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Concomitant Guillain-Barre Syndrome with COVID-19

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CONCOMITANT GUILLAIN-BARRE SYNDROME AND COVID-19

by

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ABSTRACT

The current Coronavirus disease 2019 (COVID-19) outbreak, caused by a virus called severe acute respiratory syndrome 2 (SARS-CoV-2), has become a global health emergency. Recent findings in case studies assert that the transmigration of SARS-CoV-2 to the nervous system implicates severe neurotropic pathologies, including the onset of the rare autoimmune disease called Guillain-Barré syndrome (GBS). GBS is recognized as several disorders characterized by immune-mediated polyradiculoneuropathy, which is typically preceded by an infection or other immune stimulation. The symptoms of GBS initially present as acute symmetrical ascending paresthesia, weakness, and paralysis.

This meta-analysis serves to help understand the predisposing factors (such as gender, age, comorbidities) and the clinical features of COVID-19- induced GBS. Most patients affected were 40 years or older and comprised 78.2% of all the cases. Males comprised most of the cases (62.8%; n=76). The patient mortality was 9.1%, intensive care unit (ICU) admission was 46.6%, and the need for mechanical ventilation was 35.8%. It was found that concomitant GBS and COVID-19 patients most often presented with increased cerebral spinal fluid (CSF) protein levels (88%; n=106), hyporeflexia or areflexia (87.6%) (n=106), lower limb strength and sensation impairment (91.7%; n=111), upper limb strength and sensation impairment (83.5; n=101), and somatic sensation impairment (73.6%; n=89).

It is postulated that COVID-19 triggers the onset of GBS through a “cytokine release storm” (CRS) that occurs in the early stages of the disease. The same cytokines and chemokines involved in this CRS caused by COVID-19 contribute to the onset of GBS. Predisposing factors which influence this concomitance include male gender and older age. Most of the reported

symptoms included abnormal limb functions (including paresthesia, weakness, and paralysis) and absent or weak deep tendon reflexes. The most common variant of GBS observed was AIDP, and the most significant laboratory finding among patients was high CSF protein levels.

For all the nurses (like my mother), doctors, health care workers, and other front-line workers that continue to tirelessly and selflessly risk their lives to make a difference and save the lives of others in the COVID-19 pandemic.

For my thesis chair Dr. Hale Toklu who believed in me throughout the research project. And for my thesis sub-chairs Dr. Sarfraz Ahmad and Dr. Firas Kobeissy, for dedicating time out of their schedules for meetings to give me the insight and tools necessary to complete my thesis.

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LIST OF ABBREVIATIONS AND ACRONYM

ACE2: angiotensin-converting enzyme 2

AIDP: acute inflammatory demyelinating polyradiculoneuropathy

AMAN: acute motor axonal neuropathy

AMSAN: acute motor and sensory axonal neuropathy

BBB: blood-brain barrier

CMAP: compound motor action potential

CNS: central nervous system

CRS: cytokine release syndrome

CSF: cerebral spinal fluid

COVID-19: Coronavirus disease 2019

CRS: cytokine release storm

FD: facial diplegia

GBS: Guillain-Barré Syndrome

GFAB: glial fibrillary acidic protein

IFN: interferon

IL: interleukin

PD: individualized patient data

LOS: length-of-stay (hospital)

MERS: Middle East Respiratory Syndrome

MFS: Millar Fisher Syndrome

MV: mechanical ventilation

NFL: neurofilament light

NK: natural killer

NSE: neuro-specific enolase

PCB: Pharyngeal-Cervical-Brachial

PNS: peripheral nervous system

PRISMA: Performed Reporting Item for Systematic Review and Meta-Analysis

RAS: renin-angiotensin system (pathway)

RNA: ribonucleic acid

RT-PCR: reverse transcription-polymerase chain reaction

SARS-CoV-2: severe acute respiratory syndrome 2

S100β: S100 calcium-binding protein beta

SD: standard deviation

SC: Schwann cells

SNAP: sensory nerve action potential

TNF-α: tumor necrosis factor-alpha

UCHL1: ubiquitin carboxyl-terminal hydrolase L1

WBC: white blood cell (count)

WHO: World Health Organization

CHAPTER 1: INTRODUCTION

The current outbreak of disease caused by a virus called severe acute respiratory syndrome 2 (SARS-CoV-2) has become a global health emergency. Pneumonia was the primary clinical sign of Coronavirus disease 2019 (COVID-19) that allowed case detection, preceding more recent reports of gastrointestinal symptoms and asymptomatic infection (Yuki et al., 2020). Recent findings in case studies belonging to several countries assert that the transmigration of SARS-CoV-2 to the nervous system implicates severe neurotropic pathologies, including the rise of the rare autoimmune disease called Guillain-Barré syndrome (GBS). It is postulated that COVID-19 triggers the onset of GBS similarly that cytomegalovirus, Epstein-Barr virus, Middle East Respiratory Syndrome (MERS), Hepatitis E, and Zika virus contribute to the etiology of GBS through autoimmune dysregulation (Yu et al., 2006).

COVID-19 triggers GBS onset through a "cytokine release storm" (CRS) that occurs in the early stages of the disease. The same cytokines and chemokines involved in this CRS caused by COVID-19 contribute to the onset of GBS. Details such as the type and severity of the preceding infection and patient-related host factors are the prime determinants of the onset, phenotypic form, and progression of GBS (van den Berg et al., 2014). Because SARS-CoV-2 is a novel coronavirus, little is known about the neurological deficits' spectrum, characteristics, and outcomes associated with COVID-19 and their relationship with GBS.

In recent months, there have been increasing amounts of mounting evidence reported in peer-reviewed literature, which support the association and para-infectious nature between GBS and SARS-CoV-2 (Abu-Rumeileh et al., 2021). Multidisciplinary care for patients with GBS is imperative to manage the potentially severe complications associated with the onset and

progression of GBS (van den Berg et al., 2014). Plasma exchange (a well-supported treatment for GBS) removes neurotoxic antibodies and other inflammatory mediators (van den Berg et al., 2014). Van den Berg et al. (2014) emphasizes that this treatment yields optimal outcomes when performed within the two to four weeks following the initial signs of weakness. In view of the above, this meta-analysis provides a current and comprehensive compendium of all published case series and case reports regarding the connection between COVID-19 pathology and the onset of GBS. The association between them is determined through identifying prominent clinical outcomes measures, laboratory results, neurophysiological symptoms, and data points such as age, gender, and the presence of pre-existing conditions.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

SARS-CoV-2

SARS-CoV-2 is a promiscuous virus that first emerged as a respiratory illness outbreak in Wuhan City, Hubei Province, China, and quickly escalated into a global pandemic. A novel coronavirus causes COVID-19 referred to as severe acute respiratory syndrome coronavirus 2 (formerly called 2019-nCoV) (Abolmaali et al., 2021). The deleterious effects of this virus are exemplified through data collected by the World Health Organization (WHO). The WHO was primarily informed of pneumonia cases of unknown cause on December 31st, 2019, and since then, there have been 244 million confirmed cases and, unfortunately, 4.95 million deaths worldwide as of October 25th, 2021.

Pathophysiology of SARS-CoV-2

SARS-CoV-2 belongs to a family of coronaviruses which present as enveloped positive-strand RNA with large genomes of 30-32 kb (Weiss & Leibowitz, 2011). The pathogenesis of COVID-19 can be categorically organized into three stages which correspond to separate clinical stages of the disease.

First Stage in the Pathogenesis of SARS-CoV-2

According to Mason (2020), the first stage of pathogenesis is described as an asymptomatic stage brought on by the SARS- CoV-2 virus inhalation. Following inhalation, the virus binds to the protein angiotensin-converting enzyme 2 (ACE2) on the cell surface of the epithelial cells of the nasal cavity through spike (S) protein's Receptor Binding Domain (Trougakos et al., 2021). The virus begins to replicate through this interaction by activating the renin-angiotensin system (RAS) pathway via ACE2 (Mason, 2020; Novaes Rocha, 2020; Weiss

& Leibowitz, 2011; Wiese et al., 2020). The protagonist effects of ACE2 stimulate the production of angiotensin II, which activates its respective receptor, the angiotensin II type I receptor (Novaes Rocha, 2020). The RAS pathway activation stimulates cell proliferation, fibrosis, thrombosis, and inflammation (Novaes Rocha, 2020).

Second Stage in the Pathogenesis of SARS-CoV-2

This activation leads to the second stage of pathogenesis which is brought on by cytokine release storm (CRS) that triggers a robust immune response which causes the initial clinical manifestations of COVID-19 (Mason, 2020). About 80% of patients experience mild symptoms, which present respiratory distress of the upper and conducting airways (Mason, 2020).

Third Stage in the Pathogenesis of SARS-CoV-2

About 20% of patients that contract SARS- CoV-2 progress to the disease's third stage (Mason, 2020). Mason (2020) explains that this final stage involves the virus reaching the lung's gas exchange units and infecting alveolar type II cells. In one study by Qian et al (2013), immunocytochemistry revealed that type II cells are the preferential cells which SARS- CoV-2 propagates. Through the propagation of these cells, the viral RNA synthesis and proteins are increased, and the production and release of viral particles induce the alveolar cells to undergo apoptosis (Qian et al., 2013). This sequence of events often leads to the onset of pneumonia, which causes severe scarring and fibrosis in the lungs (Mason, 2020).

Neurological Manifestations Associated with SARS-CoV-2

Although respiratory impairment is the main symptom associated with the pathology of COVID-19, there are reports of neurological manifestations associated with the disease. Opportunistic viral pathogens such as the human coronaviruses may spread into other tissues

such as the central nervous system (CNS), where additional pathologies may be induced (Desforges et al., 2014). The family of β-coronaviruses, to which SARS-CoV-2 belongs, has previously been identified within the brain (especially the brainstem) (Das et al., 2020). SARS-CoV-2 causes many neurological conditions such as ischemic changes of neurons, demyelination of nerve fibers, and diseases such as polyneuropathy, encephalitis, and aortic ischemic stroke (Tsai et al., 2004). Several pathways for the invasion of SARS-CoV-2 to the CNS have been postulated. Transmigration of SARS-CoV-2 to the brain may occur via the olfactory pathway, general circulation, or the peripheral neurons of the lungs (Das et al., 2020).

Guillain Barré Syndrome

GBS is known as several disorders characterized by immune-mediated polyradiculoneuropathy, which is typically preceded by an infection or other immune stimulation. The immune stimulation generates antibodies that cross-react with gangliosides at nerve membranes, a phenomenon is known as molecular mimicry (van den Berg et al., 2014; Shahrizaila et al., 2021). Studies conducted post-mortem show that inflammatory infiltrates containing macrophages and T-cells are the prime mediators in macrophage-mediated demyelination (Shahrizaila et al., 2021). Shahrizaila et al. (2021) explain that another histopathological component validates that GBS-associated nerve injury is antibody-mediated in the deposition of activated complement products on Schwann cells.

Pathophysiology of Guillain Barré Syndrome

Mistaken attacks on myelin sheaths or axons (the nerve conduits for sending and receiving neural signals) cause signature symptoms of GBS such as rapidly progressive ascending symmetrical weakness, paresthesia, sensory disturbance (Burns, 2008; van den Berg et

al., 2014; Nanda et al., 2021). Symptoms of GBS are highly variable with respect to the antecedent. Variability of GBS symptoms are credited to multiple factors, including the extent of sensory symptoms and weakness, the presence, distribution, and scope of cranial nerve deficits, and ataxia, pain, and autonomic dysfunction (van den Berg et al., 2014).

Subtypes of GBS

The symptoms of GBS are often specialized to the subtype of GBS present; the most prevalent subtypes include acute motor and sensory axonal neuropathy (AMSAN), acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and Miller Fisher syndrome (MFS). Other less common subtypes include paraparetic GBS, facial diplegia (FD), Pharyngeal-Cervical-Brachial (PCB) GBS, Bickerstaff brainstem encephalitis, polyneuritis cranialis, and acute autonomic neuropathy. Electrophysiologic studies characterize the specific subtype of GBS, which is crucial in determining the effective treatment per patient.

Infectious Agents Associated with GBS

Various viral agents are associated with the etiopathophysiology of GBS, such as cytomegalovirus, Epstein-Barr virus, MERS, Zika virus, and Hepatitis E. Bacterial agents that include mycoplasma pneumonia, and campylobacter jejuni are also a contributor to the onset of GBS.

Establishing the Connection Between GBS and SARS-CoV-2

While numerous peer-reviewed case reports of concomitant GBS with COVID-19 exist, there is a gap in knowledge on the correlation between the two, and the clinical characteristics of COVID-19-related GBS remain unknown. Recent findings suggest that SARS-CoV-2 is a trigger

for GBS, as it follows a similar para-infectious pattern as the other viral agents which contribute to the onset of GBS. Numerous neurological and physiologic complications arise from COVID-19-related GBS. These complications include hyponatremia, neuro-muscular respiratory failure, and coagulopathy (Abrams et al., 2020). Exploring the extent to which SARS-CoV-2 infection and GBS are related pathophysiologically is crucial in delivering the optimal treatment to patients suffering from this concomitant occurrence. Assessing the biomarkers, diagnostic parameters, and severity of injuries between cases of COVID-19-related GBS will provide better means to explore this relationship.

Significant Biomarkers Associated with GBS and SARS-CoV-2

Several biomarkers indicate the etiology of COVID-19-related GBS. The cytoskeletal protein Glial fibrillary acidic protein (GFAP) is expressed in immature Schwann cells (SC's), mature SCs surrounding unmyelinated axons, and in astroglial intermediate filaments (Notturno et al., 2009). Notturno et al (2009) assert that GFAP is often used to analyze axonal damage in chronic neuropathies. The calcium-binding peptide S100 calcium-binding protein beta (S100β) is produced mainly by astrocytes (Yardan et al., 2011). Like GFAP, it is also found primarily on astroglial and SC's, although it also has extracerebral sources (Yardan et al., 2011). S100β is released into the circulation in response to various neurological disorders, making it a strong prognostic parameter for neuropathies when present at high levels (Yardan et al., 2011). The isoenzyme Neuron-specific enolase (NSE) is cell-specific and associated with the glycolytic enzyme enolase, located in the cytoplasm and expressed abundantly in the neurons and neuroendocrine cells (Khaja et al., 2020). Khaja et al (2020) advocate that elevation in NSE levels is a valuable criterion to indicate neuronal damage, as disruption in the blood-brain barrier

(BBB) integrity and neuronal tissue damage gives rise to NSE release into the cerebral spinal fluid (CSF) and then the blood. Ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) is a multifunctional neuron-specific protein present and expressed at high levels throughout the brain. Functions of UCHL1 include repairing axons and neurons after injury, roles in axonal transport and axonal integrity maintenance, regulating synaptic function, and protecting primary neurons from injury induced by hypoxia (Liu et al., 2019). Increases in UCHL1 indicate a neuronal injury and can reliably diagnose the magnitude of multiple aspects of nervous system damage (Mondello et al., 2012). Neurofilament light (NFL) protein is another biomarker that offers clinical significance in diagnosing several neuropathies. Mariotto et al (2018) contend that CSF and serum NFL levels could reflect ongoing axonal damage in central and peripheral nervous system conditions like GBS. Recently, over a hundred case studies were reported for the GBS-associated with SARS-CoV-2 infection.

The Role of Cytokines in the Etiology of GBS and SARS-CoV-2

Cytokines are polypeptides that play essential roles in the pathophysiology of autoimmune diseases such as GBS and conditions such as COVID-19. The inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) are biomarkers that give insight into the signaling cascade in these pathologies. SARS-CoV-2 augments the "cytokine release storm" (CRS), an intense immune response catalyzed by a sharp increase of proinflammatory cytokines. Many of the cytokines that participate in the pathogenesis of COVID-19 are also involved in the onset of GBS and play a pivotal role(s) in the rapid progression of GBS (Hussain et al., 2020). IL-1β is a member of the IL-1 family, synthesized by monocytes (primarily macrophages), and SCs also produce it in the peripheral nervous system

(Lu & Zhu, 2011). IL-1β is shown to play a role(s) in the destruction and regeneration of the nerves, and similarly, it can induce both proliferation and apoptosis in cultured SCs (Lu & Zhu, 2011). Increases in IL-1β in CSF and serum are characteristic of both GBS and COVID-19. TNF-α is mainly produced by T-lymphocytes, activated macrophages, and natural killer (NK) cells and has an imperative role in the pathogenesis of GBS (Lu & Zhu, 2011). In the onset of GBS, it is upregulated and may contribute to inflammatory demyelination of the peripheral nervous system (Lu & Zhu, 2011).

Significance of Project

The objective in conducting this review was to provide an individualized patients data (IPD) meta-analysis that investigated patients' sociodemographic characteristics and significant clinical characteristics associated with concomitant GBS and COVID-19. The study was done because there is not yet an established understanding of the pathogenesis of SARS-CoV-2 associated GBS. The mechanism of neuroinvasion by SARS-CoV-2 is still poorly understood, and it is imperative to understand this phenomenon, as the neurological manifestations of COVID-19 are of growing concern.

CHAPTER 3: METHODS

A systematic review of the published research work was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to obtain IPD for the meta-analysis that was conducted (Hutton et al., 2015).

Search Strategy

A systematic review of the published research work was performed in accordance with the PRISMA statement (Hutton et al., 2015). An extensive literature search was carried out through PubMed, using the combined search terms “Guillain-Barré Syndrome” and “COVID-19”. Search years were limited to 2020 and 2021, and all case reports and case series were included in the search.

Study Selection

Only case reports and case series were included in the study. The meta-analyses, randomized controlled trials, reviews, and systemic reviews were excluded because they did not IPD. Overlapping publications were reviewed and excluded. Only articles with accessed full texts and written in the English language were included.

Exclusion Criteria for Cases

If the case was unrelated to either GBS or COVID-19, the case was excluded. If the patients had a prior history of GBS before COVID-19, they were excluded. Patients were also excluded if an infectious agent other than SARS- CoV-2 present in the blood or CSF. Patients were also required to have a confirmed COVID-19 diagnosis by either a reverse transcription-polymerase chain reaction (RT-PCR) test or the presence of serum antibodies.

Data Collection

IPD was extracted from each study and organized into several categories. The following data points were used when the data was collected:

Patient data points:

Patient age, patient gender, and presence of comorbidities

Clinical outcome measures:

Mortality (survived/ expired), hospital length-of-stay (LOS; days), reliance on mechanical ventilation (yes/ no), and Intensive Care Unit (ICU) admission (yes/ no)

Serological analysis:

The presence of anti-ganglioside in plasma was recorded (yes/ no).

CSF findings:

CSF protein (normal/ high/ low), CSF white blood cell (WBC) count (normal/ abnormal), CSF glucose (normal/ abnormal), presence of COVID-19 in CSF (yes/ no). All numerical CSF values for protein, (WBC) count, and glucose levels were recorded for each patient.

Neurological findings:

Abnormal plantar response, aphasia/ dysarthria, ataxia, dysphagia, facial palsy/ weakness/ paralysis, fecal incontinence, hypogeusia/ ageusia, hyporeflexia/ areflexia, hyposmia/ anosmia, impaired somatic sensation, impaired compound motor action potential (CMAP), impaired sensory nerve action potential (SNAP), lumbar pain, myalgia, neck flexion weakness, urinary incontinence, upper limbs affected, lower limbs affected, Upper Limb Paralysis, Lower Limb Paralysis, Upper Limb Weakness, Lower Limb Weakness, Upper Limb Paresthesia, Lower Limb Paresthesia, and the total number

of nervous system abnormalities. All values except for the total number of nervous system abnormalities were measured as absent or present.

GBS subtype classification:

The variant of GBS present in each case was recorded.

Data Coding

Upon initial data extraction from each article, the data points were placed into a Microsoft Excel document as columns with coded drop-down lists and free-response cells. Every row was dedicated to a specific patient (identified by a patient number) and completed based on the availability of data present for each case. The reference values used to determine the normal limits of laboratory data are shown in Table 1. After completing the chart, the data values were coded through the coding manual outlined in Section 1 of the Appendix.

Table 1: Reference Values for Laboratory Data

Variables	*Reference Values*
CSF Protein	High: > 45 mg/ dL
	Normal: 15 – 45 mg/ dL
	Low: < 15 mg/ dL
CSF WBC Count	Normal: 0 – 8 cells/ μL
	Abnormal: Any value out of the normal reference range
CSF Glucose (< 18 years old)	Normal: 60 – 80 mg/ dL
	Abnormal: Any value out of the normal reference range
CSF Glucose (≥ 18 years old)	Normal: 40 – 70 mg/ dL
	Abnormal: Any value out of the normal reference range

Data Analysis

The coded values from the Excel chart were transferred to the program IBM SPSS statistics version 28.0.0.0, where several analyses were run to obtain frequencies and descriptive statistics such a mean, standard deviation, and range for the data points. Cross-tabulations between two or more data points were used to express the association between some of the data points. The results from the data analysis obtained through IBM SPSS statistics were displayed in graphs that were created using Microsoft Excel and tables that were prepared in Microsoft Word.

CHAPTER 4: RESULTS

Database Search Results

The initial database search in PUBMED retrieved a total of 161 peer-reviewed articles. After removing four articles due to duplication, 157 articles were screened for their full-text availability. Eleven articles did not have free full text available for review, leaving 146 articles assessed for eligibility based on the project's inclusion criteria. There were 30 articles excluded that were found to be unrelated to GBS, and an additional 16 articles excluded that were not found to be associated with COVID-19. One hundred articles were screened for the study design characteristics, leaving 96 articles to be evaluated for the diagnostic inclusion criteria. Three articles were excluded due to either an unconfirmed COVID-19 diagnosis or a viral agent other than SARS-COV2. Thus, there were 93 articles finally included and formed the basis of research analyses, which comprised 121 patients. Table 8, located in the Appendix, provides the author(s), year, and the number of patients included in all the 121 cases. The PRISMA flow diagram illustrating the exclusion of articles is presented in Figure 1.

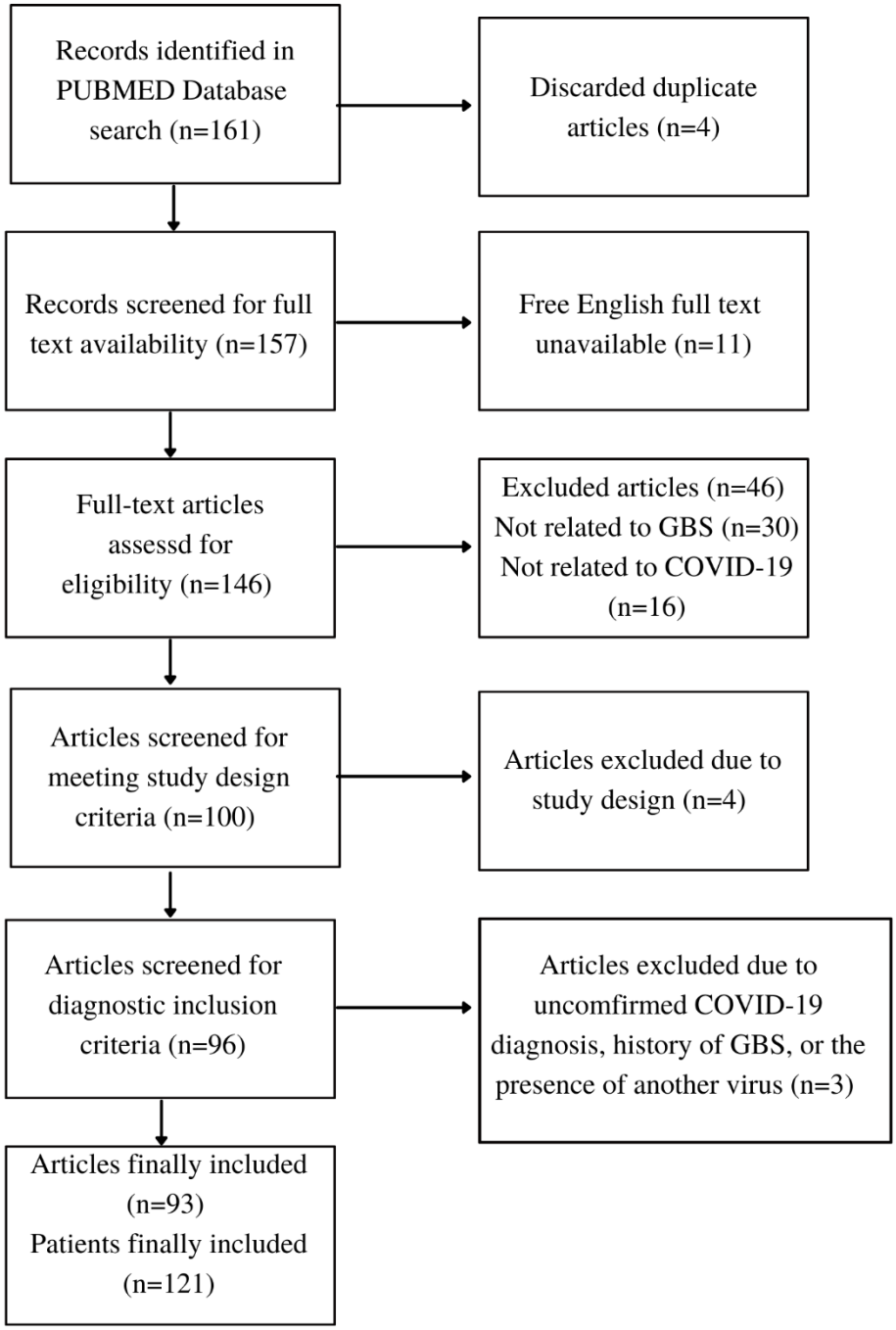

Figure 1: Article Exclusion Flow Chart (PRISMA)

Sociodemographic Patient Characteristics

Sociodemographic data were recorded for each study and analyzed based on age, gender, presence of comorbidities, hospital LOS, ICU admission, reliance on mechanical ventilation, number of days the patient was on mechanical ventilation, and mortality. All data and statistical tests were obtained through Microsoft Excel and SPSS statistics tools. Results are outlined in Table 1. The patients were about two-thirds male (62.8%; n= 76) and about one-third were female (37.2%; n= 45). The patient ages ranged from 3 to 94 years old, and the mean age among the patients was 53 years old with a standard deviation ± 18.1 (SD) 18.1 years. There were 19.2% (n= 19) of patients that were younger than 40 years old, while most of the patients (80.8%; (n= 80) were 40 years or older. Most of the patients had less than two comorbidities (80.2%; n= 97), while only 19.8% (n= 24) of patients reported having two or more comorbidities. The highest number of comorbidities reported was four from a single patient.

The patient's hospital LOS ranged from one to 76 days and had a mean value of 24 days with a standard deviation of ± 19 (SD) days. There was nearly an equal ratio of patients that stayed in the hospital for less than 20 days (51.1%; n= 24) and patients that stayed in the hospital for 20 or more days (48.9%; n= 23). A similar relationship occurred between whether patients required admission to the ICU. A slight majority of patients did not require ICU admission (53.4%; n= 62) compared to patients admitted to the ICU (46.6%; n= 43). There were roughly two-thirds of patients that did not require mechanical ventilation (64.2%; n= 77), while the remaining patients required mechanical ventilation due to respiratory failure (35.8%; n= 43). For patients who did require mechanical ventilation, the days they relied on mechanical ventilation before being extubated or expiring ranged from two to 30 days and had a mean value of 13 ±

nine days. There was a high survival rate among patients, with 90.9% (n= 110) of patients that survived and 9.1% (n= 11) of patients that expired. Of the patients who survived, 13.6% (n= 15) were not yet discharged from the hospital to their home or a rehabilitation center.

Table 2: Sociodemographic Patient Data and Clinical Outcome Measures

Category	*(mean ± SD) Range]*	*n*	*%*
Age	53 ± 18 [3-94]		
Gender	Male	76	62.8
	Female	45	37.2
Age group	<40	26	21.8
	≥40	93	78.2
# Of comorbidities	<2	97	80.2
	≥2	24	19.8
Length-of-stay in the hospital (days)	24 ± 19 [1-76]		
Length-of-stay in the hospital (days)	< 20 days	24	51.1
	≥20	23	48.9
ICU admission	Yes	54	46.6
	No	62	53.4
Mechanical Ventilation (MV)	Yes	43	35.8
	No	77	64.2
# Of days in MV	13 ± 9 [2-30]		
Mortality	Survived	110	90.9
	Expired	11	9.1

Serological Analysis

Serological studies examined the relationship between the onset of GBS and COVID-19 by identifying serum anti-ganglioside antibodies. Results are summarized in Figure 2. Only 17.9% (n=7) of patients tested positive for serum anti-ganglioside antibodies, while most of the tested patients (82.1%; n= 32) were negative.

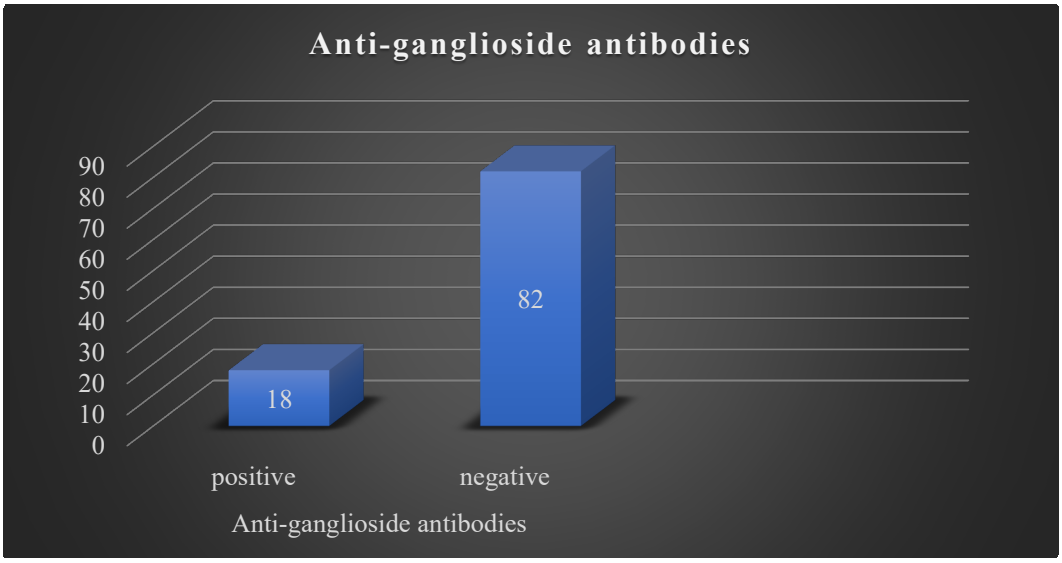

Figure 2: Anti-ganglioside Antibodies

Cerebrospinal Fluid Analysis

CSF analysis revealed that COVID-19 was detected in four cases of the 48 tested (8.3%). Protein levels in CSF were elevated in 85% of the patients (n=84), as displayed in Figure 3. Figure 3 also displays that only 14% (n=14) of the patients had a standard CSF protein value, while about one percent (n= 1) had a low CSF protein value. The most common CSF protein

value range was between 101 to 125 mg/dL, comprising 30% (n= 27) of the values among 90 total patients. The WBC count was within the normal limits in 90.1% (n=68) of the total cases (n=75). The total WBC count obtained from 55 patients ranged from zero to 18 cells/µL of blood and had a mean value of 2.7 cells with an SD ±3.7 cells/µL. The CSF glucose values were abnormal in 41.5% (n=17) of the 41 total cases. The CSF glucose values recorded among 31 patients ranged from 50 to 166 mg/dL and had a mean value of 76.7 mg/dL with an SD of ± 23.1 mg/dL.

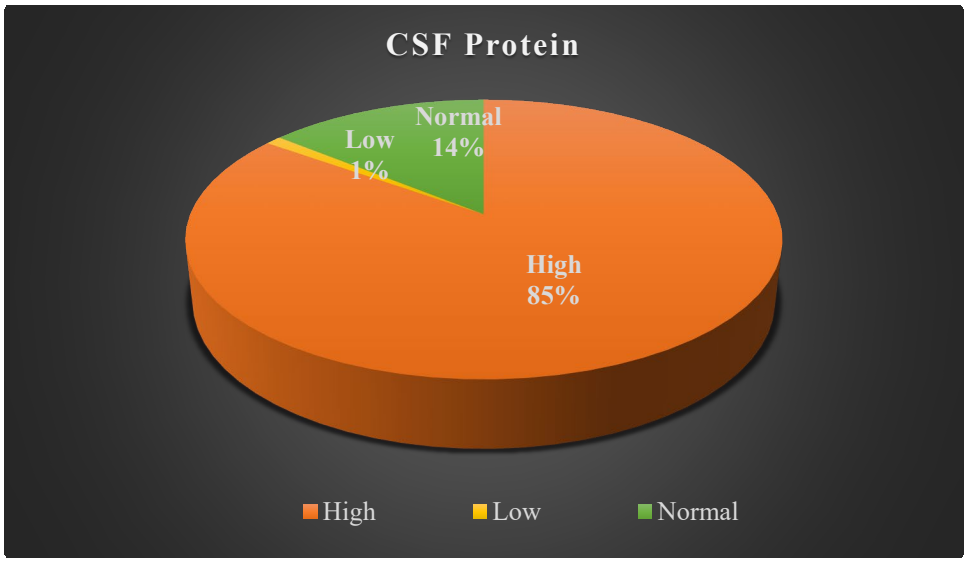

Figure 3: CSF Protein Levels

Neurological Findings

It was found that 88% (n=106) of the patients had five or more neurological symptoms. The neurological symptoms reported by each study are included in Table 2. The neurological

manifestations reported from a total of 121 cases are as follows: 6.6% report an abnormal plantar response, 14.9% report aphasia, 43% report ataxia, 19.8% report dysphagia, 42.1% report facial palsy, weakness, or paralysis, 2.5% fecal incontinence, 7.4% report urinary incontinence, 19.8% report hypogeusia or ageusia, 87.6% report hyporeflexia or areflexia, 19% report hyposmia or anosmia, 73.6% report impaired somatic sensation, 14.9% report lumbar pain, 24% report myalgia, and 9.1% report neck flexion weakness.

Table 3: Neurophysiological Abnormalities

Neurological Manifestation	*n*	*%*
Abnormal Plantar Response	8	6.6
Aphasia	18	14.9
Ataxia	53	43.8
Dysphagia	24	19.8
Facial Palsy/ Weakness/ Paralysis	51	42.1
Fecal Incontinence	3	2.5
Urinary Incontinence	9	7.4
Hypogeusia/ Ageusia	24	19.8
Hyporeflexia/ Areflexia	106	87.6
Hyposmia/ Anosmia	23	19
Impaired Somatic Sensation	89	73.6
Lumbar Pain	18	14.9
Myalgia	29	24
Neck Flexion Weakness	11	9.1

Limb Strength and Sensation

Patients presented with both upper and lower limb strength and sensation abnormalities. The findings are displayed in Figure 4. All 121 cases included data on the upper and lower limb abnormalities. A vast majority of cases reported that the patient's lower limbs were affected by either weakness, paralysis, or paresthesia (91.7%; n=111). Table 3 highlights that out of the 111

cases that reported lower limb abnormalities, 54 cases reported both paresthesia and weakness, 22 reported complete lower-limb paralysis without paresthesia, 31 cases reported weakness without paresthesia, and four cases reported paresthesia without weakness. As for the results about lower limb abnormalities, most cases (83.5%; n=101) reported that the patients' upper limbs were affected by either weakness, paralysis, or paresthesia. Table 4 highlights that out of the 101 cases that reported lower limb abnormalities, 37 cases reported both paresthesia and weakness, 17 reported complete lower-limb paralysis without paresthesia, 36 cases reported weakness without paresthesia, and 11 cases reported paresthesia without weakness. In all cases involving limb paralysis, it was assumed that patients presenting with limb paralysis also presented with limb weakness.

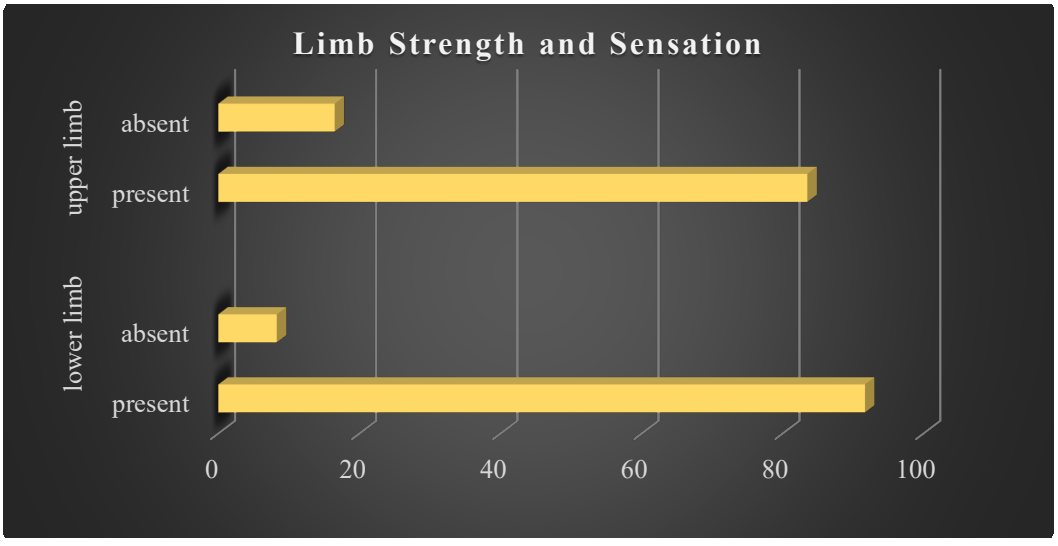

Figure 4: Limb Strength and Sensation

Table 4: Lower Limb Strength and Sensory Impairment

Lower Limb			*Weakness*		
Paresthesia			Absent	Present	Total
Absent	*Paralysis*	Absent	10	31	41
		Present	0	9	9
	Total		10	40	50
Present	*Paralysis*	Absent	4	54	58
		Present	0	13	13
	Total		4	67	71
Total	*Paralysis*	Absent	14	85	99
		Present	0	22	22
	Total		14	107	121

Table 5: Upper Limb Strength and Sensory Impairment

Upper Limb			*Weakness*		Total
Paresthesia			Absent	Present	
Absent	*Paralysis*	Absent	20	36	56
		Present	0	10	10
	Total		20	46	66
Present	*Paralysis*	Absent	11	37	48
		Present	0	7	7
	Total		11	44	55
Total	*Paralysis*	Absent	31	73	104
		Present	0	17	17
	Total		31	90	121

Electrophysiological Findings

Electrophysiological studies were conducted in many studies to explore the distal latency (ms), conduction velocity (m/s), amplitudes (mV for motor and μV for sensory), onset latency, peak latency, and F-response latency of the sensory and motor nerves. Specific nerves commonly evaluated between studies included the ulnar, peroneal, tibial, and sural nerves. Sensory nerve action potential and compound muscle action potential are displayed in Figure 5. SNAP tests were shown to have abnormal values in 82.7% (n=67) of cases. The CMAP tests also revealed that most patients received abnormal test results (96.4%; n=81).

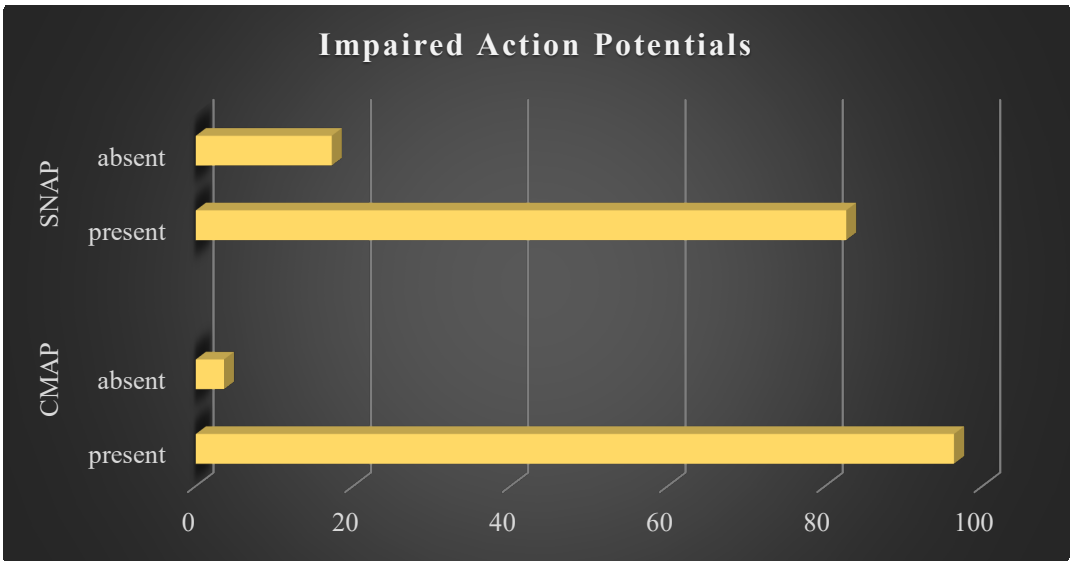

Figure 5: Impaired Action Potentials

GBS Subtype Classification

A total of 85 cases included the GBS subtype associated with the patient's diagnosis of GBS. Five cases reported overlaps of GBS variants. Three cases reported an overlap of the AIDP and AMAN variants, while one case reported an overlap of the AIDP and the AMSAN variant, and one case reported the overlap of AIDP and MFS. The AIDP variant was the most prominent subtype and comprised 51.8% (n=44) of the studies. The second most prominent variants were the axonal variants which include AMAN and AMSAN. The AMSAN variant made up 15.3% (n=13) of the classification, while the AMAN variant made up 12.9% (n=11). The MFS variant affected a total of seven patients (8.2%). The least common variants were the FD and the PCB variants of GBS, comprising 3.5% (n=3) and 2.4% (n=2), respectively. The distribution of GBS subtypes is shown in Table 6.

Table 6: GBS Subtypes

GBS Subtype	*n*	*%*
Acute inflammatory demyelinating polyneuropathy (AIDP)	44	51.8
Acute motor axonal neuropathy (AMAN)	11	12.9
Acute motor-sensory axonal neuropathy (AMSAN)	13	15.3
Miller-Fisher syndrome (MFS)	7	8.2
Facial diplegia (FD)	3	3.5
Pharyngeal-cervical-brachial (PCB)	2	2.4
AIDP and AMAN overlap	3	3.5
AIDP and AMSAN overlap	1	1.2
AIDP and MFS overlap	1	1.2

CHAPTER 5: DISCUSSION

The systematic search that was tailored to meet PRISMA requirements for meta-analyses led to the retrieval of 93 peer-reviewed articles published between April 2020 and October 2021 (Hutton et al., 2015). These articles were comprised of 15 case series and 78 case reports that collectively contained IPD for a total of 121 patients.

Sociodemographic Data Findings

The collection of sociodemographic patient data found that different age groups are disproportionately affected by concomitant GBS and COVID-19. An overwhelming majority of patients were aged 40 or older (78.2%; n=93), with the mean age being 53 ± 18 years old. This distribution is not a surprise, as COVID-19 is known to affect older people more severely. A meta-analysis performed by Starke et al. (2020) revealed a 3.5% increase in the disease severity per age year when measuring the relative risk estimate associated with age-related risk factors of COVID-19 severity. The oldest patient included in our analysis was 94 years old and only had four nervous system manifestations. Due to respiratory failure, the patient did require mechanical ventilation but could return home once stable (Manganotti et al., 2021). Seven patients were 18 years old or younger, comprising only about six percent of the total cases (Khalifa et al., 2020; Manji et al., 2020; Araújo et al., 2021; Curtis et al., 2021; El Mezzeoui et al., 2021; Mantefardo et al., 2021; Paybast et al., 2020). The youngest patient included in our study was three years old and presented a very high CSF protein value of 250 mg/dL and required mechanical ventilation (El Mezzeoui et al., 2021).

Data obtained on patient gender revealed that almost two-thirds of the cases were male (62.8%). The majority of the male patients present in the study are likely attributed to males having an increased susceptibility to the binding of the SARS-CoV-2 spike (S) glycoprotein and the ACE2 receptors on host cells, causing a downregulation in ACE2 (Gadi et al., 2020). Downregulation of ACE2 can be detrimental to patients that may already be deficient in ACE2. Gadi et al. (2020) contend that the male mortality rate for COVID-19 is influenced by the location of ACE2 on the X chromosome and how it influences an increased binding affinity between SARS-CoV-2 S protein and ACE2. Pijls et al. contend that men are not only more likely to contract COVID-19. Men also have a higher risk of acquiring severe COVID-19 symptoms once they are already hospitalized and more often require ICU admission (Pijls et al., 2021). Patients with GBS are shown to have a similar gender distribution in pathology where males are predominately affected compared to women. An epidemiological study in Finland reported that 57% (n=559) of patients with GBS were male(Sipilä et al., 2017). Another study conducted in China reported that 63% (n=276) of patients were male when investigating variation in GBS incidence. These distributions further support the male predominance associated with concomitant GBS and COVID-19.

Clinical Outcomes Measures

Clinical outcomes measures were used to assess the severity of COVID-19 related GBS. The cases that provided hospital LOS reported that about 49% of patients were in the hospital for 20 or more days. Almost half of the patients included required admission to the ICU (46.6%), which indicates that these patients were severely affected by COVID-19 and GBS. Unfortunately, 11 patients died in the hospital, comprising about nine percent of all the cases.

About 36% of the patients required mechanical ventilation due to respiratory distress or failure. SARS-CoV-2 commonly infects the host through the airways and may lead to the virus infecting the lungs' alveolar type II cells and causing them to undergo apoptosis and die (Mason, 2020). Infection through the host's airways puts the patient at high risk for pneumonia and respiratory failure, which causes lung term damage to the lungs (Qian et al., 2013). Orlikowski et al. (2004) argue that about one-third of patients with GBS require mechanical ventilation and ICU admission due to respiratory failure. Patients with GBS are historically prone to respiratory failure due to progressive respiratory muscle weakness, which causes a restrictive respiratory pattern (Teitelbaum & Borel, 1994).

Neurophysiological Findings

There are multiple theories regarding the peripheral and central nervous system damages that occur during COVID-19 infection. Several viruses are shown to have the ability of neuroinvasion (ability to penetrate the CNS), neurotropism (where they can affect neurons and glial cells), and potentially neurovirulence (where they can induce neurologic diseases) (Giraudon & Bernard, 2010; Desforges et al., 2014;). Hatch Berth et al. (2009) assert that there are two modes of viral entry into the brain: i) the hematological route and ii) the peripheral nerve route. The hematogenous route is mediated by the infection of endothelial cells via the binding to ACE2 in capillaries or by infecting leukocytes that are carried through the bloodstream (Zhou et al., 2020). These cells move through the bloodstream and are transported into the brain, surpassing the BBB due to increased permeability (Berth et al., 2009; Abu-Rumeileh et al., 2021). The peripheral nerve route of entry for viruses involves entry through peripheral nerve

endings in the skin and mucosa through neuronal retrograde dissemination, where the virus uses several mechanisms of transport within the cells to gain access to the CNS (Berth et al., 2009; Desforges et al., 2014).

Through this neuronal retrograde dissemination, CNS infection can be induced via the cranial nerves by the infection of the epithelial cells in the oral mucosa, where levels of ACE2 are highly expressed and very susceptible to binding with SARS-CoV-2 (Zhou et al., 2020). The olfactory nerve is considered a shortcut for many viruses to gain access to the brain through the olfactory bulb, after that spreading to specific brain areas, including the brainstem and the thalamus (Gutiérrez-Ortiz et al., 2020; Zhou et al., 2020). Deficits to olfactory nerve function were reported in several cases. It was found that 19.8% of patients presented with ageusia (n=24), and 19% of patients reported anosmia as a symptom (n=23). Data reported in a systemic review on COVID-19 revealed that a pooled prevalence of anosmia was 38.2% of 32,142 COVID-19 cases (Mutiawati et al., 2021).

It has been found that viruses such as SARS-CoV-2 may also enter the CNS via retrograde axonal transport through other peripheral nerves, including the trigeminal nerve, which possesses nociceptive cells in the nasal cavity (Desforges et al., 2019). Viruses may also gain access through the sensory fibers of the glossopharyngeal nerve (cranial nerve nine) and the vagus nerve (cranial nerve ten) (Desforges et al., 2020; Thomas et al., 2020; Costello & Dalakas, 2020). The glossopharyngeal nerve supplies motor innervation to the stylopharyngeus muscle (responsible for elevating the pharynx and larynx, especially in speaking and swallowing), and the vagus nerve, innervates different organs of the respiratory tract such as the larynx, trachea,

and lungs (Costello & Dalakas, 2020; Desforges et al., 2019; Thomas & M Das, 2019). SARS-CoV-2 and its effects on cranial nerves (such as the glossopharyngeal and vagus nerve) may contribute to the onset of dysphagia and aphasia. Dysphagia was present in 19.8% of cases (n=24), and aphasia was present in 14.9% (n=18) cases. These cranial nerve deficits may also contribute to the symptoms associated with respiratory distress and failure due to disruption of the innervations of the respiratory tract and lungs. Several cases also reported signs of pathology related to the facial nerve (the seventh cranial nerve). Facial nerve involvement can manifest as facial weakness, paralysis, or paresthesia, resulting in 42.1% (n= 51) cases.

It was found that 43.8% of cases reported ataxia as a symptom, and 87.8% of patients reported hyporeflexia or areflexia. The loss of deep tendon reflexes is one of the characteristic symptoms of GBS and was expected to have a high frequency among cases. The patients that were diagnosed with MFS had a higher prevalence of areflexia and ataxia, where all cases present in the study reported both as a symptom (Gutiérrez-Ortiz et al., 2020; Lantos et al., 2020; Lowery et al., 2020; Ray, 2020; Reyes-Bueno et al., 2020; Senel et al., 2020). The high frequency of areflexia and ataxia was not a surprise, as the usual triad for MFS consists of acute onset of external ophthalmoplegia, ataxia, and loss of tendon reflexes (Gutiérrez-Ortiz et al., 2020).

When neurophysiological symptoms were assessed, it was found that 88% of cases reported having five or more neurological symptoms present. Aside from hyporeflexia, areflexia, and limb impairment, the most common neurologic manifestation between patients was impaired somatic sensation. Impaired somatic sensation was reported in about three-quarters of cases

(73.6%). Somatic sensation impairment is often accompanied by myalgia and lumbar pain and was reported in 24% of patients and 14.9% of patients, respectively. For electrophysiological tests investigating either CMAP or SNAP, any patient with impaired action potentials were considered to have impaired somatic sensation. Analysis revealed that 82.7% of patients had abnormal values in SNAP testing, while 96.4% of patients had impaired CMAP. This trend was expected, as electrophysiologic studies are a vital tool used in the diagnosis of GBS. These subtypes were determined mainly through the evaluation of CMAP and SNAP tests. For studies without electrophysiological data, the GBS subtype was determined by clinical characteristics and laboratory findings. A total of 13 patients were diagnosed with the AMSAN variant of GBS. Eight out of the nine patients with AMSAN had impaired action potentials for both the SNAP and the CMAP tests, indicating the involvement of both the motor and sensory nerves. A total of 11 patients were diagnosed with the AMAN variant of GBS. Nerve conduction studies showed that all nine patients tested for CMAP had abnormal results, while only three cases showed impaired SNAP. The most common variant of GBS among patients was AIDP, comprising about half the total cases (51.8%). There was a total of five cases that presented with an overlap of AIDP and another GBS variant. Three patients were diagnosed with an overlap of AIDP and AMAN, while one patient was found to have an overlap between AIDP and AMSAN, and one had an overlap of AIDP and MFS. The least common variants reported among cases were FD which comprised < 4% of cases, and the PCB variant, < 3%.

Limb strength and sensation were measured in all the patients. It was found that 91.7% of patients reported abnormal lower limb function, while 22 cases presented with complete lower-limb paralysis. It was found that 83.5% of patients reported abnormal upper limb function, while

17 of the patients presented with complete upper limb paralysis. The difference between strength and sensation in the upper and lower limbs can be explained by the fact that GBS affects patients in a progressive, ascending manner, where lower limbs are first affected by weakness or paresthesia, and then the trunk and upper limbs. The differences in limb impairment also explain why more patients presented with lower-limb paralysis. Neurological manifestations that were not frequently reported included neck flexion weakness (present in ~9% of cases), abnormal plantar response (present in ~7% of cases), urinary incontinence (present in ~7% of cases), and fecal incontinence (present in ~3% of cases).

Laboratory Findings

Coronaviruses are thought to cause GBS either directly through the neuroinvasive capacity of SARS-CoV-2 or as an autoimmune response triggered by a CRS mediated by the inflammatory response associated with COVID-19. Reports show that GBS associated with COVID-19 differs from the typical "post-infectious" pattern of GBS and presents more commonly as an "acute para-infection" (Hussain et al., 2020). The apparent difference between these patterns of infection is that most of the infectious agents typically associated with GBS, such as varicella-zoster virus and cytomegalovirus, cause direct damage to the nerve roots due to the presence of the virus in the CSF, which appears unlikely in COVID-19 infections (Hussain et al., 2020). Our analysis observed the absence of SARS-CoV-2 in CSF when evaluating the results of cases that reported CSF PCR testing. Only four out of 48 cases (~8%) detected the presence of COVID-19 in the CSF. Similar results for the presence of COVID-19 in CSF were reported in studies on cases with COVID-19 diagnosis (without GBS). Lewis et al. reported that the CSF SARS-CoV-2 PCR resulted positive for 17/303 (6%) patients, and Lersy et al. found

that four patients (7%) had a positive SARS-CoV-2 RT-PCR result in CSF. The presence of anti-ganglioside antibodies in serum analysis was evaluated because of the typical ganglioside mimicry traditionally associated with GBS. Anti-ganglioside antibody testing revealed that only 17.9% of patients tested positive for anti-ganglioside antibodies typically associated with GBS. Similar results reported by Hasan et al. (2020) showed that only one out of 26 patients tested positive for anti-ganglioside antibodies. This trend differs from the classical GBS presentation associated with molecular mimicry and suggests that the CRS may significantly impact the onset of COVID-19 related GBS.

A surge of several cytokines, including interleukin-1β (IL-1β), IL-6, IL-17, tumor necrosis factor-α (TNF- α), interferon-γ (IFN-γ), along with other chemokines, describes the early CRS that emerges in COVID-19 infections (Hussain et al., 2020). Hussain et al. (2020) assert that many of the cytokines listed have also been tied to the pathogenesis of classical GBS. The commonality of cytokines and chemokines involved suggest that GBS is more likely attributed to the upsurge of proinflammatory cytokines, which cause the severe symptomatology associated with COVID-19, such as respiratory distress and organ failure. Lu & Zhu (2011) argue that proinflammatory cytokines mediate the recruitment of effector cells to the peripheral nervous system (PNS). The recruitment of effector cells causes a release of toxins which damage SC's and degrade the myelin sheaths of neurons (Lu & Zhu, 2011). Cytokines were not considered in the meta-analysis due to a lack of data availability among cases.

Protein levels, glucose, and WBC count were also considered as indicators of pathology. Elevations in CSF protein levels were observed in 85% of patients, with the most frequent value range being 101 to 125 mg/dL, indicating significant nervous system pathology among cases.

The highest reported CSF protein value was 620 mg/dL and was found in an 8-year-old boy with the AIDP variant of GBS and a positive CSF PCR COVID-19 test result (Curtis et al., 2021). Despite requiring four days of mechanical ventilation due to respiratory failure and presenting with lower-limb paralysis and nine other nervous system abnormalities, the patient survived and was discharged from the hospital after 11 days (Curtis et al., 2021).

Elevations in CSF protein have been observed in COVID-19 studies that are unrelated to GBS. A systemic review conducted by Lewis et al. found that 160/397 (40%) of COVID-19 patients presented with "increased protein" or protein >60 mg/dL. It is significant to note that five out of the 397 patients with increased protein values presented with CSF protein greater than 1,000 mg/dL (Lewis et al., 2021). It is important to note that there would be a higher percentage of patients that presented with elevated CSF protein in the systemic review conducted by Lewis et al. if the normal value range for CSF protein was equal to that of the range included in this current meta-analysis (>45 mg/dL). In another COVID-19 study conducted by Miller et al., it was found that CSF protein values were elevated above the normal range (>45 mg/dL) in 14 (52%) patients included in the case series. Elevations in CSF protein were also noted in a study by (Lersy et al., 2021) and showed that 22 (38%) of COVID-19 patients included in the study had a CSF value above the normal range (>45 mg/dL). The compilation of COVID-19 studies exhibits that although elevated CSF protein values were observed among COVID-19 patients, there were higher reports of elevated CSF protein values among patients with concomitant GBS and COVID-19 in the current meta-analysis.

Glucose levels were also used as an indicator of nervous system pathology, and abnormally high levels were observed in about 41.5% of patients. Three cases had type two

diabetes and presented abnormal glucose values (Nanda et al., 2021; Zubair et al., 2021). Elevated white blood cell counts were only observed in 9.9% of cases, indicating low infection levels in the CSF.

Highlights

- A majority of the patients were found to be aged 40 or older (78.2%; n=93), with the mean age being 53 ± 18 years old and the patients' ages ranging from three to 94 years old.
- It was revealed that almost two-thirds of the cases were male (62.8%).
    - This percentage can likely be attributed to males having an increased susceptibility to the binding of the SARS-CoV-2 spike (S) glycoprotein and the ACE2 receptors on host cells, causing a downregulation in ACE2 (Gadi et al., 2020)
- The cases that provided hospital LOS reported that about 49% of patients were in the hospital for 20 or more days. Almost half of the patients included required admission to the ICU (46.6%).
    - These clinical outcomes measures indicate that these patients were severely affected by COVID-19 and GBS
- About 36% of the patients required mechanical ventilation due to respiratory distress or failure.
    - Patients with GBS are historically prone to respiratory failure due to progressive respiratory muscle weakness, 0which causes a restrictive respiratory pattern (Teitelbaum & Borel, 1994).

- Deficits to olfactory nerve function were reported in several cases.
    - There were 19.8% of patients who presented with ageusia (n=24), and 19% of patients reported anosmia as a symptom (n=23).
    - The olfactory nerve is considered a shortcut for many viruses to gain access to the brain through the olfactory bulb, after that spreading to specific brain areas, including the brainstem and the thalamus (Gutiérrez-Ortiz et al., 2020; Zhou et al., 2020).
- SARS-CoV-2 and its effects on cranial nerves (such as the glossopharyngeal and vagus nerve) may contribute to the onset of dysphagia and aphasia.
    - Dysphagia was present in 19.8% of cases (n=24), and aphasia was present in 14.9% (n=18) cases.
- Several cases reported signs of pathology related to the facial nerve (the seventh cranial nerve).
    - Facial nerve involvement can manifest as facial weakness, paralysis, or paresthesia, resulting in 42.1% (n= 51) cases.
- It was found that 43.8% of cases reported ataxia as a symptom, and 87.8% of cases reported hyporeflexia or areflexia.
    - These findings were especially present in patients with MFS.
- There were 88% of cases that reported having five or more neurological symptoms present.
- Electrophysiological analysis revealed that 82.7% of cases had abnormal values in SNAP testing, while 96.4% of patients had impaired CMAP.

- The most common variant of GBS among patients was AIDP, comprising about half the total cases (51.8%).
- Significant data were found regarding limb function pathology.
    - It was found that 91.7% of patients reported abnormal lower limb function, while 22 cases presented with complete lower-limb paralysis.
    - It was found that 83.5% of patients reported abnormal upper limb function, while 17 of the patients presented with complete upper limb paralysis.
- Only four out of 48 cases (~ 8%) detected the presence of COVID-19 in the CSF.
- Elevations in CSF protein levels were observed in 85% of patients, with the most frequent value range being 101 to 125 mg/dL, indicating significant nervous system pathology among cases
- The commonality of cytokines and chemokines involved in COVID-19 and GBS suggests that GBS is most likely attributed to the upsurge of proinflammatory cytokines, which cause the severe symptomatology associated with COVID-19, such as respiratory distress and organ failure.
    - Cytokines were not considered in the meta-analysis due to a lack of data availability among cases.

APPENDIX A: CODING MANUAL

Table 7: Coding Manual

Variables	*Coding Mechanisms*
Variant of GBS	1= AIDP, 2= AMAN, 3= AMSAN, 4= MFS, 5= FD, 6= PCB
Gender	1= Female, 2=Male
Age Category	1= 0-18, 2= 19-39, 3= 40-59, 4= 60+
Mortality	1= Survived, 2= Expired, 3= Hospitalized
Reliance on Mechanical Ventilation	1= Yes, 2= No
ICU Admission	1= Yes, 2= No
CSF COVID-19 Detection	1= Yes, 2= No
CSF Protein	1= Normal, 2= High, 3= Low
CSF WBC Count	1= Normal, 2= Abnormal
CSF Glucose	1= Normal, 2= Abnormal
Serum anti-ganglioside AB's Present	1= Yes, 2= No
Abnormal Plantar Response	1= Absent, 2= Present
Aphasia/ Dysarthria	1= Absent, 2= Present
Ataxia	1= Absent, 2= Present
Dysphagia	1= Absent, 2= Present
Facial Palsy/ Weakness/ Paralysis	1= Absent, 2= Present
Fecal Incontinence	1= Absent, 2= Present
Hypogeusia/ Ageusia	1= Absent, 2= Present
Hyporeflexia/ Areflexia	1= Absent, 2= Present
Hyposmia/ Anosmia	1= Absent, 2= Present
Impaired somatic sensation	1= Absent, 2= Present
Impaired CMAP	1= Absent, 2= Present
Impaired SNAP	1= Absent, 2= Present
Lumbar Pain	1= Absent, 2= Present
Myalgia	1= Absent, 2= Present
Neck Flexion Weakness	1= Absent, 2= Present
Urinary Incontinence	1= Absent, 2= Present
Upper Limbs Affected	1= Absent, 2= Present
Lower Limbs Affected	1= Absent, 2= Present
Upper Limb Paralysis	1= Absent, 2= Present
Lower Limb Paralysis	1= Absent, 2= Present
Upper Limb Weakness	1= Absent, 2= Present

Lower Limb Weakness	1= Absent, 2= Present
Upper Limb Paresthesia	1= Absent, 2= Present
Lower Limb Paresthesia	1= Absent, 2= Present

APPENDIX B: LIST OF INCLUDED ARTICLES

Table 8: Articles Included in the Meta-Analysis

Citation	*# Of cases*	*Citation*	*# Of cases*	*Citation*	*# Of cases*
(Aasfara et al., 2021)	1	(Elkhouly & Kaplan, 2020)	1	(Marta-Enguita et al., 2020)	1
(Abbaslou et al., 2020)	1	(Ferraris et al., 2020)	1	(Masuccio et al., 2021)	1
(Abolmaali et al., 2021)	3	(Finsterer, 2021)	1	(Mokhashi et al., 2021)	1
(Abrams et al., 2020)	1	(Frank et al., 2021)	1	(Naddaf et al., 2020)	1
(Agosti et al., 2021)	1	(Ghosh et al., 2020)	1	(Nanda et al., 2021)	4
(Akçay et al., 2021)	1	(Gigli et al., 2020)	1	(Oguz-Akarsu et al., 2020)	1
(Alberti et al., 2020)	1	(Gutiérrez-Ortiz et al., 2020)	2	(Ottaviani et al., 2020)	1
(Ameer et al., 2020)	1	(Haidary et al., 2021)	1	(Padroni et al., 2020)	1
(Ansari & Hemasian, 2021)	1	(Helbok et al., 2020)	1	(Paybast et al., 2020)	2
(Araújo et al., 2021)	1	(Hirayama et al., 2020)	1	(Pelea et al., 2021)	1
(Arnaud et al., 2020)	1	(Hutchins et al., 2020)	1	(Petrelli et al., 2020)	1
(Assini et al., 2020)	2	(Ibrahim et al., 2021)	1	(Raahimi et al., 2021)	1
(Atakla et al., 2020)	1	(Jao J et al., 2021)	1	(Rajdev et al., 2020)	1
(Bigaut et al., 2020)	2	(Judge et al., 2020)	2	(Ray, 2020)	1
(Bracaglia et al., 2020)	1	(Juliao Caamaño & Alonso Beato, 2020)	1	(Reyes-Bueno et al., 2020)	1
(Bueso et al., 2021)	1	(Khaja et al., 2020)	1	(Riva et al., 2020)	1
(J. L. Chan et al., 2020)	1	(Khalifa et al., 2020)	1	(Sancho-Saldaña et al., 2020)	1
(M. Chan et al., 2021)	2	(Khan et al., 2021)	5	(Scheidl et al., 2020)	1
(Chmiela et al., 2021)	2	(Khedr et al., 2021)	5	(Sedaghat & Karimi, 2020)	1
(Civardi et al., 2020)	1	(Kilinc et al., 2020)	1	(Senel et al., 2020)	1
(Coen et al., 2020)	1	(Koca et al., 2021)	1	(Singh et al., 2021)	1

(Colonna et al., 2021)	1	(Korem et al., 2020)	1	(Singhai & Budhiraja, 2021)	1
(Curtis et al., 2021)	1	(Kumar & Chakraborty, 2020)	1	(Su et al., 2020)	1
(Defabio et al., 2021)	1	(Lantos et al., 2020)	1	(Tard et al., 2020)	1
(Diez-Porras et al., 2020)	1	(Lascano et al., 2020)	3	(Tekin et al., 2021)	1
(Dmitriy A et al., 2021)	1	(Liberatore et al., 2020)	1	(Tiet & Alshaikh, 2020)	1
(D'Orsi et al., 2021)	1	(Lowery et al., 2020)	1	(Wada et al., 2020)	1
(Dufour et al., 2021)	1	(Mackenzie et al., 2021)	1	(Webb et al., 2020)	1
(Ebrahimzadeh et al., 2021)	2	(Manganotti et al., 2021)	5	(Zhao et al., 2020)	1
(El aidouni et al., 2021)	1	(Manji et al., 2020)	1	(Zito et al., 2020)	1
(El Mezzeoui et al., 2021)	1	(Mantefardo et al., 2021)	1	(Zubair et al., 2021)	2

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