Correlation of Cerebrospinal Fluid Total Protein and Serum Neutrophil-to-Lymphocyte Ratio with Clinical Outcomes of Guillain-Barre Syndrome Variants

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ABSTRACT

Objective: To evaluate the correlation of cerebrospinal fluid total protein and serum neutrophil-to-lymphocyte ratio with the clinical outcomes and the various clinical and electrophysiological variants of Guillain-Barre syndrome.

Study Design: Cross-sectional study.

Place and Duration of the Study: Department of Neurology, Mayo Hospital and King Edward Medical University, Lahore, Pakistan, from November 2022 to April 2023.

Methodology: Fourty-six Guillain-Barre syndrome patients, aged 12-70 years, were included in the study diagnosed by using the Brighton's criteria. Functional disability and respiratory insufficiency were assessed by using the modified Hughes disability score and the Erasmus Guillain-Barre syndrome respiratory insufficiency score, respectively. Serum neutrophil-to-lymphocyte ratio and cerebrospinal fluid total protein were calculated for each patient at the time of admission.

Results: Axonal variants had a higher mean neutrophil-to-lymphocyte ratio (5.29 ± 4.38) than demyelinating variants (4.71 ± 3.4) and Miller-Fischer syndrome (3 ± 2.828). This ratio was positively correlated with the modified Hughes's disability score ($r = 0.790$, $p = 0.001$) and the Erasmus Guillain-Barre syndrome respiratory insufficiency score ($r = 0.936$, $p = 0.002$). Mean cerebrospinal fluid total protein was higher for demyelinating (218 ± 136 mg/dl) than axonal variants (86 ± 56 mg/dl) and Miller-Fischer syndrome (34 ± 21 mg/dl). However, higher modified Hughes disability score (4-6) ($r = 0.020$, $p = 0.117$) and a high Erasmus Guillain-Barre syndrome respiratory insufficiency score (5-7) ($r = 0.115$, $p = 0.302$) did not significantly affect mean cerebrospinal fluid total proteins.

Conclusion: Serum neutrophil-to-lymphocyte ratio can be regarded as a reliable biomarker to assess disease severity and clinical outcome in Guillain-Barre syndrome. Cerebrospinal fluid total protein is a poor predictor of the prognosis and severity of Guillain-Barre syndrome.

Key Words: *Guillain-Barre syndrome (GBS), Clinical outcome, Cerebrospinal fluid total protein (CSF-TP), Neutrophil-to-lymphocytic ratio (NLR), Prognostic biomarker.*

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INTRODUCTION

Guillain-Barre syndrome is an immune-mediated peripheral nerve system disorder characterised by symmetrical flaccid paralysis with areflexia that typically reaches its peak severity within four weeks.[1] Intravenous immunoglobulin and plasma exchange were found to be excellent treatment options for Guillain-Barre syndrome and are currently used frequently in clinical settings. These treatments reduce mortality rates significantly and allow the majority of patients to fully recover functionally or have minor deficits.[2]

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The reported mortality rate for Guillain-Barre syndrome in the general population ranges from 0.89 to 1.89 cases (median 1.11) per 100,000 individuals, making Guillain-Barre syndrome currently the most prevalent cause of acute flaccid paralysis. Patients with a poor prognosis may benefit from additional treatment if they are identified early when nerve degeneration may be reversible and treatment is most effective.[3] The following factors may adversely influence the outcome and prognosis: older age (>50–60 years), history of diarrheal illness with *Campylobacter jejuni* or Cytomegalovirus infection, rapid onset and progression within less than 7 days, need for mechanical ventilation in the early stages of the disease, dependence on a ventilator, and significantly decreased compound motor action potential amplitudes below 20% of the lower normal limit.[4] The wide range of clinical symptoms can mislead a diagnosis, and the failure of nerve conduction studies and CSF analysis to detect abnormalities at an early stage of the disease have rendered them ineffective as reliable prognostic markers.[5]

Predicting the progression and severity of Guillain-Barre syndrome and anticipating therapy responses are major challenges due to the lack of accurate prognostic biomarkers. Although several biomarkers related to infection, immunity, blood-brain barrier, cerebrospinal fluid, and peripheral damage are being studied, they are not widely available or cost-effective.[6] According to the available literature, a high serum neutrophil-to-lymphocyte ratio is considered an accurate marker of disease severity and poor outcomes in several neurological conditions.[7] Neutrophils are part of innate immunity, and lymphocyte counts are believed to indicate the host's immunological response.[8] In view of the immune-mediated pathophysiology of Guillain-Barre syndrome, serum neutrophil-to-lymphocyte ratio may be regarded as a basic, rapid, and cost-effective marker of inflammation in Guillain-Barre syndrome patients and may be used as an accurate marker of prognosis for patients with Guillain-Barre syndrome and their response to plasmapheresis.[9] Cerebrospinal fluid total protein levels have been found to be elevated in patients with Guillain-Barre syndrome and can provide insight into the pathogenesis of Guillain-Barre syndrome subtypes. Therefore, cerebrospinal fluid total protein can serve as a significant prognostic indicator for patients with Guillain-Barre syndrome.[10]

After an extensive review of the relevant literature, the authors failed to find any published prospective study that investigated this particular aspect. The findings of this study may help in the development of reliable biomarkers for assessment of Guillain-Barre syndrome prognosis and early intervention, which may ultimately improve patient outcome. Therefore, the aim of the current study was to evaluate the clinical prognostic value of CSF total protein and serum neutrophil-to-lymphocyte ratio, as well as their associations with the clinical and electrophysiological subtypes of Guillain-Barre syndrome.

METHODOLOGY

A cross-sectional study was conducted at the Department of Neurology of Mayo Hospital, and King Edward Medical University, Lahore, after approval from the institutional review board of King Edward Medical University (letter no. 90/RC/KEMU, dated 31 October 2022). Patients of both genders, aged 12 to 70 years, who met the Brighton's criteria for Guillain-Barre syndrome were eligible to participate in the study. The criteria included: a monophasic course with a 12-28-day period between onset and nadir; bilateral symmetrical flaccid weakness of limbs; reduced or absent deep tendon reflexes in weak limbs; lack of an alternative diagnosis for weakness; and a CSF cell count of 50ml or less. All patients below 12 years of age, those who refused lumbar puncture or consent to participate in the research, and those with alternative causes of acute flaccid paresis were excluded from the study. The study employed a simple, convenient sampling method, and the sample size of 46 patients was calculated by taking a confidence level of 95%, an absolute precision of 10%, and the expected percentage of primary demyelinating variants of Guillain-Barre syndrome as 54.67%. The formula for approximating a proportion was utilised to obtain this estimation. All the subjects who met the inclusion criteria were included and followed during their hospitalisation period. Written informed consent was obtained from all recruited patients.

Data were collected on demographic information, onset of illness, time elapsed before hospitalisation, history of fever and infective illness, clinical symptoms and signs, including sphincter involvement, autonomic disturbances, sensory or motor complaints, facial weakness, ocular or bulbar involvement, examination findings, such as muscle strength using the Medical Research Council (MRC) sum score, and disability level using the modified Hughes disability score at admission and discharge. Nerve conduction studies were conducted at the time of hospital admission to classify the various types of Guillain-Barre syndrome.

Neutrophil and lymphocyte counts were obtained from venous blood serum samples collected on Day 1 of the hospital admission. Serum neutrophil-to-lymphocyte ratios (NLRs) of 3 or above were categorised as mild (NLR = 3-6), moderate (NLR = 7-9), or severe (NLR >9). Lumbar puncture was performed on the first day of admission to measure CSF total protein; levels more than 45 mg/dl were considered high. Based on the manifestations and involvement of motor or sensory nerves, different variants of Guillain-Barre syndrome were categorised into acute motor axonal neuropathy (AMAN), acute sensory axonal neuropathy (ASAN), acute motor and sensory axonal neuropathy (AMSAN), acute inflammatory demyelinating polyneuropathy (AIDP), and Miller-Fisher syndrome (MFS).

The clinical outcomes were assessed using Erasmus GBS respiratory insufficiency score (EGRIS) and the modified Hughes disability score. The EGRIS, which ranged from 0 to 7, determined the need for mechanical ventilation based on the Medical Research Council sum score, days between weakness onset and hospitalisation, and facial or bulbar involvement. The MRC sum score was defined as the total of the MRC scores of six various groups of muscles assessed bilaterally. The MRC sum score ranging from 0 (indicating tetraplegia) to 60 (indicating normal strength), categorised into three levels: 0-35 (quadriplegia to severe quadriparesis), 36-48 (moderate quadriparesis), and 49-60 (normal strength). The EGRIS score was further classified into low risk (0–2), moderate risk (3–4), and high risk (5-7) for mechanical ventilation. The modified Hughes disability score categorised functional disability at admission from 0 to 6, indicating normal function, minor symptoms, independent walking up to 5 metres, walking with assistance, being bedridden, respiratory failure, and death.

Patients were categorised into two groups based on the modified Hughes disability score: 0–2 and 3 on the first day of hospital admission and following plasmapheresis. Poor clinical outcome was defined as the inability to walk 5 metres independently (Modified Hughes disability score of 3 or higher) and a high risk of mechanical ventilation (EGRIS score of 5 or higher).

Data analysis was performed using SPSS version 20. The qualitative variables such as gender, clinical features (facial paresis, bulbar palsy, ocular and sphincteric involvement), autonomic dysfunction, and nerve conduction study findings were presented as n (number) and % (percentage). The quantitative variables, including time to onset from presentation, age, EGRIS score, modified Hughes disability score, CSF-TP, and serum NLR, were expressed as mean and standard deviation. The correlation between mean CSF-total protein, serum neutrophil-to-lymphocyte ratio, EGRIS score for mechanical ventilation, and modified Hughes disability score at discharge was assessed using Spearman's coefficient of analysis. A p-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 46 individuals with Guillain-Barre syndrome were included in this research. Their clinical and biochemical characteristics are summarised in Table I. Among the 46 patients, 44 (95.7%) had abnormal nerve conduction studies, whereas 2 (4.34%) had normal findings. Patients were categorised according to their electrophysiological findings into the following variants: AIDP (14 cases, 32%), AMAN (22 cases, 50%), AMSAN (4 cases, 9.1%), ASAN (2 cases, 4.6%), and MFS (2 cases, 4.6%).

The mean ± SD of CSF-TP was higher for the demyelinating variant (218 ± 136 mg/dl) than the axonal (86 ± 56 mg/dl) and MFS (34 ± 21 mg/dl) variants. Axonal variants had a higher mean NLR (5.29 ± 4.38) than demyelinating (4.71 ± 3.4) and MFS (3 ± 2.828) variants. Furthermore, the correlation analysis revealed that serum NLR had a positive correlation with both the modified Hughes disability score ($r = 0.790$, $p = 0.001$) and the EGRIS score ($r = 0.936$, $p = 0.002$). However, CSF-TP did not show a significant correlation with modified Hughes disability score of 4-6 ($r = 0.020$, $p = 0.117$) at discharge or the EGRIS score ($r = 0.155$, $p = 0.302$) for mechanical ventilation, as shown in Table II.

DISCUSSION

GBS is an acute inflammatory polyradiculoneuropathy with subtypes such as acute motor axonal neuropathy, acute inflammatory demyelinating polyradiculoneuropathy, and acute motor and sensory axonal neuropathy. AIDP is the most common form of GBS, whereas AMAN was the most prevalent variant in the authors' study. Despite the more recent advancements, it is still unclear whether axonal GBS is more common in Asia than in Europe or North America. In addition to acute flaccid paralysis, atypical presentations, including cranial nerve palsy, have also been documented.[10] Of them, facial palsy is the most prevalent (24–60%) and has been found in 47% of study participants. 60 percent of patients had a prior history of illness, most commonly a respiratory tract infection. Autonomic dysfunction was reported by 17% of patients.

This research analysed the potential correlation between serum neutrophil-to-lymphocyte ratio, cerebrospinal fluid total protein, and clinical outcomes of GBS variants. The present study found that demyelinating variants had a higher mean cerebrospinal fluid total protein level than axonal variants and Miller-Fisher syndrome. In addition, the study found that axonal variants had a higher mean serum neutrophil-to-lymphocyte ratio than demyelinating variants and Miller-Fisher syndrome. The pathophysiology of the disease can explain the higher CSF-TP levels in demyelinating variants. Demyelinating variants of GBS are characterised by an immune-mediated attack on the myelin sheath that surrounds the peripheral nerves. This leads to demyelination and damage to the nerve fibres, resulting in a breakdown of the blood-nerve barrier and an increase in the permeability of the blood-cerebrospinal fluid barrier. This, in turn, led to an increase in CSF-TP levels as proteins from the blood leak into the cerebrospinal fluid. Therefore, a higher CSF-TP level in demyelinating variants was consistent with the pathophysiology of the disease.[11]

Table I: Demographic and the clinical characteristics of study participants (n=46).

Comparison of Mean ± SD of CSF-TP with GBS variants		
GBS Variant	**CSF-TP (mean ± SD mg/dl)**	**NLR (mean ± SD)**
Demyelinating	218 ± 136	4.71 ± 3.4
Axonal	86 ± 56	5.29 ± 4.38
Miller Fischer syndrome (MFS)	34 ± 21	3 ± 2.828
Interpretation: Demyelinating variant has a higher mean CSF-TP compared to the axonal variant and MFS variant. Axonal variant has a higher mean NLR compared to the demyelinating variant and MFS variant.		
Correlation analysis between serum NLR and clinical scores		
Clinical score	**Correlation (r)**	**p-value**
Modified Hughes disability score	0.790	0.001
EGRIS score	0.936	0.002
Interpretation: Serum NLR shows a significant positive correlation with modified Hughes disability score. Serum NLR also exhibits a strong positive correlation with the EGRIS score.		
Correlation analysis between CSF-TP and clinical scores		
Modified Hughess disability score	0.020	0.117
EGRIS Score	0.155	0.302
Interpretation: CSF-TP does not show a significant correlation with modified Hughes disability score. CSF-TP also does not show a significant correlation with the EGRIS score.		

Table II: The comparison of CSF-TP and serum NLR with GBS variants and the correlation analysis between these variables and clinical scores.

Characteristic	Value
Age (years)	14-70
Mean (SD)	38.8 (16.6)
<50 years	30 (65.2)
≥50 years	16 (34.8)
Gender	
Male	30 (65.2%)
Female	16 (34.8%)
Season	
Summer	25 (54.3%)
Winter	21 (45.7%)
Onset of symptoms (days)	1-28
Mean (SD)	8.46 (6.3)
Preceding history of infection	28 (60.9%)
No history	18 (39.1%)
Respiratory infection	15 (32.6%)
Gastrointestinal illness	10 (21.7%)
Chickenpox	1 (2.1%)
COVID-19	2 (4.2%)
Facial weakness	22 (47.82%)
Unilateral facial weakness	9 (19.6%)
Bilateral facial weakness	13 (28.8%)
Bulbar Palsy	14 (30%)
Ophthalmoplegia	5 (10.8%)
Autonomic disturbances	8 (17.39%)
Hypotension	5 (10%)
Uncontrolled Hypertension	2 (4.4%)
Resting tachycardia	1 (2.1%)
Sphincteric involvement	None
Nosocomial infections	6 (13%)
Urinary tract infection	2 (6.52%)
Respiratory tract infection	2 (4.34%)
Line sepsis	2 (4.34%)
CSF analysis on average (days)	7
Mean (SD)	5.52(4.6)
CSF total protein level (mg/dl)	121 (109)
Serum neutrophil-to-lymphocyte ratio (average)	18.2
Mean (SD)	4.87 (3.96)
NLR <3(Normal)	12 (26)
NLR 3-6 (Mild)	21 (41.8)
NLR 7-9 (Moderate)	5 (10.8)
NLR >9 (Severe)	8 (17.4)
MRC sum score at admission Mean (SD)	37.8 (4.5)
Moderate (36-48)	40 (87)
Severe (0-35)	3(6.5)
Normal (49-60)	3 (6.5)
Modified Hughes disability score at admission;	3.6(0.6)
Mean (SD)	3 (6.5)
0-2	43 (93.4)
≥3	
EGRIS score; Mean (SD)	3.46(1.37)
Low risk (0-2)	10(21.7)
Moderate risk (3-4)	28(60.9)
High risk (5-7)	08((17.4)
Modified Hughes disability score at discharge;	2.93(1.09)
Mean (SD)	27(60)
0-2	18(40)
≥3	
Patients requiring mechanical ventilation	4 (8.7%)
Death	1 (2.2%)

A study by Wakerley *et al.* found that CSF-TP levels were higher in demyelinating variants of GBS than in axonal variants.[12] This was consistent with the finding of the current study that demyelinating variants of GBS had a higher mean CSF-TP level than axonal variants and Miller-Fisher syndrome.

On the other hand, the higher NLR levels in axonal variants can be explained by the role of neutrophils and lymphocytes in the immune response to nerve damage. Axonal variants of GBS are characterised by an immune-mediated attack on the axons of the peripheral nerves. This leads to axonal degeneration and damage to the nerve fibres, resulting in the release of axoplasmic proteins and activation of the innate immune system. Neutrophils are known to play a role in the early stages of the immune response to nerve damage, while lymphocytes are involved in the later stages of the immune response. Therefore, a higher NLR in axonal variants may reflect the early immune response to nerve damage, which is characterised by the influx of neutrophils.[13] The study found that the neutrophil-to-lymphocyte ratio was positively correlated with Hughes disability score and EGRIS score. The findings of this study were consistent with the previous studies that reported a correlation between serum neutrophil--to-lymphocyte ratio and disease severity in various neurological conditions. For instance, a previous study found that the serum neutrophil-to-lymphocyte ratio was a potential prognostic marker in patients with acute ischaemic stroke.[14] A study by Wang *et al.* concluded that patients of COVID-19 with a high NLR value had a significantly higher risk of respiratory failure and longer hospital stays.[15] Another study by Jahan *et al.* also aimed to evaluate the predictive value of NLR in GBS patients. They found that patients with a higher NLR value had a longer hospital stay and a higher risk of mechanical ventilation.[16]

However, this research also provided an evidence that total protein in the CSF fluid may not be a valid indicator of the severity of the illness in GBS patients. The weak association between cerebrospinal fluid total proteins and clinical scores, including EGRIS and modified Hughes disability score, implied that alternative biomarkers could be more accurate in forecasting disease outcomes. Although cerebrospinal fluid total protein levels may be higher in demyelinating variants, they may not be useful in guiding the treatment decisions or predicting the clinical outcomes. Contrary to this, a previous study found that cerebrospinal fluid protein levels were significantly associated with disease severity and functional outcomes in GBS patients.[17] However, there were other studies that reported conflicting results regarding the correlation of cerebrospinal fluid total protein with disease severity in GBS. For instance, a study by van den Berg *et al.* reported that cerebrospinal fluid protein levels were not significantly associated with disease severity or the clinical outcomes in GBS patients.[18] Several factors can influence the CSF-TP levels, including the timing of the LP and the stage of the disease. Elevated CSF protein levels were found in approxi-

mately 50% of patients in the first 3 days after the onset of weakness, which increased to 80% after the first week.[19] In contrast, CSF-TP levels could be lower as the illness progresses and the blood-cerebrospinal fluid barrier became less permeable when the blood-nerve barrier was restored, owing to the fact that the timing of the lumbar puncture might potentially affect the levels of CSF-TP. Therefore, in GBS patients, CSF-TP levels may not be a reliable indicator of the prognosis or severity of the illness.

The research had several limitations that need to be taken into account. First, the research was conducted at just one site with a relatively small sample size. Therefore, in order to generalise the results, more extensive and diverse populations of patients must be included in subsequent studies. Additionally, the pathophysiological mechanisms that could be responsible for the observed correlations between these biomarkers and disease outcomes were not investigated in the research. Consequently, further studies are required to investigate the underlying pathophysiological processes and the potential application of these bioindicators in order to guide the treatment decisions.

CONCLUSION

Given the results obtained from the study, it can be concluded that the neutrophil-to-lymphocyte ratio can be regarded as an accurate biomarker for both the assessment of prognosis and the severity of Guillain-Barré Syndrome (GBS). Conversely, cerebrospinal fluid total protein is a less reliable indicator of the severity and prognosis of GBS. This study suggested that physicians should consider the neutrophil-to--lymphocyte ratio, as it could potentially guide treatment decisions and help improve the clinical outcomes. Furthermore, this research opened avenues to investigate the potential application of these biomarkers in the future in order to assess the long-term prognosis of GBS.

ETHICAL APPROVAL:

This study was approved by the Institutional Review Board of King Edward Medical University in Lahore, Pakistan, and complied with all relevant ethical guidelines.

PATIENTS' CONSENT:

The participants gave informed consent, and their anonymity and confidentiality was maintained throughout the duration of the study. The information gathered will only be used for this study and will not be shared with any unauthorised individuals or organisations.

COMPETING INTEREST:

The authors declared that there was no conflict of interest regarding the publication of this paper. The research had been conducted in an objective and unbiased manner, and no financial or personal relationships influenced the design, execution, or interpretation of the study. The authors had no affiliations with any organisation or entity with a financial interest in the subject matter discussed in the manuscript.

AUTHORS' CONTRIBUTION:

SB: Conception and design of the study, data analysis and interpretation, and critical revision of the manuscript for key intellectual content.
AN: Data acquisition, data analysis, manuscript drafting, editing and revision.
AN: Acquisition, analysis and interpretation of data, and critical revision of manuscript for final approval.
AN: Conception and design of the study, interpretation of data, revision and approval for final submission.
MZ: Analysis and interpretation of data, and critical revision for the final approval.
All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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