ORIGINAL ARTICLE

Relationship Between Acute Phase Reactants and Disability in Guillian-Barré Syndrome During the COVID-19 Pandemic

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Backround. Guillain-Barré syndrome (GBS) is an immune-mediated disease that affects the peripheral nervous system and may occur after some bacterial-viral infections.

Aim. The aim of this study is to determine and compare the epidemiological, clinical and laboratory characteristics of the patients followed up in our clinic with the diagnosis of GBS in the 15 month periods before and after March 2020. At the same time, we aimed to examine the importance of these markers as prognostic indicators by investigating the relationship of D-dimer, CRP, albumin and transferrin levels with Hughes functional grading scale score (HFGSS).

Material and Methods. The medical files of the patients who were followed up with the diagnosis of GBS between December 2018 and May 2021 were retrospectively analyzed. The patients were divided into groups as pandemic, pre-pandemic, post-COVID-19 and non-COVID-19. Epidemiological and clinical characteristics of GBS patients and plasma D-dimer, serum albumin, CRP and transferrin levels were recorded.

Results. No significant difference was found between the pandemic and pre-pandemic periods in terms of age, gender, GBS subtype, seasonal distribution and treatment characteristics of GBS patients. PostCOVID-19 GBS patients had significantly higher HFGSS both at admission and at discharge ($p < 0.05$). In post-COVID-19 GBS patients good-excellent negative correlation between transferrin and albumin levels and HFGSS at hospital admission and discharge, positive correlations with CRP levels were observed.

Conclusion. Post-COVID-19 GBS patients had worse HFGSS at both admission and discharge. CRP was positively correlated with HFGSS whereas transferrin and albumin showed negative correlation with HFGSS. © 2021 Instituto Mexicano del Seguro Social (IMSS). Published by Elsevier Inc. All rights reserved.

Key Words: COVID-19, Guillain Barre syndrome, Acute phase reactants, Hughes functional grading scale, Transferrin, D-dimer.

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated disease that affects the peripheral nervous system and may occur after some bacterial-viral infections. The classic form of acute inflammatory demyelinating polyneuropathy (AIDP) is characterized by ascending flaccid paralysis, decreased deep tendon reflexes, sensory, motor and autonomic symptoms. Although the classic and most common form of GBS is AIDP, there are also other forms such as acute motor axonal neuropathy (AMAN), acute motor-sensory neuropathy (AMSAN), Miller Fisher syndrome (MFS). GBS may occur a few days to 6 weeks after bacterial or viral infections such as Campylobacter jejuni, Haemophilus influenzae, Mycoplasma pneumoniae, Influenza, Epstein-Barr virus, Cytomegalovirus, and Zika virus (1–3). Vaccines, previous surgery, malignancy and some drugs can also cause GBS.

The diagnosis of GBS is made by the patient's medical history and neurological examination. Electrophysiological

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studies and cerebrospinal fluid (CSF) studies can be used to support the diagnosis or exclude other diseases in the differential diagnosis. Increased protein level and normal cell count (<50 cells per µL) in CSF (albuminocytological dissociation) are significant for GBS (4,5).

Acute phase reactants are proteins whose serum concentrations increase or decrease during inflammation. Proteins whose levels increase during inflammation are called positive acute phase reactants, and proteins whose levels decrease during inflammation are called negative acute phase reactants. Proteins such as C-reactive protein (CRP), ferritin, fibrinogen, and procalcitonin are positive acute phase reactants, while proteins such as albumin, transferrin, and transthyretin are negative acute phase reactants. CRP is synthesized by the liver in case of systemic inflammation and its level increases rapidly. It is a protein that does not have variation of age, gender and diurnal rhythm (6). Albumin is a negative acute phase protein whose serum levels are down-regulated in response to the inflammatory state (7). Transferrin is a blood-plasma glycoprotein that plays an important role in iron metabolism and is responsible for ferric ion distribution. Transferrin also acts as a marker for inflammation and its levels decrease during inflammation (8). D-dimer is a soluble fibrin degradation product resulting from the regular breakdown of thrombus by the fibrinolytic system. While the circulating D-dimer concentration is low in healthy individuals, it is elevated in conditions associated with thrombosis. It has been shown that D-dimer levels are increased due to some homeostatic abnormalities in Coronavirus disease–2019 (COVID-19) and this increase is associated with disease severity and poor prognosis (9,10).

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a disease that emerged in China in December 2019 and caused a pandemic all over the world. The first detected case of COVID-19 in Turkey was announced by the Ministry of Health of the Republic of Turkey on March 11, 2020. Although COVID-19 is a disease that primarily affects the respiratory system, it is known to cause various neurological manifestations by affecting the central and peripheral nervous system in approximately 35–40% of patients (11,12) There are studies showing that COVID-19 is associated with serious neurological diseases such as ischemic stroke, intracranial hemorrhage, acute myelitis, and acute encephalitis (13–15). The relationship of SARS-CoV-2 with GBS continues to be discussed today. In addition to studies stating that SARS-CoV-2 is associated with GBS and some subtypes and that COVID-19 causes an increase in GBS cases, there are also some studies which is stating the opposite (16–19).

Our aim in this study is to determine and compare the epidemiological, clinical and laboratory characteristics of the patients followed up in our clinic with the diagnosis of GBS in the 15 month periods before and after March 2020, the date of the first COVID-19 case in Turkey. Also, we aimed to examine the importance of these markers as prognostic indicators by investigating the relationship of D-dimer, CRP, albumin and transferrin levels with GBS disability scores in GBS patients with a history of COVID-19.

Material and Methods

The medical files of the patients who were followed up with the diagnosis of GBS in the Neurology Department of Atatürk University Faculty of Medicine between December 2018 and May 2021 were retrospectively reviewed. Those with GBS between December 2018 and February 2020 were accepted as the pre-pandemic group, and those with GBS between March 2020 and May 2021 were considered as the pandemic group. Those with a history of COVID-19 within 6 weeks before GBS were considered as the post-COVID-19 GBS group, and those without GBS were considered as the non-COVID-19 GBS group. Epidemiological characteristics of GBS patients, onset symptoms, subtype, season of admission, CSF characteristics, pre-infection status, GBS clinical disability scores at admission and at discharge, treatment informations and durations, intensive care and mechanical ventilation needs and plasma D-dimer, serum albumin, CRP and transferrin levels were recorded. The results of SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) in CSF of GBS patients with a history of COVID-19 were recorded.

Diagnosis of GBS was established according to the National Institute of Neurological Disorders and Stroke (NINDS) criteria and confirmed by CSF examination and nerve conduction studies (NCS) (20). CSF examination was performed 7–14 d after the onset of GBS symptoms. CSF cell number, sodium, chloride, protein and glucose levels were examined. Routine blood chemistry and complete blood count were done. SARS-CoV-2 infection was confirmed by SARS-CoV-2 RT-PCR.

NCS was performed with the Nihon Kohden Neuropack® X1 MEB-2300 device by the same technician 2–5 d after the onset of symptoms. Standard procedure was used in all patients. Motor (median, ulnar, tibial, peroneal) and sensory (median, ulnar, sural and superficial peroneal) conduction studies were performed in at least four nerves. In addition, median, ulnar and tibial nerve F wave responses were recorded, and needle electromyography (EMG) was performed simultaneously using needle electrodes. According to clinical and electrophysiological data, patients were classified as AIDP, AMAN, AMSAN and MFS.

Disease severity was evaluated according to the Hughes functional grading scale (from 0 = normal to 6 = dead) which had been developed by Hughes RA, et al (21).

Table 1. Clinical, demographic and laboratory characteristics of the patients

Characteristic	Pandemic Group (*n*: 20)	Pre-Pandemic Group (*n*: 12)	*p*	Post-COVID-19 GBS (*n*: 12)	Non-COVID-19 GBS (*n*: 20)	*p*
Age (mean ± SD)	57.4 ± 14.3	46.3 ± 19.5	0.12	57.4 ± 14.4	50.9 ± 16.9	0.27
Gender (*n*, %)						
Female	9 (45%)	7 (58.3%)	0.47	7 (58.3%)	9 (45%)	0.47
Male	11 (55%)	5 (41.7%)		5 (41.7%)	11 (55%)	
GBS Type (*n*, %)						
AIDP	10 (50%)	6 (50%)	0.58	6 (50%)	10 (50%)	0.88
AMSAN	7 (35%)	3 (25%)		4 (33.3%)	6 (30%)	
AMAN	3 (15%)	2 (16.7%)		2 (16.7%)	3 (15%)	
MFS	0	1 (8.3%)		-	1 (5%)	
Seasonal Distribution (*n*, %)						
Spring	5 (25%)	4 (33.3%)	0.06	3 (25%)	6 (30%)	0.78
Summer	4 (20%)	-		1 (8.3%)	3 (15%)	
Autumn	8 (40%)	2 (16.7%)		5 (41.7%)	5 (25%)	
Winter	3 (15%)	6 (50%)		3 (25%)	6 (30%)	
HFGSS (median, min-max)						
Admission	4 (1-5)	2 (2-5)	0.41	4 (2-5)	2 (1-5)	0.048[a]
Discharge	3 (4-0)	1 (1-6)	0.30	3.5 (1-4)	1 (0-6)	0.049[a]
Length of Hospitalization (Days)	14 (7-57)	8.5 (7-90)	0.52	15 (7-57)	8.5 (7-90)	0.39
Treatment (*n*, %)						
IVIG	16 (50%)	10 (31.25%)	0.81	8 (66.7%)	18 (90%)	0.1
IVIG, Plasmapheresis	4 (12.5%)	2 (6.25%)		4 (33.3%)	2 (10%)	
Mechanical Ventilation (*n*, %)	3 (15%)	2 (16.7%)		3 (25%)	2 (10%)	
Ex (*n*, %)	-	1 (8.3%)	0.9	-	-	0.26
Antecedent events						
Upper respiratory infection	-	2 (16.7%)	0.008[b]		2 (10%)	<0.0001[b]
Gastroenteritis	3 (15%)	2 (16.7%)			5 (25%)	
Pneumonia	1 (5%)	2 (16.7%)			3 (15%)	
COVID-19	12 (60%)			12 (100%)	-	
none	4 (20%)	6 (50%)			10 (50%)	
Initial Symptom (*n*, %)						
Weakness	10 (50%)	4 (33.3%)	0.27	8 (66.7%)	6 (30%)	0.09
Tingling - Numbness	6 (30%)	4 (33.3%)		1 (8.3%)	9 (45%)	
Swallowing Difficulty	-	2 (16.7%)		-	2 (10%)	
Facial Paralysis	3 (15%)	1 (8.3%)		2 (16.7%)	2 (10%)	
Imbalance	-	1 (8.3%)		-	1 (5%)	
Breathing Difficulty	1 (5%)	-		1 (8.3%)	-	

n: number; [a]Mann-Whitney *U* Test; [b]χ^2 Test; AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor-sensory axonal neuropathy; MFS: Miller Fisher Syndrome; IVIG: Intravenous immunoglobulin; PLZ: Plasmapheresis; HFGSS: Hughes functional grading scale score.

Patients with a history of diabetes mellitus, malignancy, rheumatological disease, demyelinating disease, pregnancy, surgery in the last 3 months, thromboembolic events, and patients with alcoholism, toxic substance, metal or drug exposure that may cause acute neuropathy were excluded from the study. In the pandemic group one patient had rheumatoid arthritis, one patient had multiple sclerosis, and one patient had exposure to toxic substances; in the pre-pandemic group one patient was excluded because of diabetes mellitus and one patient with a history of thromboembolic events. The files of 37 patients were reviewed, and the study was continued with 32 patients who met the inclusion criteria.

The study was approved by the ethics committee of Atatürk University Faculty of Medicine (24.06.2021.5/89).

Statistical Analysis

Summary statistics of all participants were obtained based on the means and standard deviations for normally distributed data and, medians and min-max for non-normal distributed data. The distribution of normality was assessed with the D'Agostino-Pearson test. Nominal categorical variables were assessed with the χ^2 test. Continuous variables with normal distribution belonging to two groups were compared using the student *t*-test whereas non-normal distributed data were compared using the Mann Whitney *U* test. Spearman rank correlation was used for the assessment of correlation between non-parametric variables. A two-tailed *p*-value <0.05 was considered statistically significant. All statistical analyzes were performed using

Table 2. Characteristics of post-COVID-19 GBS patients

GBS patients with a history of COVID-19	Age/Gender	Time between COVID-19-GBS (Week)	GBS subtype	CSF protein (mg/dL)	CSF Sars-Cov-2 RT-PCR	Mechanical ventilation	HFGSS at admission	HFGSS at Discharge	Length of Hospitalization (Days)	The treatment received
1	56/F	1	AIDP	58	NEG	NO	2	1	7	IVIG
2	50/F	6	AMAN	65	NEG	NO	4	3	17	IVIG
3	57/M	4	AMSAN	91	NEG	NO	4	3	7	IVIG
4	66/F	6	AMAN	61	NEG	NO	4	4	7	IVIG
5	57/F	simultaneous	AIDP	159	NEG	YES	5	4	55	IVIG, PLZ
6	88/F	6	AMSAN	48	NEG	NO	4	4	12	IVIG
7	27/F	6	AIDP	54	NEG	NO	2	1	14	IVIG
8	72/M	4	AMSAN	111	NEG	YES	5	4	26	IVIG, PLZ
9	78/M	3	AIDP	132	NEG	NO	3	2	7	IVIG
10	72/M	simultaneous	AMSAN	88	NEG	YES	4	4	21	IVIG, PLZ
11	62/F	5	AIDP	111	NEG	NO	3	2	16	IVIG, PLZ
12	36/M	3	AIDP	104	NEG	NO	4	4	14	IVIG

M: Male; F: Female; AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor-sensory axonal neuropathy; MFS: Miller Fisher Syndrome; IVIG: Intravenous immunoglobulin; NEG: Negative; PLZ: Plasmapheresis; CSF: Cerebrospinal fluid; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RT-PCR: Real-time reverse transcriptase-polymerase chain reaction; HFGSS: Hughes functional grading scale score.

Medcalc statistics software (MedCalc, version 16 trial, Ostend, Belgium).

Results

11 male and 9 female patients in the pandemic group and there were 5 male and 7 female patients in the pre-pandemic group. The clinical and demographic characteristics of the patients according to the groups are given in Table 1. Hughes functional grading scale scores (HFGSS) of the post-COVID-19 GBS group which is calculated at hospital admission and discharge were higher than those of the non-COVID-19 GBS group ($p < 0.05$) (Table 1). 12 patients in the pandemic group had a history of COVID-19 in the last 6 weeks. Two of these patients had GBS concurrently with COVID-19. SARS-CoV-2 RT-PCR was negative in CSF in all post-COVID-19 GBS patients. The characteristics of post-COVID-19 GBS patients are given in Table 2 in detail. CSF protein and plasma D-dimer levels were significantly higher in the post-COVID-19 GBS group compared to the non-COVID-19 GBS group; serum transferrin and albumin levels were low ($p < 0.05$) (Table 3). A good-excellent negative correlation was observed between admission-discharge HFGSS and serum albumin and transferrin levels of the post-COVID-19 GBS group (Albumin: p: 0.03, r: –0.61; p: 0.03, r: –0.6; Transferrin: p: 0.0004, r: –0.82; p: 0.0049, r: –0.75) (Figure 1A, 1B). There was no significant correlation between D-dimer levels of the post-COVID-19 GBS group, admission-discharge HFGSS and treatment duration (D-dimer: p: 0.11, r: 0.48; p: 0.57, r: 0.18; p: 0.15, r: 0.44) (Figure 1C). A positive correlation was observed between admission-discharge HFGSS and serum CRP levels in the post-COVID-19 GBS group (CRP: p: 0.009, r: 0.71; p: 0.048, r: 0.57) (Figure 1D).

Discussion

HFGSS were significantly higher in the post-COVID-19 GBS group compared to the non-COVID-19 GBS group both at admission and discharge. This result may lead to the conclusion that the prognosis is worse in GBS patients with a history of COVID-19. Two of our patients had GBS simultaneously while they were hospitalized with the diagnosis of COVID-19. Both of these patients' HFGSS were high, had long duration of hospitalization and mechanical ventilation and dual therapy (IVIG, plasmapheresis) was needed for these two patients (Table 2). Although HFGSS were found to be high in post-COVID-19 GBS; symptoms such as fatigue, weakness, malaise, and muscle pain can be seen frequently in COVID-19 patients and persist for a long time. This may have affected the evaluation of patients' HFGSS. Also mild cases may have refrain from going to the hospital during the pandemic.

The relationship of SARS-CoV-2 with GBS continues to be discussed today. While some studies state that SARS-CoV-2 is associated with GBS and that COVID-19 causes an increase in GBS cases, there are some studies that state the opposite (16–19). Although the term of GBS associated with COVID-19 has been used frequently in the literature, the pathogenesis of GBS in COVID-19 is still unclear. However, it is thought that some different mechanisms may play a role in the neurological damage process of COVID-19. Endothelial cells, glial cells, and neurons express angiotensin-converting enzyme receptor 2 (ACE2) and type II transmembrane serine protease (TMPRSS2),

Table 3. Levels of acute phase reactants and CSF characteristics by groups

Acute phase reactants	Pandemic Group (*n*: 20)	Pre-Pandemic Group (*n*:12)	*p*	Post-COVID-19 GBS (*n*:12)	Non-COVID-19 GBS (*n*:20)	*p*
Albumin (g/dL) (mean ± SD)	3.51 ± 0.67	3.87 ± 0.56	0.13	3.33 ± 0.71	3.83 ± 0.54	0.03[a]
CRP (mg/L) (median, min-max)	5.72 (1.54-101)	3.18 (3.1-122)	0.45	3.91 (1.98-101)	7.56 (1.54-122)	0.22
D-dimer (ng/mL) (median, min-max)	540 (30-2990)	316 (129-862)	0.22	717.5 (361-2990)	292 (30-862)	<0.0001[b]
Transferrin (g/L) (mean ± SD)	2.07 ± 0.7	2.42 ± 0.73	0.18	1.81 ± 0.64	2.43 ± 0.67	0.01[a]
CSF Characteristics						
Protein (mg/dL) (median, min-max)	57.5(45-159)	67.5(25-208)	0.95	89.5 (48-159)	53.5 (25-208)	0.01[b]
Glucose (mg/dL) (median, min-max)	66.5(51-118)	65 (48-83)	0.54	69 (52-105)	65 (48-118)	0.27
Sodium (mmol/L) (mean ± SD)	144.5 ± 4.65	141 ± 10.18	0.06	143.9 ± 4.1	141.6 ± 9.04	0.41
Chloride (mmol/L) (mean ± SD)	124.2 ± 2.66	123.2 ± 3.04	0.36	124 (120-1279	124 (119-128)	0.96

n: number; [a]Student *t*-test; [b]Mann-Whitney *U* Test; CRP: C-reactive protein; CSF: Cerebrospinal Fluid.
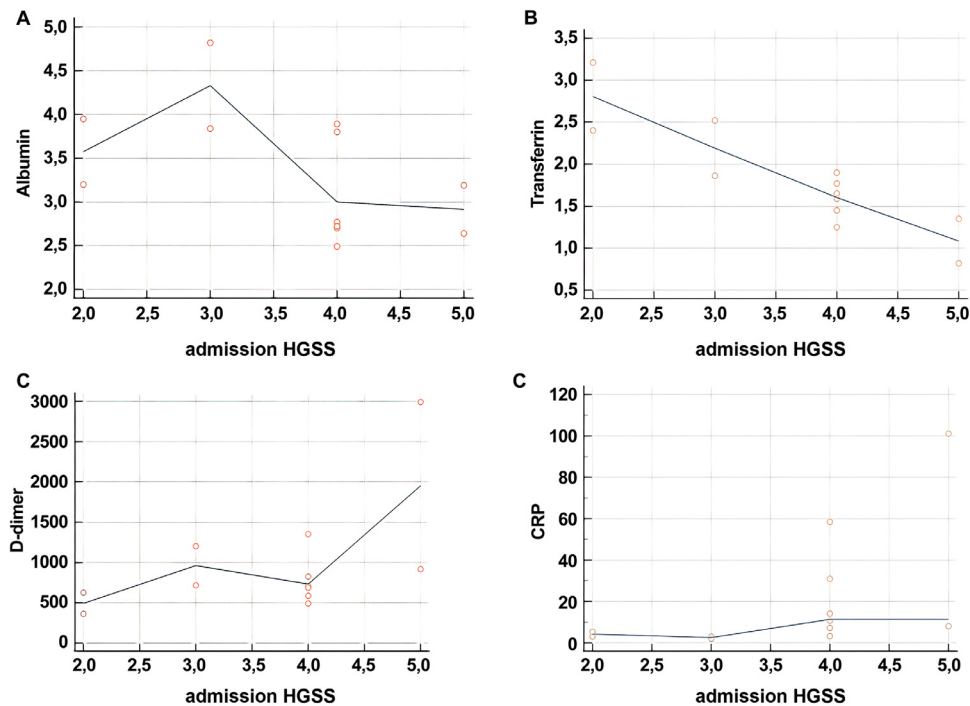

Figure 1. Spearman correlation between transferrin, albumin, CRP, and D-dimer levels and admission Hughes functional grading scale scores. CRP: C-reactive protein, GBS: Guillain Barre Syndrome, HFGSS: Hughes functional grading scale score. A. There was a good negative correlation between albumin levels and admission HFGSS (*p*: 0.03, *r*: –0.61). B. There was a excellent negative correlation between transferrin levels and admission HFGSS (*p*: 0.0004, *r*: –0.82). C. There was no significant correlation between D-dimer levels and admission HFGSS (*p*: 0.11, *r*: 0.48). D. A positive correlation was observed between CRP levels and admission HFGSS (*p*: 0.009, *r*: 0.71).

which are essential for SARS-Cov-2 virus entry into cells. It is thought that the virus passes through the olfactory nerve or enteric nervous system to the blood circulation via retrograde axonal transport and to the central nervous system by crossing the blood-brain barrier by direct damage mechanism. A post-mortem study demonstrated the presence of SARS-CoV-2 RNA in neuroanatomical areas of the olfactory tract, which supports a direct mechanism of injury (22).

However, Finsterer J, et al. (17) stated in a review in which they evaluated 220 GBS patients associated with COVID-19, that there were no patients in whom SARS-

CoV-2 could be detected in the CSF. In a recent case report, it was reported that SARS-CoV-2 was positive in CSF for the first time in a pediatric GBS patient (23). In our study, all 12 patients in the post-COVID-19 group were SARS-CoV-2 PCR negative in CSF and we could not find data to support the direct mechanism of injury. Although it is very difficult to generalize about the direct damage mechanism in a single CSF PCR positive case, we believe that more clear information will emerge as the number of studies on this subject increases.

The second week of COVID-19 infection is the hyper-inflammatory phase and during this period, serum levels of

some inflammatory parameters such as IL-2, IL-2R, IL-6, IL-10, IFN- γ, TNF-α, CCL2, procalcitonin, CRP increase (24,25). Significant cytokine increase has been reported in GBS and its subtypes in experimental autoimmune neuritis, which is an animal model of GBS (26). Cell-mediated immunity plays an important role in the immunopathology of all GBS types, particularly AIDP (27). Gigli GL, et al. (28) showed that IL-6, IL-8, TNF-α levels were high in the serum of SARS-CoV-2-associated GBS patients, and also, IL-8 concentration was significantly higher in CSF. Th17 cells are an important subset of T-cells characterized by IL-17 production. IL-17 is a highly inflammatory cytokine with potent effects on stromal cells in many tissues. Th17 cells are known to play an important role in the pathogenesis of various immune-mediated diseases such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease (29). In a recent bioinformatics analysis; Th17 cell differentiation and cytokine response was identified as an important process connecting COVID-19 to GBS (30). In our study, transferrin and albumin levels, which are negative acute phase reactants, were found to be significantly lower in the post-COVID-19 GBS group compared to the non-COVID-19 GBS group; D-dimer levels were found to be high. In addition, good-excellent negative correlation was observed between transferrin and albumin levels and hospital admission-discharge HFGSS in post-COVID-19 GBS patients, and a positive correlation with CRP levels. The severity of acute inflammatory response reflected by acute phase reactants was tightly linked to the clinical outcomes. Our results supported that dysregulated hyper-inflammatory response may have an important role in the GBS-COVID-19 relationship. We found that plasma D-dimer levels, a popular parameter in assessing the prognosis of COVID-19, were not equally successful in assessing the prognosis of post-COVID-19 GBS, but instead, especially transferrin levels were negatively correlated with good-excellent admission-discharge HFGSS.

There are some limitations in our study, such as the small number of patients, the lack of data on the clinical status of COVID-19 patients during the active period of infection, and the possibility that HFGSS may be affected by persistent symptoms such as fatigue and muscle pain in patients with a history of COVID-19. We think that large-scale further studies on this subject will be useful in evaluating the relationship between COVID-19 and GBS.

Conclusion

No significant difference was found between the pandemic and pre-pandemic periods in terms of age, gender, GBS subtype, seasonal distribution and treatment characteristics of GBS patients. AMSAN was the most common axonal subtype in both pandemic and pre-pandemic periods. Post-COVID-19 GBS patients had significantly higher HFGSS both at admission and discharge. All patients in the post-

COVID-19 group were negative for SARS-CoV-2 RT-PCR in the CSF. In post-COVID-19 GBS patients, serum albumin and transferrin levels are low; D-dimer levels were significantly higher. In post-COVID-19 GBS patients, a good-excellent negative correlation was observed between transferrin and albumin levels and hospital admission-discharge HFGSS, and a positive correlation with CRP levels. There was no significant correlation between D-dimer levels and HFGSS.

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Conflict of Interest

The authors declare no potential conflict of interest.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2021.10.002.

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