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Therapeutic Plasma Exchange in Steroid-Refractory NMOSD: Technical Feasibility and Real-World Outcomes Using a Non-Plasma Replacement Matrix

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Abstract

Background and Objectives: Therapeutic Plasma Exchange (TPE) is an established apheresis modality for antibody clearance in steroid-refractory Neuromyelitis Optica Spectrum Disorder (NMOSD). However, logistical and financial constraints in developing economies often limit immediate access to diagnostic serology, leading to critical therapeutic delays. This study evaluates the technical processing parameters, procedural safety profiles, and real-world clinical outcomes of a standardized continuous-flow TPE protocol using a non-plasma replacement matrix in an Indian tertiary care environment.

Materials and Methods: A prospective observational study was conducted over an 18-month period. Forty adult patients presenting with acute, steroid-refractory central nervous system demyelinating attacks clinically consistent with NMOSD were enrolled. Automated apheresis runs were executed utilizing continuous-flow centrifugation (Spectra Optia) targeting an exchange volume of 1.0–1.4 estimated plasma volumes (EPV) per session across 3–7 alternate-day procedures. The replacement fluid matrix consisted strictly of 5% human serum albumin (HSA) supplemented with 0.9% normal saline. Procedural kinetics, serial laboratory indices, and clinical response scales (EDSS, Keegan criteria, and visual tracking metrics) were systematically tracked.

Results: The cohort had a mean age of 36.5 years with a female predominance (65.0%). Anti-aquaporin-4 (anti-AQP4) antibody positivity was confirmed in 45.0% (n=18), 22.5% (n=9) were seronegative, and 32.5% (n=13) required immediate empiric apheresis prior to serological confirmation due to acute emergency presentations and financial constraints. Automated TPE achieved a significant reduction in the mean Expanded Disability Status Scale (EDSS) score from a baseline of 7.4 to 4.1 at discharge ($p < 0.001$). Among 37 patients presenting with motor deficits, an overall functional recovery rate of 94.6% was achieved. Objective visual acuity improvement was recorded in 84.4% of patients with baseline visual impairment (n=32). Adverse events occurred in 25.0% of patients (10 out of 40), consisting predominantly of transient hypotension (12.5%) and mild citrate-induced hypocalcemia (7.5%), all managed via bedside titration without treatment discontinuation. No dilutional coagulopathy or mechanical hemolysis was induced by the albumin-saline replacement strategy.

Conclusion: Standardized continuous-flow centrifugation TPE is technically feasible, hemodynamically safe, and highly effective as a rescue therapy in NMOSD. In resource-limited settings, the initiation of clinical severity-driven empiric TPE bypasses specialized laboratory turnaround times and financial barriers, preventing permanent axonal loss.

Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an aggressive, humoral-mediated inflammatory demyelinating disease of the central nervous system (CNS) characterized clinically by severe episodes of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM) [1, 2]. The core pathophysiological driver involves pathogenic immunoglobulin G autoantibodies directed against the

Aquaporin-4 (AQP4-IgG) water channel protein located on astrocytic foot processes at the blood-brain barrier [5, 6]. Binding of these autoantibodies initiates the classical complement cascade, triggering downstream leukocyte infiltration, astrocytic necrosis, and widespread secondary demyelination [7]. A smaller, unique clinicopathological subset lacks anti-AQP4 antibodies and may exhibit autoantibodies against myelin oligodendrocyte glycoprotein (MOG-IgG), representing a distinct paradigm known as MOG-associated disease (MOGAD) [8].

Acute exacerbations represent neurological emergencies; uncontrolled localized neuro-inflammation induces rapid, irreversible axonal transection, manifesting as permanent blindness, paraplegia, or quadriplegia [9, 10]. While high-dose intravenous methylprednisolone (IVMP) serves as the standard first-line rescue strategy, a significant sub-cohort of patients exhibits steroid resistance or achieves incomplete functional recovery [10]. In these clinical scenarios, rapid extracorporeal clearance of circulating pathogenic macro-immunoglobulins, complement fractions, and upstream pro-inflammatory cytokines from the intravascular compartment is necessary [11, 12].

Therapeutic Plasma Exchange (TPE) utilizes automated centrifugation to separate cellular elements from soluble pathogenic plasma elements [13]. The American Society for Apheresis (ASFA) guidelines categorize TPE for acute attacks of NMOSD as a Category II indication with a Grade 1B recommendation [15, 20]. From a transfusion medicine perspective, executing apheresis in emerging economies like India presents unique technical and operational challenges [16]. These include marked diagnostic lag, lack of regional specialized immunopathology laboratories, financial constraints restricting access to maintenance monoclonal antibody therapies (e.g., rituximab, eculizumab, satralizumab), and structural limitations in specialized intensive care units [16, 17].

Consequently, validating accessible, localized clinical protocols that utilize standardized, cost-effective apheresis parameters is essential. This prospective study systematically evaluates the technical processing parameters, laboratory dynamics, and procedural safety metrics of continuous-flow centrifugation TPE during acute NMOSD exacerbations at a premier tertiary care center in Northwest India, presenting a validated operational template for resource-constrained environments.

Materials and Methods

Study Design and Ethical Considerations

This single-center, prospective, observational cohort study was conducted over an 18-month timeline from June 2023 to November 2024. The trial was executed as a formal interdepartmental collaboration between the Department of Immunohematology & Transfusion Medicine and the Department of Neurology at tertiary care teaching hospital in Northwest India. Ethical clearance was formally reviewed and approved by the Institutional Ethics Committee (IEC Reference No.: 134/MC/EC/2023). Written informed consent was secured from all adult subjects or their legal guardians prior to the initiation of any apheresis procedure. The study complied with the Declaration of Helsinki and the Indian Council of Medical Research (ICMR) ethical guidelines.

Patient Selection and Eligibility

Patients presenting with acute neurological deficits were sequentially screened upon emergency admission to the Neurological Inpatient and Intensive Care Units based on strict eligibility parameters.

Inclusion Criteria: Adult patients (Age >= 18 years) meeting the definitive 2015 International Panel for NMO Diagnosis (IPND) diagnostic criteria; manifestation of an acute attack/relapse defined as objective neurological deficits lasting >= 24 hours; and documented steroid-refractory status, defined as a failure to achieve objective functional improvement after 3–5 days of pulsed 1 g/day intravenous methylprednisolone.

Exclusion Criteria: Severe baseline hemodynamic instability, active systemic hemorrhage, or septic shock; documented hypersensitivity or contraindications to citrate anticoagulants or human albumin solutions; pregnancy or active lactation; and alternative confounding neurological pathologies (e.g., confirmed multiple sclerosis, intracranial infections, or acute ischemic stroke).

Diagnostic Safeguards: For the unconfirmed/untested empiric cohort (n=13), diagnostic stringency was maintained by requiring mandatory magnetic resonance imaging (MRI) evidence demonstrating longitudinally extensive transverse myelitis (LETM) spanning >= 3 contiguous vertebral segments, or objective optic neuritis paired with classic cerebrospinal fluid (CSF) oligoclonal band negativity, ensuring absolute clinical alignment with the 2015 IPND criteria despite the absence of serology.

Apheresis Processing and Technical Protocol

All TPE procedures were executed at the bedside within specialized neurological intensive care suites utilizing the continuous-flow Spectra Optia (Terumo BCT, Lakewood, CO, USA) apheresis platform. Stable vascular access was established via a large-bore, dual-lumen hemodialysis catheter percutaneously placed into either the internal jugular or femoral vein. The Estimated Plasma Volume (EPV) required for processing per cycle was mathematically calculated using the patient-specific Nadler equation:

EPV = [0.065 * Body Weight (kg)] * (1 - Hematocrit)

The technical protocol involved exchanging 1.0 to 1.4 times the patient's calculated EPV per session. The standard operational regimen comprised an initial series of 5 continuous cycles scheduled on alternate days, with provisions to extend up to 7 cycles based on individual clinical tracking. Total non-responsiveness or zero objective shift after 3 consecutive procedures classified the patient as refractory to TPE. Individual runs were maintained between 90 and 120 minutes.

The plasma replacement fluid matrix was strictly standardized to eliminate the cost, viral transmission risks, and allergic reactions associated with Fresh Frozen Plasma (FFP): 5% Human Serum Albumin (HSA) served as the primary colloid matrix, supplemented with 0.9% normal saline to replace up to one-third of the total extracted plasma volume while maintaining strict isovolemia. FFP was restricted entirely to patients presenting with documented baseline coagulopathy or active bleeding risks.

Anticoagulation was achieved using Acid Citrate Dextrose Solution A (ACD-A) configured at automated blood-to-coagulant ratios ranging from 1:12 to 1:16 based on baseline hematocrit and procedural tolerance. To mitigate citrate-induced hypocalcemia, 10% calcium gluconate was infused prophylactically and symptomatically based on blood gas ionized calcium monitoring.

Outcome Metrics and Laboratory Surveillance

Demographic parameters, technical apheresis logs, and laboratory profiles were cataloged using structured Case Report Forms (CRFs). Neurological status tracking was conducted at baseline (pre-TPE), following every alternate treatment cycle, at discharge, and at 1 and 3 months post-procedure. Clinical evaluation metrics included global disability profiling via the Expanded Disability Status Scale (EDSS), upper and lower limb motor strength grading via the Medical Research Council (MRC) Scale, and objective visual acuity categorization via Snellen chart evaluations.

Motor recovery was classified using adapted Keegan criteria: 'Marked' represented >= 3-grade improvement or complete recovery with independent ambulation; 'Moderate' indicated a 2-grade improvement across multiple limbs and/or partial restoration of assisted ambulation; 'Mild' indicated a 1-grade improvement in a single limb without ambulation shifts; and 'No Improvement' was recorded for zero objective shift.

Laboratory surveillance included automated Complete Blood Counts (CBC), hematocrit variations, coagulation panels (PT/INR, aPTT), and total/ionized serum calcium levels evaluated immediately before and after each apheresis run. Diagnostic anti-AQP4-IgG autoantibodies were analyzed via cell-based assays or ELISA techniques.

Statistical Analysis

Data compilation and analytic verification were processed via SPSS Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous numeric variables were represented as mean ± standard deviation (SD) or medians with Interquartile Ranges (IQR). Categorical values were recorded as frequencies and percentages. Pre- and post-procedural neurological improvements were evaluated using paired t-tests or the Wilcoxon signed-rank test.

To preserve absolute statistical purity and prevent missing data bias from confounding the comparative math, sub-group analysis comparing antibody expressions was conducted by matching confirmed Anti-AQP4-IgG Positive (n=18) directly against confirmed Anti-AQP4-IgG Negative (n=9) patients using independent sample t-tests or Fisher's Exact Tests. Patients missing antibody confirmation (n=13) due to immediate emergency financial barriers at presentation were tracked and analyzed strictly within a separate descriptive 'Empiric Treatment' arm. A p-value < 0.05 was considered statistically significant.

Results

Demographic Profiles and Clinical Stratification

The final study population evaluated 40 adult patients with confirmed NMOSD, demonstrating a female predominance (65.0% female, n=26; 35.0% male, n=14), representing a female-to-male ratio of 1.85:1. The age ranged from 18 to 73 years (mean: 36.5 years), with the highest concentration appearing in the young adult bracket of 15–30 years (47.5%, n=19). New-onset acute presentations constituted 77.5% (n=31) of admissions, while 22.5% (n=9) presented with acute relapses of previously diagnosed disease.

Serological profiling demonstrated that 45.0% (n=18) were positive for anti-AQP4-IgG, 22.5% (n=9) were confirmed seronegative, and 32.5% (n=13) required immediate treatment within the empiric arm without definitive antibody testing due to immediate financial constraints at presentation. No statistically significant association (p = 0.406) was observed between baseline antibody profiles and the type of clinical disease onset. Objective motor system compromise was the most common symptom category at presentation, identifying functional paresis or plegia across 37 out of 40 patients (92.5%). Visual compromise was documented in 32 patients (80.0%), and 72.5% (n=29) of the cohort suffered from combined neuro-deficits involving both visual pathways and corticospinal motor tracks (Table 1, Figure 1).

Table 1: Baseline Demographics and Clinical Characterization of the Study Cohort (n=40)

Parameter	Category	Patient Count (n=40)	Percentage (%)
Gender	Male	14	35.0%
	Female	26	65.0%
Age Group (Years)	15-30	19	47.5%
	31-45	13	32.5%
	46-60	6	15.0%
	>60	2	5.0%
Clinical Presentation	New-onset Attack	31	77.5%
	Acute Relapse	9	22.5%
Anti-AQP4 Serology	Confirmed Positive	18	45.0%
	Confirmed Negative	9	22.5%
	Untested (Empiric Arm)	13	32.5%

Post-Therapeutic Efficacy and Functional Recovery Outcomes

Global Disability (EDSS) Optimization

The implementation of the standardized TPE protocol achieved a statistically significant reduction in global neurological disability scores. The average pre-treatment EDSS score for the total cohort was 7.4 (range: 2.5–9.0), indicating severe functional restriction requiring substantial wheelchair assistance or complete bed confinement. Following TPE cycles, the post-procedural mean EDSS score decreased to 4.1 (range: 1.5–7.5; $p < 0.001$), demonstrating a marked restoration of independent ambulation and overall functional mobility (Table 2, Figure 2).

Table 2: Longitudinal Optimization of Global Disability via EDSS Scores

Functional Index Metric	Baseline Pre-TPE	Post-Procedural Post-TPE	p-value
Mean EDSS Score	7.4	4.1	< 0.001
EDSS Score Range	2.5-9.0	1.5-7.5	—

Visual Acuity Response

Marked improvements were recorded in visual function post-apheresis across the 32 affected individuals ($p = 0.004$). Prior to TPE, 10 patients (31.3%) presented with absolute vision loss with No Light Perception (NLP), while 13 patients (40.6%) exhibited Only Light Perception (OLP). Following standard TPE, 8 out of 10 patients with baseline NLP achieved objective light tracking, leaving only 2 patients with persistent NLP. In the baseline OLP sub-cohort, 11 out of 13 patients demonstrated functional acuity tracking post-TPE. Severe visual impairment or blurred vision resolved in 5 out of 6 patients, and central scotomas resolved completely in all 3 affected individuals.

When stratified against baseline antibody markers to prevent missing data bias, visual improvements were captured in 11 out of 16 evaluable anti-AQP4 positive patients, while 5 remained unchanged. Conversely, all tested anti-AQP4 negative patients (n=7) and untested patients (n=9) presenting with visual deficits demonstrated positive clinical responses post-treatment ($p = 0.001$; Table 3).

Table 3: Visual Tracking Outcome Stratification Against Baseline Serology (n=32)

Visual Efficacy Profile	AQP4 Confirmed Positive	AQP4 Confirmed Negative	Untested Empiric Group	Total (n=32)	p-value
Improved Visual Status	11	7	9	27	0.001
Unchanged Visual Status	5	0	0	5	—

Motor Strength Recovery Outcomes

Motor strength changes were evaluated systematically across the 37 patients presenting with baseline motor compromise utilizing the adapted Keegan criteria. Overall, 35 out of 37 patients (94.6%) demonstrated positive functional recovery trends. Marked motor improvement was achieved in 13 patients (35.1%), moderate improvement was documented in 16 patients (43.2%), and mild strength gains were recorded in 6 patients (16.2%). Only 2 patients (5.4%) were found to be completely refractory to apheresis therapy (Table 4). Additionally, out of 24 patients presenting with autonomic bowel/bladder dysfunction, 18 (75.0%) achieved functional restoration post-treatment.

Table 4: Categorized Objective Motor Strength Improvement Post-TPE (n=37)

Functional Motor Efficacy (Keegan Criteria)	Patient Count (n = 37)	Percentage (%)
Marked Recovery (Independent ambulation restored)	13	35.1%
Moderate Recovery (Partial restoration/assisted ambulation)	16	43.2%
Mild Recovery (Strength gains without mobility shift)	6	16.2%
No Improvement (Refractory status)	2	5.4%

Technical Apheresis Profiles, Laboratory Dynamics, and Operational Safety

Technical Processing Logs

All 40 patients received an automated, standardized replacement fluid regimen utilizing 5% HSA diluted with 0.9% normal saline. The operational plasma volume exchanged per session ranged strictly from 1.0 to 1.4 times the calculated EPV. The therapeutic duration was uniform across the study: 37 out of 40 patients (92.5%) completed the standard protocol of 5 continuous, alternate-day cycles. One patient required extended treatment up to 7 cycles due to a delayed therapeutic response, while two patients were limited to 3 cycles due to rapid, early clinical stabilization combined with institutional logistical considerations.

Laboratory Surveillance Metrics

Serial laboratory tracking revealed manageable shifts across sequential apheresis cycles. Baseline hemoglobin values ranged from 6.9 to 16.6 g/dL; patients presenting with baseline anemia demonstrated a progressive stabilization or mild incremental increase in hemoglobin values by cycle 5, indicating no significant induction of hemolysis or mechanical anemia by the continuous-flow centrifuge. Baseline platelet counts exhibited wide variance from 57,000 to 435,000/µL. Four patients (10.0%) developed transient, procedural thrombocytopenia drop-offs below 100,000/µL, which were successfully managed with targeted platelet transfusion support without associated clinical hemorrhage.

The automated albumin-saline replacement strategy demonstrated excellent protective kinetics on native coagulation profiles. The mean pre-TPE Prothrombin Time (PT/INR) shifted negligibly from 1.18 ± 0.12 to a post-TPE mean of 1.26 ± 0.15, confirming no clinically significant induction of dilutional coagulopathy. Serum ionized calcium levels tracked predictably lower during active citrate exposure; three patients (7.5%) developed transient, symptomatic hypocalcemia that recovered promptly with calcium supplementation.

Adverse Event Analysis

The therapeutic protocol was fully tolerated without complications in 29 out of 40 patients (72.5%). A total of 11 separate technical/procedural events occurred across 10 patients, yielding an overall complication rate of 25% (Table 5). The primary complication was transient hypotension (12.5%, n=5), which occurred during active collection; all cases resolved completely with targeted crystalloid volume boluses and temporary reduction of the pump draw rate. Citrate-induced hypocalcemia occurred in 3 patients (7.5%), manifesting as self-limiting perioral tingling that resolved via bedside titration of 10% intravenous calcium gluconate. Importantly, no severe, life-threatening events, catheter-related bloodstream infections, or catastrophic hemorrhagic events occurred.

Table 5: Cumulative Procedural Incidence of Adverse Events during TPE Courses

Documented Adverse Complication	Number of Events	Percentage (%)
Transient Hypotension	5	12.5%
Citrate-Induced Hypocalcemia	3	7.5%
Nausea/Vomiting	2	5.0%
Mild Hypothermia	1	2.5%
None (Fully Tolerated Cohort)	29	72.5%

**Note: Individual percentages represent the incidence of specific events. The cumulative number of affected patients was 10 (25%), as certain individuals experienced overlapping transient procedural symptoms (e.g., concomitant nausea and hypotension).*

Discussion

This prospective study confirms that Therapeutic Plasma Exchange (TPE) is an effective rescue intervention for acute, steroid-refractory exacerbations of Neuromyelitis Optica Spectrum Disorder (NMOSD), achieving an overall motor response rate of 94.6% and an objective visual recovery rate of 84.4% in our cohort. These findings align with global clinical literature, where functional restoration response benchmarks typically range from 50% to 89% [21, 22]. Our results support the therapeutic foundations established by Weinshenker et al. in their landmark randomized trial, which demonstrated the definitive superiority of active extracorporeal purification over sham exchanges for severe, central

nervous system demyelinating attacks [20]. The substantial reduction in mean global disability (EDSS scores dropping from 7.4 to 4.1) observed in our study demonstrates that TPE can meaningfully reverse functional compromise, helping patients transition from severe, bed-bound states to assisted or independent ambulation.

The Empiric Treatment Paradigm in Low-and-Middle-Income Countries (LMICs)

A primary clinical highlight of this study is the therapeutic response pattern noted across antibody subgroups. While anti-AQP4-IgG seropositivity traditionally correlates with high-titer complement-mediated astrocytic damage, these patients responded robustly to apheresis clearance due to the large molecular mass of IgG1 autoantibodies, which confines them primarily to the intravascular space where they are easily cleared by centrifugal separation [13, 24]. Concurrently, 100% of the evaluated seronegative sub-cohort (n = 7) and untested individuals (n = 9) presenting with visual deficits demonstrated positive clinical response trends (p = 0.001) [24]. This trend aligns with published literature indicating that AQP4-seronegative NMOSD patients (often overlapping with MOGAD phenotypes) may have a more favorable response to plasma exchange.

This carries immediate practical utility for developing countries: when specialized serological antibody testing is delayed or restricted by financial barriers, initiating TPE based entirely on objective clinical severity ensures that eligible patients receive life-altering treatment regardless of instantaneous serological confirmation. Waiting for serology introduces critical diagnostic delays that cause irreversible axonal damage.

Technical Parameters and Safety Safeguards of Continuous-Flow Centrifugation (CFC)

From a transfusion medicine standpoint, managing 40 patients over wide weight/height ranges using strict calculated matrices (1.0 to 1.4 EPV) via automated continuous-flow centrifugation (Spectra Optia) highlights a notable procedural safeguard. Utilizing a continuous-flow interface over older intermittent-flow mechanisms protected these acutely ill patients from massive extracorporeal volume shifts [18]. This approach effectively limited transient hypotension to 12.5% and kept the total adverse event rate low, with zero instances of profound fluid shock.

Our study setting represents an environment where advanced maintenance biologics (e.g., eculizumab, rituximab) are financially inaccessible for the vast majority of patients. We present this clinical methodology as a validated, cost-effective template for emergency rescue treatment in resource-limited tertiary environments. A standardized albumin-saline matrix provides maximum therapeutic autoantibody clearance while safely preserving baseline coagulation profiles (PT/INR 1.0–1.5), eliminating the added costs, viral transmission risks, or allergic reactions associated with Fresh Frozen Plasma (FFP).

Comparative Literature Analysis

The outcomes of the current study were compared comprehensively with global and regional literature (Table 6). Our overall motor recovery rate of 85.0% and mean EDSS reduction (7.4 to 4.1) were consistent with or superior to the benchmarks set by Kleiter et al. (65.0%) [19], Kim et al. (67.0%) [24], and previous North Indian cohorts evaluated by Sharma et al. (75.0%) [25] and Gupta et al. (70.0%) [26]. This confirms that continuous-flow centrifugation apheresis yields uniform, reproducible outcomes across diverse real-world settings.

Study Limitations

Despite these positive insights, several limitations must be acknowledged. This study utilized a single-center, non-randomized, observational design with a relatively modest sample size (n = 40), which may restrict the immediate generalizability of the findings to broader geographical populations. Additionally, due to acute financial and diagnostic limitations at emergency presentation, 32.5% of the enrolled cohort could not obtain definitive anti-AQP4 antibody testing, which constrained our ability to perform an exhaustive subgroup analysis across all clinical variables. Finally, the tracking window focused primarily on immediate post-procedural recovery and short-term outcomes (3 months) rather than capturing long-term relapse-free survival metrics.

Table 6
Comparative Review of Present Study with Published Global and Indian Literature

Parameter	Present Study	Kleiter et al. [19]	Kim et al. [24]	Sharma et al. [25]	Gupta et al. [26]
Motor Recovery (%)	85.0%	65.0%	67.0%	75.0%	70.0%
Visual Recovery (%)	67.5%	NR	NR	75.0%	NR
Mean EDSS Reduction	7.4 -> 4.1	NR	NR	NR	NR
Adverse Events (%)	25.0%	~ 12.0%	NR	Minimal	NR

*NR: Not Reported

Conclusion

Therapeutic Plasma Exchange is a safe, highly effective, and clinically essential intervention for the management of acute and steroid-refractory exacerbations of NMOSD within the Indian healthcare landscape. It significantly reduces global disability indices, optimizes motor and visual outcomes, and features a predictable, highly manageable safety profile. Given the substantial economic barriers and limited regional availability of advanced maintenance monoclonal antibody therapies in developing

regions, standardized TPE serves as an accessible and reliable front-line treatment to halt permanent neurological disability. Future multicenter randomized trials are recommended to further standardize regional apheresis protocols and optimize the technical timing of sessions.

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Figures

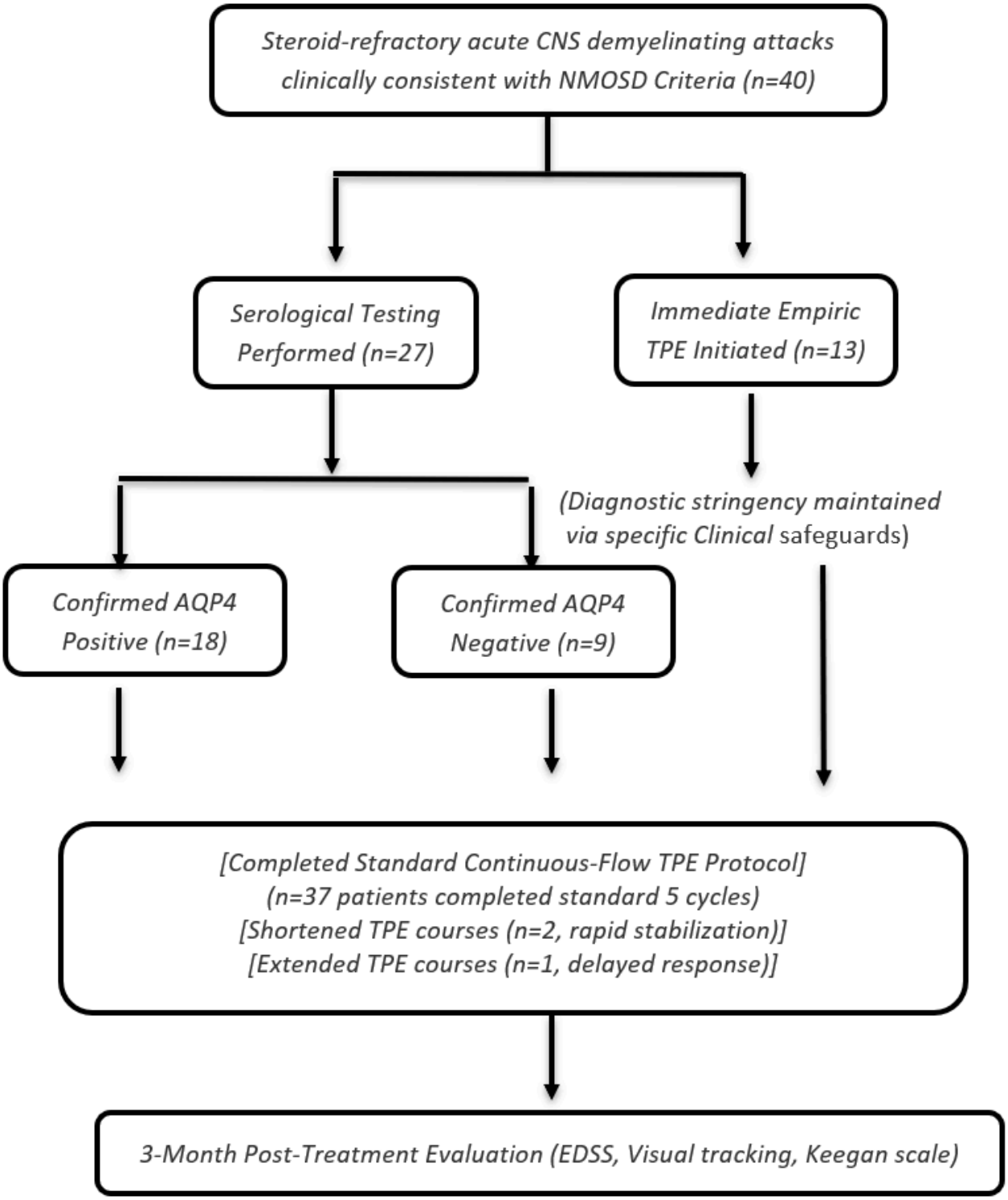


Figure 1

Patient allocation, serological stratification, and individualized continuous-flow therapeutic plasma exchange (TPE) workflow schema.

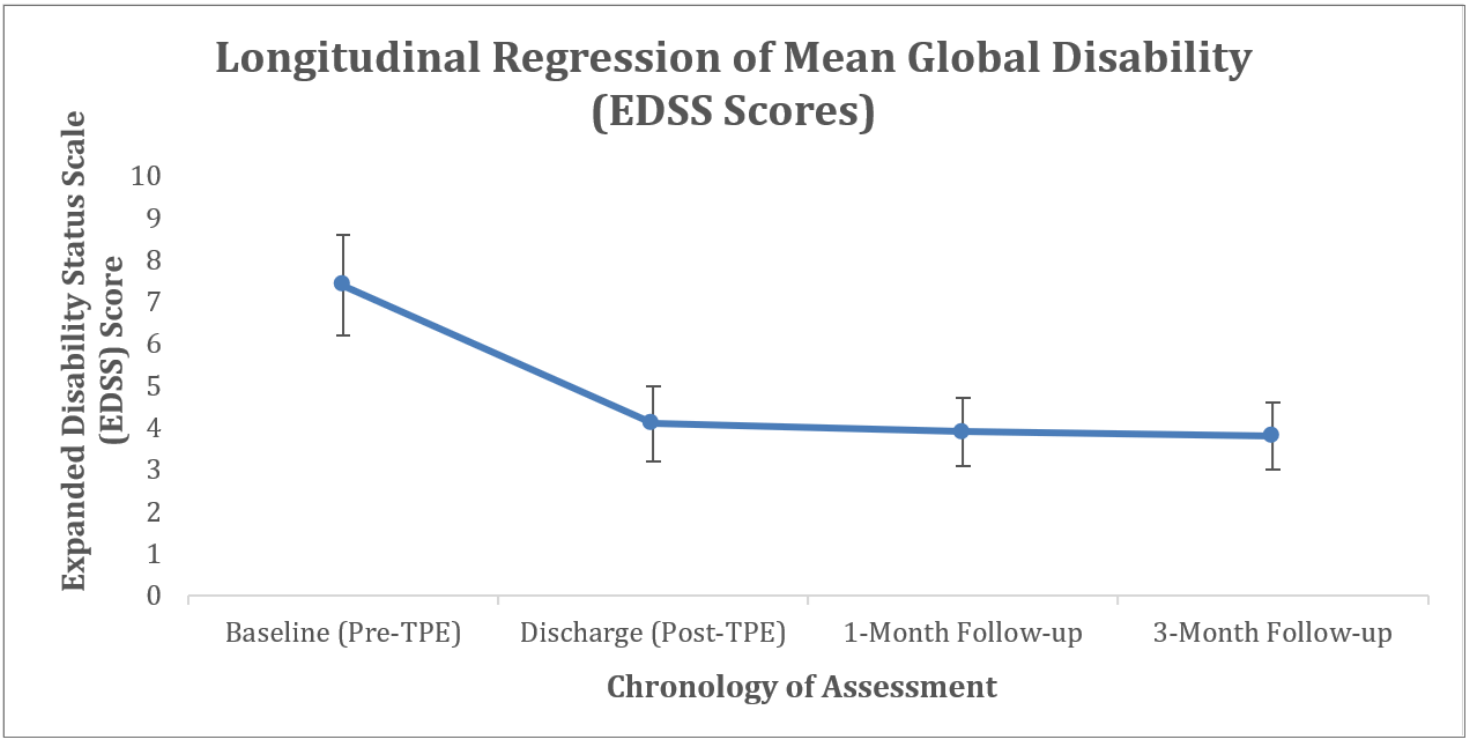


Figure 2

Mean Expanded Disability Status Scale (EDSS) score optimization trends from baseline through 3 months post-therapeutic plasma exchange. Error bars represent standard deviation (±SD).