wheelchair
5: Needing auxiliary ventilation for at least part of the day
6: Death

In this study, baseline characteristics, symptoms, examinations, and electrophysiological patterns related to GBS were compared in the 2 groups, and mortality and disability scores before and after treatment were considered as end point variables based on the system that was explained.

To deal with the possible confounding effect of the difference in factors that trigger GBS in different seasons, the study period was chosen to include all seasons.

The analysis was performed using SPSS software Version 26.0 (IBM). Continuous variables were expressed as the mean ± standard deviation in normal distributions and the median (interquartile range [IQR]) for non-normal distributions. Categorical variables were shown as frequencies and percentages. To compare the 2 groups, the chi-square test was used for qualitative variables, and the t test or the Mann-Whitney U test was used for quantitative variables based on variable distribution. $P < 0.05$ was considered statistically significant.

Results

A total of 116 patients who met the inclusion criteria were included in the study. A total of 60 patients (51.7%) had proven COVID-19 infection, and 56 patients (48.3%) were without a history of COVID-19 infection. The COVID-19 group patients were older than patients without COVID-19 history (56.2 ± 16.86 years vs 47.46 ± 19.25 years; $P = 0.011$), and diabetes was more prevalent among patients with COVID-19 history (35% vs 16.1%; P = 0.020). Table 1 demonstrates demographic and baseline clinical characteristics.

Despite 7 of COVID-19-positive patients (11.6%), none of the patients without a history of COVID-19 showed dysarthria and autonomic disturbance ($P = 0.013$ and P = 0.013, respectively). Some GBS-related symptoms and physical examination patterns—including stock gloves and abnormal position—were more prevalent in COVID-positive patients (73.3% vs 42.8%; $P < 0.001$, 48.3% vs 23.2%; $P = 0.002$, respectively).

Patients with a COVID-19 history had a higher level of serum inflammatory markers, although there was no significant difference in cerebrospinal fluid (CSF) analyses between the 2 groups of patients.

The classic form of GBS was the most common phenotype in both groups (95% vs 82.1%; $P = 0.064$), 2 patients in the COVID-19 group (3.3%) and 9 (16.1%) patients in the non-COVID-19 group showed pure paraparesis phenotype. Axonal mechanism of nerve injury occurred in 27 patients (45%) in the COVID-19 group and 32 patients in the non-COVID-19 group (57.1%), which was statistically nonsignificant (P = 0.191). However, the analysis showed a significantly different distribution of electrophysiological patterns, so the AMAN pattern was less frequent in the COVID-19 group (9 [15%] vs 22 [39.9%]; $P = 0.012$) (Table 2).

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Table 1. Baseline Demographic Variables

Baseline Characteristic		COVID-19 Patients N = 60	Non COVID-19 Patients N = 56	*P* Value
Mean Age (SD) – years		56.2 ± 16.8	47.46 ± 19.25	0.011
Sex – no (%)	Male	35(58.3%)	33(58.9%)	0.948
	Female	25(41.7%)	23(41.1%)	
Clinical presentation				
Dyspnea - no (%)		22(36.7%)	2(3.6%)	<0.001
Anosmia – no (%)		3(5%)	0(0%)	0.244
Diarrhea – no (%)		13(21.7%)	12.(21.4%)	0.975
Headache – no (%)		10(16.7%)	0(0%)	0.001
Myalgia – no (%)		17(28.3%)	1(1.8%)	<0.001
Comorbidities				
Diabetes – no (%)		21(35%)	9(16.1%)	0.020
Hypertension – no (%)		26(43.3%)	16(28.6%)	0.098
Ischemic Heart disease – no (%)		10(16.7%)	5(8.9%)	0.215
Hyperlipidemia – no (%)		13(21.7%)	9(16.1%)	0.442
Hypothyroidism – no (%)		4(6.7%)	4(7.1%)	0.919
Chronic Kidney disease – no (%)		5(8.3%)	4(7.1%)	0.811

Table 2. GBS Characteristics

GBS characteristic		COVID-19 Patients N = 60	Non COVID-19 Patients N = 56	*P* Value
Symptoms and Physical examination				
Dysarthria – no (%)		7(11.6%)	0(0%)	0.013
Paresthesia – no (%)		42(70.0%)	35(62.5%)	0.154
Paraparesia – no (%)		11(18.3%)	9(16.1%)	0.747
Quadriparesia – no (%)		48(80%)	44(78.6%)	0.849
Ataxia – no (%)		6(10.0%)	6(10.7%)	0.751
Urinary retention – no (%)		4(6.6%)	3(5.3%)	0.696
Urinary incontinency – no (%)		4(6.6%)	2(3.5%)	0.679
Hyporeflexia – no (%)		54(90.0%)	53(94.6%)	0.999
Hyperreflexia – no (%)		2(3.3%)	2(3.5%)	0.999
Bulbar symptoms – no (%)		8(13.3%)	3(5.3%)	0.112
Dysautonomia– no (%)		7(11.6%)	0(%)	0.013
Stock-Glove – no (%)		44(73.3%)	24(42.8%)	<0.001
Sensory level – no (%)		2(3.3%)	1(1.7%)	0.999
Abnormal Position – no (%)		29(48.3%)	13(23.2%)	0.002
Facial involvement – no (%)		9(15.0%)	2(3.5%)	0.029
GBS Phenotype – no (%)	Classic	57(95.0%)	46(82.1%)	0.064
	Paraparesia	2(3.3%)	9(16.1%)	
	Miller Fischer	1(1.7%)	1(1.8%)	
Axonal – no (%)		27(45.0%)	32(57.1%)	0.191
Demyelinating – no (%)		33(55.0%)	23(41.1%)	
EMG/NCS Pattern – no (%)	AIDP	33(55.0%)	23(41.1%)	0.012
	AMAN	9(15%)	22(39.3%)	
	AMSAN	18(30%)	11(19.6%)	
Blood Lab tests – Median (IQR)	WBC - × 109/L	10.8(6.4)	6.2(2.8)	0.842
	ESR – mm/h	24(25)	10.5(8.5)	0.029
	CRP – mg/L	7(17)	1(4.5)	0.002
CSF Lab tests – Median (IQR)	WBC - × 109/L	2(4)	2(7.5)	0.747
	Protein – mg/dL	69(59)	41.5(138.75)	0.673
	Glucose – mg/dL	75(15)	68(14.75)	0.672

Most patients in both groups underwent plasma exchange, 9 (15%) in the COVID-19 group and 2 (3.6%) in the non-COVID-19 group received intravenous immunoglobulin (IVIG), which was nonsignificant (P = 0.118). Although almost half of the patients in both groups were admitted to the ICU, the COVID-19 grousp required mechanical ventilation more (16.6% vs 0%; $P < 0.001$). Median disability scores were not different before or after treatment (4[1] vs 4[1]; P = 0.176 and 3 [2] vs 2 [1]; P = 0.114, respectively). Also, the median response to the treatment score was equal (P = 0.385) (Table 3).

Six patients (10%) in the COVID-19 group died, while all patients in the non-COVID-19 group were discharged alive (P = 0.028).

The subgroup analysis did not show any difference in the response to treatment scores based on phenotype, type of treatment, or electrophysiological pattern between the 2 groups. Table 4 demonstrates the details of subgroup analyses.

Discussion

This study included 60 GBS patients with recent or concomitant COVID-19 infection. It has been shown in several studies that symptomatic COVID-19 is more frequent in elderly and diabetic patients, which may be caused by older age, with a mean age of 56.2 years versus 47 years and a

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Table 3. Disease Severity, Treatment, and Prognostic Factors

Disease Severity, Treatment, and Prognostic Factor		COVID-19 Patients N = 60	Non COVID-19 Patients N = 56	*P* Value
Treatment type – no (%)	IVIG	9(15.0%)	2(3.6%)	0.118
	Plasma Exchange	47(78.3%)	50(89.3%)	
	IVIG + Plasma Exchange	4(6.7%)	4(7.1%)	
Median Symptoms to Treatment Time (IQR) – days		7.0(10.25)	7.0(9.0)	0.857
Ventilation Equipment – no (%)	None	25(41.7%)	55(98.2%)	<0.001
	Nasal cannula or Mask	25(41.7%)	1(1.8%)	
	Mechanical Ventilation	10(16.6%)	0(0.0%)	
ICU Admission – no (%)		29(48.3%)	29(51.8%)	0.710
Median Length of ICU Admission (IQR) – days		9.5(12.0)	4.0(10.0)	<0.001
Median Length of Hospitalization (IQR) – days		17.0(7.25)	15.0(6.0)	0.112
Median Disability score before treatment (IQR)		4.0(1.0)	4.0(1.0)	0.176
Median Disability score after treatment (IQR)		3.0(2.0)	2.0(1.0)	0.114
Median Response to Treatment Score (IQR)		1.0(1.0)	1.0(1.0)	0.385
Mortality – no (%)		6(10.0%)	0(0.0%)	0.028

Table 4. Median Response to Treatment Score (IQR)

			COVID-19	Non COVID-19	*P* Value
Median Response to Treatment Score (IQR)	Treatment type	IVIG	1.0(0.0)	1.0(0.0)	0.999
		Plasma Exchange	1.0(2.0)	1.0(0.0)	0.440
		IVIG + Plasma Exchange	0.5(1.0)	0.5(1.75)	0.886
	Phenotype	Classic	1.0(1.0)	1.0(0.0)	0.317
		Paraparesia	0.5(0.0)	1.0(0.0)	0.327
		Miller Fisher	N/A	N/A	N/A
	EMG/NCS	AIDP	1.0(1.0)	1.0(0.0)	0.454
		AMAN	1.0(1.5)	1.0(0.0)	0.334
		AMSAN	1.0(1.0)	1.0(0.0)	0.238

higher prevalence of diabetes in the COVID-19 group (7). In our study, almost 60% of patients in each group were men, similar to a previous study on GBS epidemiology in Isfahan (8). However, 1 systematic review on GBS in the COVID-19 population suggested a male-to-female ratio of 2.5 to 1, which was significantly higher than other studies (9).

Although serum inflammatory markers were significantly higher in the COVID-19 population, CSF analysis showed no difference between the 2 groups, as Keddie et al declared in their study (10).

Some clinical manifestations were more common in the COVID-19 group—including dysarthria, stock-glove pattern, and dysautonomy. Dysautonomy is one of the important complications of COVID-19 disease, whether during hospitalization or after discharge of these patients. (11). On the other hand, dysautonomy, as a clinical manifestation of Guillain-Barre syndrome, occurs in more severe diseases (12). In this study, the COVID-19 group had more frequent dysautonomia, which may have a role in prognosis and mortality.

The same proportion of the 2 groups of patients were admitted to the ICU, although the length of stay in the ICU and the need for mechanical ventilation was higher in the COVID group ($P < 0.001$).

A systematic review of 77 COVID-19-related GBS patients reported that AIDP (59 cases out of 77) is the most common electrophysiological type, followed by AMSAN (10 cases) and AMAN (8 cases) (13). Some other articles suggest that demyelinating type is the most common pattern (14, 15). In our study, the most common electrophysiological type of disease in the COVID-19 group was AIDP (55%), followed by AMSAN (30%) and AMAN (15%), which was similar to other studies on this population of patients, while the statistical analysis showed a difference with the non-COVID-19 group ($P = 0.012$). The group of non-COVID-19 patients included 41% of the AIDP pattern, followed by 39% of AMAN, which was higher than the COVID-19 group. Meanwhile, in Isfahan's study, with a 5-year duration, ASMAN was the most common electrophysiological pattern in non-COVID-19 patients (8). This difference may be due to the duration of our study, which was 2 years.

Since the IVIG availability was less during the treatment of patients, the majority of patients in both groups underwent plasma exchange, and IVIG was used in 15% and 3% of patients in the COVID-19 and non-COVID-19 groups, respectively.

We found no difference between the GBS disability score before treatment between the 2 groups (median, 4), and there was no difference in disability score after receiving treatments and the rate of response to treatment based on the reduction of disability score was also the same. In subgroup analyses, response to treatment in each electrophysiological pattern was equal in both groups. It can be concluded that despite the differences in the electrophysiological pattern of COVID-19-related GBS patients found in this study and other studies, the response to treatment in that specific electrophysiological pattern is not different.

Six patients died in the COVID-19 group, while no deaths occurred in the non-COVID-19 group. Although this difference is significant ($P = 0.028$), COVID-19 itself can be fatal, and this difference may not be attributed to the greater severity of GBS disease. The similarity of the GBS

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disability score, both before and after treatment, confirms this issue. However, it is possible that the COVID-19 disease, by causing complications such as dysautonomia that was mentioned earlier, causes more deaths. On the other hand, IVIG treatment prescribed for GBS disease can also contribute to mortality through the aggravation of the procoagulant state in COVID-19 disease.

This study had some limitations. This study may be underpowered due to its small sample size. We included patients who had COVID-19 symptoms during the last 4 weeks and had proven disease either through PCR or lung HRCT; thus, it was not possible for us to comment on differences between post- and parainfection. Additionally, our sample does not include all COVID-19 patients because some of them had asymptomatic involvement.

Conclusion

Patients with COVID-19 experienced a greater need for mechanical ventilation. We concluded that although there may be differences in the clinical manifestations and electrophysiological findings of COVID-19-related GBS patients compared with other GBS patients, there is no significant difference in treatment response and outcomes.

Authors' Contributions

Behnaz Ansari: Research study conception and design, revision, and critique of the manuscript

Niloofar Rezaei: collecting data, statical analyses, interpretation of results, revision

Mohsen Kheradmand: Data collection and organization

Mohammad Amin Najafi: Data collection and organization

Keivan Basiri: research study conception and design, critique of the manuscript.

Ethical Considerations

This study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1401.207). Participants were fully informed about all stages of the study, and written consent was obtained before beginning. In the written consent, participants were informed that their personal information would be protected.

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Conflict of Interests

The authors declare that they have no competing interests.

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