Retrospective and Prospective Study of Serum CRP, PLR, NLR, Nerve Conduction Study, Clinical Disability Score and Lumbar Puncture Analysis in Guillain Barre Syndrome

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Abstract:
Background: Guillain-Barre syndrome (GBS) is a severe autoimmune condition in which the body's immune system targets healthy nerve cells in the peripheral nervous system. This results in polyradiculoneuropathy, causing symptoms such as weakness, numbness, and tingling sensations, which may progress to paralysis. Inflammatory responses triggered by GBS can lead to elevated levels of C-reactive protein (CRP) in the body.
Objective: The objective of this research was to examine the correlation between inflammatory markers, including CRP, Neutrophil to lymphocyte ratio (NLR), and Platelet to lymphocyte ratio (PLR), and the clinical severity and electrophysiological results from nerve conduction studies in individuals diagnosed with GBS. **Methodology:** This study included 50 patients (33 male,17 female) who met the clinical criteria for GBS and were between10 to 70 years of age with a mean of 33.46 ± 12.25 years within the first 2 weeks of onset of illness were enrolled. Apart from the routine examination all the subjects underwent evaluation for the inflammatory markers enumerated, nerve conduction studies and assessment of their clinical severity. **Results:** The study group comprised 50 individuals with a mean age 36.28 ± 23.75 years (n = 33 males, 66%), with a male-to-female ratio of 1.9.The most prevalent form of nerve conduction abnormality was sensorimotor axonopathy, which affected 34% (17) of the patients. The severity of the disease was reflected in the elevated levels of serum CRP, NLR, and PLR. In addition to inflammatory markers, significant involvement of cranial nerves was strongly linked to severe disability in GBS patients. **Conclusions:** This study demonstrated that higher levels of serum CRP, NLR, and PLR are linked with several factors in GBS patients, including gastroenteritis, craniobulbar involvement, disability score, and the absence of motor and sensory nerve responses. These in turn have a negative impact on the clinical severity in GBS patients. Therefore, these surrogate inflammation markers can be used to prognosticate in subjects suffering from GBS.

Keywords: Guillain-Barre syndrome, C-reactive protein, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Hughes disability score.

Introduction

Guillain–Barre syndrome (GBS) is an autoimmune condition affecting the peripheral nervous system, typically occurs following an infection and is characterised by a fast advancing paralysis accompanied by sensory and autonomic dysfunction.[1] Each year, approximately 1–2 individuals per 100,000 population are diagnosed with GBS.[2] Its incidence increases with age with a predilection for male sex.[3] Substantial evidence supports an infectious origin for GBS, with its pathogenesis likely involving the generation of autoantibodies or the attraction of inflammatory cells to the myelin sheath surface or the node of Ranvier, leading to temporary disruption of signal transmission.[4,5]

Several types of GBS are distinguished according to their underlying pathology, clinical manifestations, and neurophysiological characteristics.[6]Although the condition's acute phase exhibits a 4% mortality rate, 14% of individuals who survive endure substantial impairment after one year[7].Several factors like advanced age, higher levels of impairment or muscle weakness upon hospital admission, a brief period between the onset of symptoms and hospitalisation, prior episodes of diarrhoea, dysfunction of the autonomic nervous system, the requirement for mechanical ventilation (MV), and the absence or reduced amplitude of compound muscle action potential (CMAP) have been consistently recognised as indicators of poor prognosis in Guillain-Barré syndrome. [7-10] Approximately 40% of the survivors suffer from weakness, persistent pain and needprofessional intervention.As a result, there is growing interest in identifying biomarkers that can predict the prognosis and clinical outcomes of GBS.Research has shown that patients with GBS with a poor prognosis often exhibit altered levels of various biomarkers such as reduced concentrations of albumin (an acute phase protein), bilirubin, uric acid (UA), thyroid-stimulating hormone (TSH), sodium (hyponatremia) and higher levels of specific novel inflammatory indicators, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and C-reactive protein (CRP), increased liver enzymes as well as cerebrospinal fluid (CSF) proteins, have been linked to unfavourable outcomes in GBS.[11-15]In the diagnostic process and categorisation, electrophysiological techniques, including nerve conduction studies (NCS), play a crucial role.[16]

Distinct diagnostic criteria have been proposed for assessing acute inflammatory demyelinating neuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN). To accurately diagnose Guillain-Barré syndrome subtypes, understand the underlying pathophysiological processes, and evaluate prognosis, it is crucial to conduct repeated nerve conduction studies.[17] Therefore, this study aimed to evaluate the association between CRP, LNR, PLR, and clinical severity in patients with GBS using the GBS disability score (GDS).

Materials and methods

A retrospective and prospective study was conducted in the Department of Neurology at JSSAHER between the period ofJanuary 2019 to December2023. Using Brighton's Criteria, 50 participants (33 male and 17 female) meeting the inclusion and exclusion requirements were chosen for the study ().SUBJECTS EXCLUDED included patients who had diseases or treatments affecting nerve conduction studies,concomitant inflammatory disease whether infectious or non-infectious, within the last two weeks, tumours, metastases, and immunomodulatory therapy within the last six months,history of surgery or significant trauma within the last two weeks, patients with system failure (respiratory, hepatic,renal, cardiac), pregnant females and those with severe psychiatric illnesses .

The data was collected and recorded as per the proforma designed for this study. Hughes and Rees scale was adopted for assessment of clinical GBS severity [18]. Laboratory investigations includingcomplete blood count (CBC), erythrocyte sedimentation rate (ESR), blood glucose level, liver function tests (LFT) and renal functiontest, results of quantitative evaluation of serum CRP, NLR, and PLR and ECG were performed.Nerve conduction studies (NCSs) which were done with an EMG machine (Nihon kohden, Model number DC-940BK) within 2 weeks of onset of symptoms were collected.

Study Assessments of end points: Correlation between Serum CRP, NLR, PLR, Clinical disability score, NCS, and LP analysis with GBS severity was analysed.

Statistical analysis

The obtained data were tabulated and analysed using the Statistical Package of Social Science software (SPSS version 20, IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and median. Categorical variables were compared using the chi-squared test. An ANOVA test was applied to evaluate the relationship between serum CRP, NLR, and PLR levels as well as the clinical severity of GBS using the Hughes disability scale. Differences were considered statistically significant if the p-value was ≤ 0.05.

Results

The age and sex distribution of the subjects included in this study is given in Table 1. 35 subjects (70%) had no sensory symptoms and 29(58%) had no Cranial Nerve involvement.

The CRPlevels varied between 0.26 and 165.00, with a mean of 18.97 ±31.36. The NLR ranged from 0.710 to 10.150, with a mean of 3.31 ± 2.32. The PLR varied from 58.06 to 416.60, with a mean of 146.23 ± 65.55. (Table 1)

Table 1: Distribution of the patients based on mean age, age groups, gender, sensory symptoms, cranial nerve involvement and mean CRP and mean NLR

Age	**n**	**Minimum**	**Maximum**	**Mean ± S.D**
	50	2.0	85.0	36.28 ± 23.75
Parameters				**n (%)**
Age Groups (n=50)		< 10 yrs		9 (18%)
		11 to 20 yrs		8 (16%)
		21 to 30 yrs		8 (16%)
		31 to 40 yrs		2 (4%)
		41 to 50 yrs		6 (12%)
		51 to 60 yrs		8 (16%)
		61 to 70 yrs		4 (8%)
		> 70 yrs		5 (10%)
Gender (n=50)		Females		17 (34%)
		Males		33 (66%)
Sensory symptom (n=50)		Absent		35 (70%)
		Present		15 (30%)
		Total		50 (100%)
Cranial Nerve Involvement (n=50)		Absent		29 (58%)
		Present		21 (42%)

	n	**Minimum**	**Maximum**	**Mean**	**SD**
CRP	50	0.26	165.00	18.97	31.36
NLR	50	0.710	10.150	3.31	2.32
PLR	50	58.06	416.60	146.23	65.55

The most frequent type of nerve conduction observed was sensorimotor axonopathy, affecting 34% of patients. A prevalent condition amongst 32% of the patients was sensorimotor demyelinating neuropathy. Motor demyelinating neuropathy occurred in 30%, while motor axonopathy was the least prevalent, found in only 4% of the patients. Among 50 patients, 84% had normal lumbar puncture analysis – (LPA) cell counts, while the remaining 16% of patients showed high LPA cell counts. The Clinical Disability Scores showed that the majority (42%) had a score of 3.0, indicating a moderate level of disability, 36% had a score of 4.0, representing a slightly higher level of disability, followed by 14% and 8% of the patients had a disability score of 5 and 6 respectively.

We compared CRP, NLR, and PLR levels across different Hughes clinical disability scores in our group of 50 patients. The grouphaving a score of 3 (21 patients) showed CRP levels ranging from 0.63 to 86.18 (17.52 ± 26.18). Those patients having a score of 4

(18 patients) had CRP levels ranging from 0.26 to 54.07 (9.13 ± 15.54). Patients scoring 5 (7 patients) had CRP levels between 3.00 and 90.49 (26.37 ± 31.98). The group having a score of 6 (4 patients) had levels ranging from 1.45 to 165.00 (57.94 ± 73.01).
Among 21 patients having a disability score of 3, the NLR levels varied from 0.85 to 5.10 (2.67 ± 1.15). In 18 patients having a score of 4, the NLR levels ranged from 0.71 to 8.7 (2.68 ± 2.021). In 7 patients having a score of 5, NLR levels were between 2.80 and 8.30 (5.25 ± 2.38). And in the group of 4 patients having a score of 6 had NLR levels ranging from 1.79 to 10.15, (6.10 ± 4.52).
The PLR levels when compared to Hughes clinical disability score showed the following findings. In the case of score 3, the Hughes clinical disability score varied from 59.18 to 187.96 (117.41 ± 31.14). For score 4, the scores ranged from 58.06 to 291.60 (137.92 ± 57.55). For score 5, the range ranged from 153.69 to 416.60 (220.01 ± 90.89). For Score 6, the range was 164.16 to 308.89 (205.82 ± 69.00). (Table 2)

Table 2: Distribution of the patients based on nerve conduction, LPA cell count, Hughes disability score, CRP, NLR and PLR (Hughes clinical disability score)

Parameters							**n (%)**
Nerve conduction study (n=50)			Motor axonopathy				2 (4%)
			Motor demyelinating neuropathy				15 (30%)
			Sensorimotor axonopathy				17 (34%)
			Sensorimotor demyelinating neuropathy				16 (32%)
LPA- Cell Count (n=50)			High				8 (16%)
			Normal				42 (84%)
Hughes clinical disability score (n=50)			Score 3.0				21 (42%)
			Score 4.0				18 (36%)
			Score 5.0				7 (14%)
			Score 6.0				4 (8%)
Hughes clinical disability score		**n**	**Minimum**	**Maximum**	**Mean**	**SD**	**p value**
CRP	Score 3	21	0.63	86.18	17.52	26.18	0.033*
	Score 4	18	0.26	54.07	9.13	15.54	
	Score 5	7	3.00	90.49	26.37	31.98	
	Score 6	4	1.45	165.00	57.94	73.01	
NLR	Score 3	21	0.850	5.100	2.67	1.15	0.002*
	Score 4	18	0.710	8.700	2.68	2.01	

	Score 5	7	2.800	8.300	5.25	2.38	
	Score 6	4	1.790	10.150	6.10	4.52	
PLR	Score 3	21	59.18	187.96	117.41	31.14	0.001*
	Score 4	18	58.06	291.60	137.92	57.55	
	Score 5	7	153.69	416.60	220.01	90.89	
	Score 6	4	164.16	308.89	205.82	69.00	

***Significant**

There was significant association between CRP and Hughes Clinical Disability score (p=0.033).There was also statistically significant association between NLR and Hughes Clinical Disability score (p=0.002).Even association between PLR and Hughes clinical Disability score was statistically significant (p=0.001).The Chi-square test revealed no significant association between nerve conduction and Hughes Clinical Disability Score ($\chi 2$=7.48; p=0.587). The results of the chi-square test indicated that there was no statistically significant association between LPA Cell count and Hughes Clinical Disability Score ($\chi 2$= 4.82; p=0.185).The LPA protein levels ranged from a minimum of 47.70 to a maximum of 398.40 (107.47 ± 77.73). (Table 3)

Table 3: Association of nerve conduction with Hughes clinical disability score, LPA cell count with Hughes clinical disability score, mean LPA-protein of the patients

Nerve Conduction	**Hughes clinical disability score (n / %)**				
	Score 3	**Score 4**	**Score 5**	**Score 6**	**Total**
Motor axonopathy	1 (4.8)	1 (5.6%)	0 (0.0%)	0 (0.0%)	2 (4.0%)
Motor demyelinating neuropathy	5 (23.8%)	4 (22.2%)	5 (71.4%)	1 (25.0%)	15 (30.0%)
Sensorimotor axonopathy	8 (38.1%)	7 (38.9%)	1 (14.3%)	1 (25.0%)	17 (34.0%)
Sensorimotor demyelinating neuropathy	7 (33.3%)	6 (33.3%)	1 (14.3%)	2 (50.0%)	16 (32.0%)
Total	21 (100.0%)	18 (100.0%)	7 (100.0%)	4 (100.0%)	50 (100.0%)
Chi-square value- 7.48, p value-0.587					
LPA- Cell Count	**Hughes clinical disability score (n / %)**				**Total**
	Score 3	**Score 4**	**Score 5**	**Score 6**	
High	3 (14.3%)	3 (16.7%)	0 (0.0%)	2 (50.0%)	8 (16.0%)
Normal	18 (85.7%)	15 (83.3%)	7 (100.0%)	2 (50.0%)	42 (84.0%)
Total	21 (100.0%)	18 (100.0%)	7 (100.0%)	4 (100.0%)	50 (100.0%)

Chi-square value- 4.82, p value-0.185					
LPA- Protein	**n**	**Minimum**	**Maximum**	**Mean**	**SD**
	50	47.70	398.40	107.47	77.730

Discussion

Despite its low mortality rate, GBS has the potential to induce severe functional limitations.Various clinical and laboratory indicators can be used to predict the extent of disability. Consequently, identifying factors that could lead to severe impairment early on may aid in reducing morbidity as well as mortality rates, and enhance the overall disease management.Nevertheless, limited research has been carried out to evaluate GBS severity and the factors influencing its severity.Our study revealed that various factors were significantly linked with increased disability in Guillain-Barré syndrome. These included the patient's age, prior infections, requirement for intensive care and mechanical ventilation, development of complications, and elevated levels of certain blood markers (CRP, NLR, and PLR) during the acute phase of the illness.

The International Guillain-Barré Syndrome Outcome Study reported that the median age of patients with GBS was 51 years, with a 1.5 ratio of males to females and the higher percentage of patients fell within the 50-69 year age bracket.[19] Our study revealed that the mean age of the of the subjects was 36 years, with a gender distribution showing nearly twice as many males as females (ratio 1.9).In contrast to other autoimmune conditions, GBS exhibits a higher prevalence among men compared to women, and its incidence rises by 20% for each decade increase in age.[3] Additionally, numerous studies on GBS outcomes have demonstrated that advanced age correlates with poorer prognoses. [8, 19, 20]

During neurological assessment, 29 patients (58%) exhibited cranial nerves involvement, which was linked to early-onset disability.Gorgulu et al., reported that 31.4% of their patients had cranial nerve involvement.[21] The involvement of cranial nerve was high in number in our study compared to Gorgulu et al. study.[21] Tunc A. reported that a comparable percentage (27%) of GBS patients exhibited cranial nerve involvement, which was determined to have a notable correlation with more severe initial disability. [10] Verma et al. examined a cohort where 30% were GBS patients and their findings indicated thatcranial nerves involvement was linked to the necessity of MV. However, this association did not reach statistical significance when subjected to multivariate analysis. [9] Moreover, a high incidence of cranial nerve involvement is observed in patient with GBS requiring MV,[12] which is closely linked with the immediate prognosis of any severe illness.[7]

Complications related to treatment or autonomic dysfunction are commonly seen in GBS, with cardiovascular issues being the most common which stem from autonomic dysfunction, affect approximately two-thirds of GBS patients.[21,22] Consequently, it is

very important for the attending physician to identify and address complications effectively, thereby reducing the morbidity and mortality risk in GBS patients.[23]

In our study, we employed the Hughes disability scale to determine the clinical severity of GBS.The majority of the patients(42%) had a score of 3.0, indicating a moderate level of disability. These findings aligned with the results reported by Parmar et al., whose study revealed that the vast majority (83.7%) of their Guillain-Barré syndrome patients were classified as grade 4.[24]

Research has established that inflammatory process are essential in the initiation and advancement of GBS.[9, 25,26] Our study demonstrated that GBS patients exhibited elevated levels of plasma CRP, NLR, and PLR, which are recognised inflammatory indicators. These parameters showed a significant association with more severe initial disability, a finding that aligns with observations from previous investigations.[10,21,27,28] Research has shown that autoimmune disorders, like GBS, can trigger an increase in inflammation, which may lead to higher levels of CRP production. Even though CRP response lacks specificity in disease diagnosis, increased levels can play a critical role in determining the prognosis and guiding the clinical management of the condition.Conversely, certain research has emphasised the significance of NLR and PLR as novel biomarker for detecting inflammation.[29-32] Bercianoet al. demonstrated demyelination in spinal root sections exclusively associated with macrophages, alongside the presence of T lymphocytes and neutrophil leukocytes.[33] This was believed to enhance the role of neutrophils and lymphocytes in the development of GBS pathogenesis.[34] A study conducted by Ozdemir identified the admission NLR as a crucial biomarker for AIDP.[34] Vaishvani et al. observed elevated baseline CRP levels in individuals with GBS; however, there remains a paucity of research regarding the relationship between GBS and CRP.[35]

Serum CRP, NLR, and PLR were significantly associated with disability scores and absent motor and sensory nerve responses. However, the nerve conduction assessment and LPA cell counts showed a significant correlation with the disability score. Results of our study aligned with those reported by Rajabally and Uncini, who identified several factors linked to a poor prognosis, including a higher Guillain-Barré syndrome disability score at the two-week mark, a history of diarrhoeal illness prior to onset, the manifestation of faciobulbar palsy, the requirement for mechanical ventilation, reduced CMAP amplitude, and the absence of motor responses.Furthermore, Corredor et al. examined the factors influencing motor recovery following GBS in children using univariate analysis. Their findings revealed that impairment of cranial nerves, the requirement for ventilatory support, the manifestation of quadriplegia, and unresponsive motor nerves were linked to a prolonged period of motor function restoration.A study by Walgaard et al. examined factors influencing GBS prognosis and found that advancing age, antecedent diarrhoea, and reduced Medical Research Council (MRC) sum scores were linked to poorer outcomes after the initial four

weeks.[8] Nevertheless, Tunc et al. discovered that preceding events showed no correlation with low HDS scores.

Research indicates elevated levels of these biomarkers in various neurological conditions, including multiple sclerosis, stroke, and Becket's disease. [36-38] The possibility of pure macrophage-associated demyelination in spinal root sections was evaluated by identifying the presence of neutrophils, leukocytes, and T lymphocytes. [33] This assessment underscores the significance of lymphocytes and neutrophils in GBS pathogenesis.In line with this, research has indicated that NLR and PLR serve as potential inflammatory markers in GBS patients [28,39], potentially aiding in predicting disease outcomes [40], as demonstrated in our investigation.Nevertheless, our research had some limitations. The primary limitation was the absence of a healthy control group. Additionally, the study was carried out at a single centre with a less number of participants, encompassing various GBS subtypes. Not all patients received standardised treatment, and their follow-up period was restricted. The study did not examine other pro-inflammatory cytokines such as TNF-α, IFN-g, IL-1b and IL-6. Furthermore, we did not perform serial nerve conduction studies or analyse these inflammatory markers over time.

Conclusion

Identifying the early-stage risk factors that may lead to severe impairment in GBS can assist healthcare professionals in developing appropriate treatment strategies.The study findings suggest that that CRP, NLR, and PLR demonstrate strong associations with the severity of the disease and disability scores. NLR, which has been extensively researched as a marker for GBS severity, could prove to be an effective indicator of disease intensity when used in combination with CRP and PRP. This study proposed that utilising multiple inflammatory biomarkers in conjunction could offer a valuable method for evaluating the clinical severity of GBS.

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