International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Evolving Therapeutic Paradigms and Biomarker-Driven Prognostication in Guillain-Barré Syndrome: A Comprehensive Multicenter Evaluation

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Abstract

Background: Guillain-Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy characterized by diverse clinical trajectories and complex pathophysiological mechanisms. Despite established immunomodulatory therapies such as plasma exchange and intravenous immunoglobulin (IVIg), morbidity and mortality remain substantial, necessitating refined prognostic biomarkers and optimized therapeutic protocols. Objectives: This study aims to evaluate the correlation between serum neurofilament light chain (sNfL) levels, anti-ganglioside antibody profiles, and long-term functional recovery in GBS patients, while comparing the therapeutic efficacy of contemporary immunotherapeutic regimens. Methods: A retrospective multicenter cohort of 248 confirmed GBS patients treated between January 2020 and December 2025 was analyzed. Clinical severity was assessed using the Erasmus GBS Outcome Score (EGOS) and the Hughes Functional Grade Scale. Serum biomarkers were quantified using single-molecule array (Simoa) technology at admission and day 14 post-treatment. Results: Elevated baseline sNfL levels strongly correlated with poorer 6-month functional outcomes (Spearman's rho = 0.74, $p < 0.001$). Patients presenting with axonal variants (AMAN/AMSAN) demonstrated significantly higher peak sNfL concentrations compared to those with acute inflammatory demyelinating polyneuropathy (AIDP). Combination therapy (IVIg followed by targeted neurorehabilitation) showed superior reduction in mechanical ventilation duration compared to IVIg monotherapy (mean reduction: 4.2 days, $p = 0.012$). Conclusion: Serum neurofilament light chain serves as a robust biomarker for axonal damage and functional prognosis in GBS. Integrating sNfL quantification with standard clinical grading scales enhances risk stratification and personalized therapeutic management.

Keywords: Guillain-Barré Syndrome; Neurofilament Light Chain; Intravenous Immunoglobulin; Biomarkers; Prognostication; Immunomodulation

1. Introduction

Guillain-Barré syndrome (GBS) represents the most common cause of acute neuromuscular paralysis worldwide, with an estimated global incidence of 1.1 to 1.8 per 100,000 persons annually. The condition is classically defined by rapidly progressive, symmetrical ascending limb weakness, hyporeflexia or areflexia, and variable autonomic dysfunction. Pathologically, GBS encompasses multiple clinical variants, predominantly acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor-sensory axonal neuropathy (AMSAN). While molecular mimicry following antecedent infections (such as Campylobacter jejuni, cytomegalovirus, and SARS-CoV-2) is well-established as the initiating trigger, the precise determinants of clinical severity and treatment responsiveness remain incompletely elucidated.

Current standard-of-care treatments—namely therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIg)—have significantly improved survival and reduced the time to motor recovery. However, approximately 20% of patients remain unable to walk independently at six months post-onset, and mortality rates persist between 3% and 7%, typically secondary to autonomic instability, respiratory failure, or secondary nosocomial infections. Furthermore, a subset of patients exhibits a poor response to initial IVIg or TPE courses, a phenomenon historically described as treatment-related fluctuation (TRF) or sheer therapeutic refractoriness.

Accurate early prognostication is paramount for clinical decision-making, patient counseling, and resource allocation. Traditional clinical scoring systems, such as the Erasmus GBS Outcome Scale (EGOS) and Modified Erasmus GBS Outcome Scale (mEGOS), rely heavily on age, antecedent diarrhea, and baseline Medical Research Council (MRC) sum scores. Although useful, these clinical models lack molecular precision. In recent years, neurofilament light chain (NfL)—a structural component of the axonal cytoskeleton released into the cerebrospinal fluid and peripheral blood following axonal injury—has emerged as a powerful fluid biomarker for neurodegeneration. This study investigates the prognostic utility of serum NfL (sNfL) alongside anti-ganglioside antibody profiling in a large multicenter cohort, evaluating their capacity to predict short- and long-term clinical trajectories.

2. Methods

2.1 Study Design and Patient Population

We conducted a retrospective analysis of prospectively collected data from a multicenter registry encompassing four tertiary care academic medical centers between January 2020 and December 2025. Inclusion criteria were: (1) fulfillment of the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for GBS; (2) hospital admission within 7 days of symptom onset; (3) complete clinical records including nerve conduction studies (NCS); and (4) availability of serum samples collected at baseline (admission) and day 14. Exclusion criteria included alternative diagnoses of neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), significant concurrent central nervous system disorders, or incomplete follow-up data at 6 months.

2.2 Clinical Assessments and Outcome Measures

Demographic data, antecedent infection history, clinical variant classification, and baseline disability grades were systematically recorded. Disease severity was evaluated using the Hughes Functional Grade Scale (ranging from 0 [healthy] to 6 [death]). The primary endpoint was functional independence, defined as a Hughes grade ≤ 2 at 6 months. Secondary endpoints included duration of mechanical ventilation, length of intensive care unit (ICU) stay, and occurrence of treatment-related fluctuations.

2.3 Biomarker Quantification

Serum samples were centrifuged within 60 minutes of collection, aliquoted, and stored at -80°C until biochemical analysis. Serum neurofilament light chain (sNfL) concentrations were measured using a high-sensitivity Single Molecule Array (Simoa) digital immunoassay platform (Quanterix, Billerica, MA). Laboratory personnel blinded to the clinical status and therapeutic assignment performed all assays in duplicate. Anti-ganglioside antibodies (anti-GM1, anti-GD1a, anti-GQ1b) were detected using standardized line immunoassay and enzyme-linked immunosorbent assay (ELISA) protocols.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Cohort (N = 248)

Characteristic	Overall Cohort (n=248)	AIDP Variant (n=162)	Axonal Variants (AMAN/AMSAN, n=86)
Age, years (mean ± SD)	51.4 ± 14.8	52.1 ± 14.2	50.0 ± 15.9
Male sex, n (%)	148 (59.7%)	98 (60.5%)	50 (58.1%)
Antecedent Diarrhea, n (%)	92 (37.1%)	42 (25.9%)	50 (58.1%)
Baseline Hughes Grade (median, IQR)	4 (3 - 5)	4 (3 - 4)	4 (3 - 5)
Mechanical Ventilation, n (%)	64 (25.8%)	36 (22.2%)	28 (32.6%)
Baseline sNfL, pg/mL (median, IQR)	84.2 (42.1 - 156.0)	62.5 (35.0 - 112.4)	138.6 (78.2 - 245.1)

3. Results

3.1 Clinical Subtypes and Biomarker Correlations

Among the 248 evaluated patients, 162 (65.3%) were classified as having acute inflammatory demyelinating polyneuropathy (AIDP), 72 (29.0%) with acute motor axonal neuropathy (AMAN), and 14 (5.6%) with acute motor-sensory axonal neuropathy (AMSAN). Antecedent gastrointestinal infections were significantly more frequent in patients with axonal variants compared to AIDP (58.1% vs. 25.9%, $p < 0.001$). Anti-GM1 or anti-GD1a antibodies were detected in 68 patients (27.4%) and showed robust association with the axonal subtype.

Serum neurofilament light chain (sNfL) levels measured at admission demonstrated profound elevation across all GBS cohorts compared to healthy reference intervals (< 15 pg/mL). Baseline sNfL levels were significantly higher in patients presenting with axonal variants (median 138.6 pg/mL) than in those with demyelinating disease (median 62.5 pg/mL, $p < 0.001$). Furthermore, admission sNfL strongly correlated with baseline Hughes Functional Grade (Spearman's rho = 0.68, $p < 0.001$) and MRC sum score (rho = -0.62, $p < 0.001$).

3.2 Prognostic Value of sNfL and Clinical Scores

At the 6-month follow-up evaluation, 184 patients (74.2%) achieved functional independence (Hughes grade ≤ 2). Univariate logistic regression identified age, baseline Hughes grade, mechanical ventilation

requirement, and admission sNfL concentration as significant predictors of poor functional outcome. Receiver operating characteristic (ROC) curve analysis evaluated the predictive performance of admission sNfL for 6-month functional dependence, yielding an area under the curve (AUC) of 0.84 (95% CI: 0.79 – 0.89), which was comparable to the Erasmus GBS Outcome Score (EGOS AUC = 0.82).

Table 2: Multivariate Logistic Regression Analysis for Predictors of 6-Month Functional Dependence (Hughes Grade > 2)

Variable	Odds Ratio (OR)	95% Confidence Interval	Wald Statistic	p-value
Age (per 10-year increase)	1.42	1.18 – 1.71	12.45	< 0.001
Baseline Hughes Grade (per grade)	2.15	1.64 – 2.82	18.32	< 0.001
Axonal Variant (vs. AIDP)	2.38	1.32 – 4.30	8.14	0.004
Baseline sNfL (> 100 pg/mL)	3.85	2.04 – 7.28	15.60	< 0.001
Antecedent Diarrhea	1.52	0.88 – 2.62	2.18	0.139

3.3 Therapeutic Comparisons and Clinical Outcomes

Regarding therapeutic interventions, 142 patients received intravenous immunoglobulin (IVIg, 2g/kg over 5 days) as primary therapy, 76 patients underwent therapeutic plasma exchange (TPE, 5 sessions), and 30 patients received sequential combination therapy based on institutional protocol adjustments. No statistically significant differences were observed between IVIg and TPE monotherapy regarding 6-month functional outcome or mortality. However, patients receiving early targeted rehabilitation combined with immunomodulation demonstrated significantly reduced hospitalization durations (median 18.4 vs. 24.2 days, p = 0.003).

4. Discussion

Guillain-Barré syndrome remains a critical neurological emergency requiring timely diagnosis, vigilant monitoring, and aggressive supportive care. The findings of this multicenter cohort study reinforce the critical role of axonal degeneration in dictating long-term neurological disability. While clinical rating scales like the Hughes grade and EGOS provide valuable macroscopic evaluations, they inherently lag behind molecular pathological changes occurring within the peripheral nerve architecture.

Our investigation highlights serum neurofilament light chain as an exceptionally sensitive and reliable fluid biomarker for GBS severity and prognosis. Because neurofilaments are exclusively expressed in neurons and released upon axonal breakdown, sNfL concentration directly reflects the magnitude of structural nerve damage. The significantly elevated sNfL levels observed in patients with axonal variants (AMAN/AMSAN) corroborate the hypothesis that axonal forms of GBS entail more extensive

neuroaxonal destruction and consequently poorer regenerative capacity compared to primary demyelinating pathology.

Comparing immunotherapeutic modalities yielded consistent alignment with prior randomized clinical trials demonstrating equivalent efficacy between IVIg and plasma exchange. Nevertheless, the identification of treatment-related fluctuations and refractory disease subsets underscores the imperative for precision medicine approaches in GBS. Future therapeutic trials should incorporate sNfL kinetics to monitor treatment responsiveness dynamically and guide decisions regarding secondary or augmented immunotherapy courses.

4.1 Limitations

Several limitations of this study merit consideration. First, the retrospective design introduces potential selection and documentation biases, although multicenter data collection and standardized biomarker assays mitigate institutional variations. Second, serum sampling time points were standardized at admission and day 14; more granular serial sampling could provide deeper insights into neurodegeneration kinetics. Third, while our cohort size (N = 248) is robust for a rare condition, subgroup analyses for rare GBS variants (such as Miller Fisher syndrome or pharyngeal-cervical-brachial variants) warrant larger, dedicated prospective cohorts.

5. Conclusion

Serum neurofilament light chain quantification serves as a highly robust biomarker for axonal damage and functional prognostication in Guillain-Barré syndrome. Integrating sNfL measurements with established clinical scoring systems enhances risk stratification, empowering clinicians to identify high-risk patients early and tailor therapeutic and rehabilitative strategies accordingly. Further prospective validation in global clinical trials is warranted to establish universal cutoff thresholds for clinical practice.

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