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Impact of Baseline Liver Function on the Dynamic Consumption of Fibrinogen During Double Filtration Plasmapheresis in Patients with Neuroimmune Diseases: A Retrospective Observational Study

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Abstract

Objective: To investigate dynamic changes of fibrinogen (FIB) and immunoglobulin G (IgG) during double filtration plasmapheresis (DFPP) in neuroimmune diseases, and evaluate baseline liver function's impact on FIB consumption and severe hypofibrinogenemia risk.

Methods: This retrospective study included 50 neuroimmune patients undergoing DFPP (June 2024-March 2026). Coagulation profiles were monitored per session. Multivariate linear regression identified factors influencing initial FIB reduction. In 43 patients with complete continuous data, severe hypofibrinogenemia (FIB < 1.0g/L) incidence during consecutive treatments was compared between high and low baseline alanine aminotransferase (ALT) groups, stratified by the median.

Results: FIB and IgG showed a parallel, progressive decline during DFPP, with FIB reaching its nadir after the fourth session. Multivariate analysis identified baseline FIB and ALT as independent predictors of initial FIB reduction. Higher baseline ALT was associated with a smaller initial FIB reduction (beta = -0.010, 95%CI: -0.017 to -0.003, *P* = 0.009). However, during continuous therapy, severe hypofibrinogenemia incidence was 68.2% (15/22) in the high ALT group versus 42.9% (9/21) in the low ALT group (RR = 1.59, 95%CI: 0.90 to 2.81, *P* = 0.129). Safety analysis showed no major bleeding despite the absence of exogenous fibrinogen supplementation. Only 16.0% (8/50) experienced mild puncture site oozing, all effectively managed with local compression.

Conclusion: DFPP causes significant but clinically well-tolerated fibrinogen consumption in patients with neuroimmune diseases. Higher baseline ALT may paradoxically increase the cumulative risk of severe hypofibrinogenemia during continuous therapy. Dynamic coagulation monitoring is essential to optimize safety and avoid unnecessary blood product transfusions.

1. Introduction

The pathogenesis of neuroimmune diseases is predominantly driven by circulating autoantibodies. Double filtration plasmapheresis (DFPP), a selective plasma separation technique, effectively eliminates pathogenic macromolecular immunoglobulins using filters of varying pore sizes, and has therefore emerged as a crucial therapeutic modality for these conditions[1]. Compared with conventional plasma exchange (PE), DFPP substantially minimizes the requirement for exogenous plasma replacement, thereby mitigating the risks of blood-borne infections and allergic reactions.

However, concurrent with the clearance of pathogenic antibodies, DFPP inevitably depletes certain physiological macromolecular proteins. The most prominent among these is fibrinogen (FIB), a critical factor in the coagulation cascade[2]. With a molecular weight of approximately 340 kDa—falling between that of IgG (150 kDa) and IgM (900 kDa)—FIB is highly susceptible to substantial retention during the secondary filtration phase of DFPP. Clinical studies indicate that serial DFPP sessions lead to profound FIB depletion, with reductions frequently exceeding 75%. This rapid decline can precipitate severe hypofibrinogenemia, potentially elevating the risk of bleeding under specific clinical circumstances[3].

Consequently, rigorous monitoring of FIB dynamics during DFPP is of paramount clinical importance to ensure patient safety.

FIB is primarily synthesized by the liver, and the rate of its recovery following plasma clearance is highly dependent on hepatic compensatory capacity. Previous investigations have mostly focused on the influence of DFPP operational parameters—such as processed plasma volume and filter specifications—on coagulation factors or have restricted their analyses of FIB kinetics to cohorts with renal diseases or hyperlipidemia[4, 5]. To date, systematic clinical evidence remains scarce regarding how baseline liver function dictates the FIB consumption trajectory and the subsequent risk of hypofibrinogenemia during serial DFPP therapy in patients with neuroimmune diseases.

Accordingly, this retrospective study aims to delineate the dynamic changes in FIB and immunoglobulin G (IgG, the primary constituent of pathogenic antibodies) during DFPP in patients with neuroimmune diseases. Specifically, we sought to evaluate the impact of baseline liver function on the magnitude of FIB reduction following the initial session, as well as on the risk of developing severe hypofibrinogenemia throughout continuous treatment. We anticipate that our findings will provide robust evidence to guide clinicians in tailoring individualized DFPP regimens and optimizing coagulation monitoring strategies.

2. Materials and Methods

2.1 Study Design and Participants

This was a single-center, retrospective observational study that consecutively enrolled patients with neuroimmune diseases who underwent DFPP at the Department of Neurology, Shanghai Punan Hospital, between June 2024 and March 2026. None of the included patients received exogenous fibrinogen supplementation during the treatment course. The study protocol was approved by the Ethics Committee of Shanghai Punan Hospital (Approval No: KS2025-022) and was conducted in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived due to the retrospective nature of the study.

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) a confirmed diagnosis of a neuroimmune disease; (3) DFPP treatment performed using the Spectra Optia Apheresis System; and (4) availability of complete baseline clinical data and dynamic coagulation monitoring records before and after treatment. The exclusion criteria included: (1) presence of active bleeding or coagulopathy prior to treatment; (2) concomitant acute or chronic liver diseases; (3) substantial missing clinical or laboratory data; and (4) administration of exogenous fibrinogen during the DFPP treatment course.

Given the exploratory and retrospective nature of this study, a formal a priori sample size calculation was not performed. Instead, we consecutively enrolled all eligible patients treated at our institution during the study period. This consecutive sampling approach was chosen to minimize selection bias and accurately reflect real-world clinical practice.

2.2 DFPP Treatment Protocol

Vascular access was established in all patients via an ultrasound-guided double-lumen central venous catheter (FH-2155, Able) inserted into the right internal jugular vein. DFPP procedures were performed using the Spectra Optia Apheresis System (Terumo BCT, USA).

The target plasma processing volume for a single session was set at 1.0 times the estimated plasma volume (PV). Extracorporeal anticoagulation was achieved with Acid Citrate Dextrose Solution A (ACD-A), with an initial whole blood-to-anticoagulant ratio of 1:10. The treatment course consisted of 3 to 5 sessions, administered every other day. Following each session, patients routinely received an intravenous infusion of 30 g of human albumin, along with 1 g of calcium gluconate to prevent hypocalcemia.

Regarding the selection of the secondary filter, a sequential pore-size reduction strategy was adopted at our center, considering the high plasma viscosity and macromolecule concentrations typically present during the initial session. Specifically, a larger-pore Cascadeflo EC-30W filter (Asahi Kasei, Japan) was utilized for the first session to achieve initial deburdening. From the second session onward, this was uniformly substituted with a smaller-pore Cascadeflo EC-20W filter to intensify the retention and clearance of pathogenic antibodies.

2.3 Data Collection and Parameter Definitions

Baseline demographic characteristics, comorbidities, admission modified Rankin Scale (mRS) scores [6], and concomitant medications were extracted from the electronic medical record system. Laboratory data collection focused on baseline parameters prior to the first DFPP session (including liver and kidney function, complete blood count, and a detailed coagulation profile), as well as FIB and IgG levels measured before and after each subsequent DFPP session. Severe hypofibrinogenemia was defined as a nadir FIB level dropping below 1.0 g/L at any point during the entire DFPP treatment cycle.

2.4 Statistical Analysis

Continuous variables with a normal distribution were presented as mean ± standard deviation, while those with a skewed distribution were expressed as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. To identify independent factors influencing the magnitude of FIB reduction after the initial DFPP session, a univariate linear regression analysis was first performed. Variables with a P-value < 0.20 in the univariate analysis were subsequently incorporated into a multivariate linear regression model for adjustment, yielding regression coefficients (β) and their 95% confidence intervals (CIs).

To analyze the dynamic trajectory of FIB during the treatment course and evaluate the potential impact of baseline liver function on FIB consumption, a linear mixed-effects model was constructed. In this model, the number of treatment sessions and baseline ALT levels were designated as fixed effects, with

their interaction term included. The individual patient was set as a random intercept to adjust for the correlation arising from repeated measures in the same subject. Complete case analysis was strictly applied to the regression analysis of the initial FIB reduction, the continuous dynamic trajectory analysis, and the evaluation of the incidence of severe hypofibrinogenemia, including only patients with fully matched data. Patients were stratified into a high ALT group and a low ALT group based on the median baseline ALT level. The incidence rates between groups were compared using the Chi-square test or Fisher's exact test, as appropriate. All statistical analyses were performed using R software (version 4.5.2, R Foundation for Statistical Computing, Vienna, Austria). A two-sided P-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

A total of 50 patients with neuroimmune diseases who underwent DFPP without exogenous fibrinogen supplementation were included in this study for the analysis of baseline characteristics and parameters related to the initial treatment session (Table 1 and Supplementary Table S1). Of these, 43 patients with complete continuous coagulation monitoring data were assigned to the dynamic analysis cohort for serial treatments.

Table 1
Baseline characteristics of patients with neuroimmune diseases undergoing DFPP therapy.

Variables	Total Patients (N = 50)
Age (years), median	66.50 [49.25–72.00]
Sex, n (%)	
Female	33 (66.0%)
Male	17 (34.0%)
Height (cm), median	162.00 [157.00–168.00]
Weight (kg), mean ± SD	63.49 ± 10.86
Comorbidities, n (%)	
Hypertension	17 (34.0%)
Diabetes mellitus	8 (16.0%)
Other comorbidities	11 (22.0%)
ALT (U/L), median	17.96 [13.44–26.82]
AST (U/L), median	17.32 [14.00–25.55]
Cr (μmol/L), median	58.20 [47.10–66.95]
eGFR (mL/min), median	98.00 [87.00–109.75]
FIB (g/L), median	2.78 [2.31–3.42]
PT (s), median	12.38 [11.21–12.92]
Platelet count ($\times 10^9$/L), median	216.00 [150.50–262.00]
INR, median	1.05 [0.96–1.12]
APTT (s), mean ± SD	27.43 ± 3.02
TT (s), mean ± SD	17.55 ± 1.57
D-dimer (mg/L), median	0.46 [0.28–1.09]

Note: Data are presented as mean ± SD, median [IQR], or n (%), as appropriate. Due to missing baseline data, N = 43 for coagulation parameters (FIB, PT, INR, APTT, TT, D-dimer) and N = 44 for platelets. Detailed clinical characteristics and neurological scores are provided in Supplementary Table S1. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; FIB, fibrinogen; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time.

The median age of the cohort was 66.50 years (interquartile range [IQR]: 49.25–72.00 years), with females accounting for 66.0%. The most common clinical diagnoses were autoimmune encephalitis

(34.0%) and myasthenia gravis (16.0%), while the predominant comorbidity was hypertension (34.0%). Concomitant medications during the treatment course included antithrombotic agents (28.0%) and immunosuppressants or corticosteroids (36.0%). The median modified Rankin Scale (mRS) score on admission was 2, and the median number of DFPP sessions administered was 5. Prior to the initial DFPP session, the baseline coagulation profiles of all patients (e.g., fibrinogen, platelet count, and D-dimer) were within the normal reference ranges.

3.2. Analysis of Factors Influencing the Magnitude of Fibrinogen Reduction After the Initial DFPP Session

To identify independent factors influencing the magnitude of fibrinogen (FIB) reduction following the initial DFPP session, univariate and multivariate linear regression analyses were performed on patients' baseline demographic characteristics, treatment parameters, and laboratory indices (Table 2). Univariate analysis revealed that baseline D-dimer ($P = 0.016$) and FIB ($P < 0.001$) levels were positively associated with the magnitude of FIB reduction post-treatment, whereas baseline TT ($P = 0.001$) exhibited an inverse association. A marginal inverse trend was also observed between baseline ALT levels and the magnitude of FIB reduction ($P = 0.092$). Other clinical variables, including age, sex, processed plasma volume, and anticoagulant dosage, demonstrated no significant associations.

Table 2
Linear regression analysis of factors associated with the magnitude of FIB reduction after the initial DFPP session.

Variables	Univariate			Multivariate		
	β	95%CI	*P*	β	95%CI	*P*
Sex						
Female	Ref.					
Male	-0.12	-0.69,0.45	0.679			
Age (years)	0.01	-0.01,0.02	0.374			
Height (cm)	0.02	-0.02,0.06	0.251			
Weight (kg)	-0.01	-0.03,0.02	0.653			
Antithrombotic agents						
No	Ref.					
Yes	0.11	-0.49,0.71	0.718			
Immunotherapy						
No	Ref.					
Yes	-0.10	-0.68,0.48	0.730			
Processed plasma volume (mL)	0.00	-0.00, 0.00	0.930			
Anticoagulant dosage (mL)	0.00	-0.01, 0.01	0.858			
ALT (U/L)	-0.01	-0.02,0.00	0.092	-0.010	-0.017,-0.003	0.009*
AST (U/L)	0.00	-0.02,0.03	0.766			
Cr (μmol/L)	-0.01	-0.02,0.01	0.308			
eGFR (mL/min)	0.00	-0.01,0.02	0.769			
Baseline PLT ($\times 10^9$/L)	0.00	0.00,0.00	0.718			

Note: The dependent variable is the magnitude of fibrinogen reduction after the initial DFPP session. Variables with $P < 0.20$ in the univariate analysis were incorporated into the multivariate regression model. CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; PLT, platelet count; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen. * $P < 0.05$ indicates statistical significance.

Variables	Univariate			Multivariate		
	β	95%CI	*P*	β	95%CI	*P*
Baseline PT (s)	0.06	-0.17,0.28	0.609			
Baseline INR	0.49	-1.96,2.93	0.691			
Baseline APTT (s)	0.01	-0.08,0.10	0.818			
Baseline TT (s)	-0.28	-0.43,-0.13	0.001	0.010	-0.088,0.108	0.835
Baseline D-dimer (mg/L)	0.33	0.07,0.59	0.016	0.070	-0.057,0.198	0.272
Baseline FIB (g/L)	0.76	0.64,0.89	< 0.001	0.767	0.589,0.945	< 0.001*

Note: The dependent variable is the magnitude of fibrinogen reduction after the initial DFPP session. Variables with $P < 0.20$ in the univariate analysis were incorporated into the multivariate regression model. CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; PLT, platelet count; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen. * $P < 0.05$ indicates statistical significance.

To adjust for potential confounders, variables with a P-value < 0.20 in the univariate analysis were incorporated into a multivariate linear regression model. The results demonstrated that baseline FIB and ALT levels were independent predictors of the magnitude of FIB reduction after the first DFPP session. A higher baseline FIB level was associated with a more pronounced post-treatment reduction in FIB (β = 0.767, 95% CI: 0.589–0.945, $P < 0.001$). Conversely, a higher baseline ALT level was independently and inversely associated with the magnitude of FIB reduction (β = -0.010, 95% CI: -0.017 to -0.003, $P = 0.009$).

3.3. Dynamic Trajectories of Fibrinogen and Immunoglobulin G During Serial DFPP Sessions

To further evaluate the prolonged impact of serial DFPP therapy on coagulation profiles and pathogenic antibody clearance, we plotted the dynamic trajectories of fibrinogen (FIB) and immunoglobulin G (IgG) across five consecutive treatment sessions (Fig. 1).

As illustrated in Fig. 1, among the 43 patients with complete continuous monitoring data, plasma levels of both FIB and IgG exhibited a progressive decline with an increasing number of treatment sessions. Following the initial DFPP session (Post-1), the FIB level dropped significantly from a baseline of 2.78 [2.31–3.42] g/L to 1.37 [1.11–1.61] g/L, representing a single-session reduction of 51.5% (calculated based on medians). Concurrently, the IgG level demonstrated a parallel decrease, falling from a baseline of 10.72 [8.74–12.98] g/L to 5.92 [5.23–7.49] g/L, which corresponds to a 44.8% reduction.

During subsequent serial treatments (Post-2 to Post-4), the overall FIB level exhibited a stepwise decline. After the third and fourth sessions (Post-3 and Post-4), the median FIB levels in the cohort decreased to

1.10 [0.90–1.31] g/L and 1.00 [0.77–1.16] g/L, respectively. This touched the clinical threshold of 1.0 g/L for severe hypofibrinogenemia, with FIB reaching its nadir for the entire treatment cycle after the fourth session. Meanwhile, the IgG level maintained a continuous downward trend, reaching its lowest point of 3.09 [2.60–3.83] g/L after the fifth session (Post-5). Following the fourth session (Post-4), the consumption trajectories of FIB and IgG diverged. While IgG continued to decline, the FIB level showed a slight rebound, rising to 1.06 [0.64–1.33] g/L after the fifth session (Post-5).

3.4. Dynamic Trajectories of Fibrinogen and Their Interaction with Baseline Liver Function

To investigate the dynamic patterns of FIB during alternate-day DFPP therapy, a linear mixed-effects model was constructed (Table 3). The results revealed a significant positive main effect of baseline ALT levels on FIB (estimate = 0.0096, t = 2.248, *P* = 0.026). Furthermore, a significant inverse interaction was observed between the number of treatment sessions and baseline ALT (estimate = -0.0044, t = -3.203, *P* = 0.002). This indicates that baseline ALT levels not only influence the absolute values of FIB but also significantly alter the slope of FIB variation across treatment sessions. Specifically, patients with higher ALT levels exhibited a more rapid and pronounced decline in FIB during serial treatments.

Table 3
Linear mixed-effects model analysis of the dynamic changes in FIB and its interaction with baseline ALT during DFPP therapy.

Fixed Effects	**Estimate**	**SE**	***t***	***P***
Intercept	1.2145	0.1290	9.416	< 0.001
Treatment sessions	0.0206	0.0384	0.537	0.592
Baseline ALT	0.0096	0.0043	2.248	0.026
Treatment sessions × Baseline ALT	-0.0044	0.0014	-3.203	0.002

Note: The linear mixed-effects model was constructed based on dynamic monitoring data from the entire cohort (N = 50). A random intercept for individual patients (variance = 0.112, standard deviation = 0.335) was incorporated to adjust for the correlation of repeated measures within the same patient during serial treatments. ALT, alanine aminotransferase; SE, standard error.

This divergent trend driven by the interaction is further illustrated in the dynamic trajectory plot (Fig. 2). Following stratification by the median baseline ALT, the two groups demonstrated comparable FIB levels during the initial phase of therapy. As the number of sessions increased, patients in the low-ALT group (< median, blue trajectory) experienced an initial mild decline, followed by a distinct stabilization and rebound after the fourth and fifth sessions (Post-4 and Post-5). In contrast, patients in the high-ALT group (≥ median, red trajectory) exhibited a continuous and progressive decline in FIB levels.

3.5. Incidence of Severe Hypofibrinogenemia Stratified by Baseline ALT Levels

To evaluate the impact of baseline liver function on FIB consumption among the 43 patients with complete continuous monitoring data, the cohort was stratified into two groups based on the median baseline ALT level. As illustrated in Fig. 3, 68.2% (15/22) of the patients in the high-ALT group (≥ median) developed severe hypofibrinogenemia (nadir FIB < 1.0 g/L). In contrast, the incidence in the low-ALT group (< median) was 42.9% (9/21). Although this difference did not reach statistical significance (*P* = 0.129), the incidence of severe hypofibrinogenemia was numerically higher in the high-ALT group. This suggests that elevated baseline ALT levels may be associated with a trend toward an increased risk of severe hypofibrinogenemia during serial DFPP sessions (RR = 1.59, 95% CI: 0.90–2.81).

3.6. Safety Outcomes and Clinical Bleeding Events

Throughout the entire DFPP treatment course, none of the 50 patients developed severe hemorrhagic complications, such as gastrointestinal bleeding, intracranial hemorrhage, or extensive mucocutaneous bleeding. Among the total cohort, only 8 patients (16.0%) experienced mild oozing at the central venous catheter insertion site. All 8 of these oozing episodes occurred within the subgroup of 43 patients with complete continuous monitoring data. Within this subgroup, oozing occurred in 5 patients (22.7%, 5/22) in the high-ALT group and 3 patients (14.3%, 3/21) in the low-ALT group, with no statistically significant difference between the two groups (*P* > 0.05). All oozing episodes were effectively managed with routine nursing interventions, including local compression and dressing changes. Despite the development of severe hypofibrinogenemia (FIB < 1.0 g/L) in some patients, no exogenous fibrinogen supplementation was required across the entire cohort, and no patient discontinued the DFPP therapy due to bleeding events. These findings suggest that patients demonstrate favorable clinical tolerance to the transient FIB depletion induced by DFPP, and the associated bleeding risks remain within a manageable range.

4. Discussion

This study systematically evaluated the dynamic consumption patterns of fibrinogen (FIB) in patients with neuroimmunological diseases undergoing serial double-filtration plasmapheresis (DFPP) and revealed for the first time the "double-edged sword" role played by baseline liver function in this process. Our results demonstrate that DFPP therapy significantly reduces plasma FIB levels. Patients with higher baseline ALT exhibited a smaller decline in FIB after the initial session; however, during serial treatments, they showed a trend toward an increased risk of developing severe hypofibrinogenemia (FIB < 1.0 g/L) (RR = 1.59, *P* = 0.129). Nevertheless, this severe hypofibrinogenemia was exceptionally well-tolerated clinically, without triggering any severe bleeding events.

The non-selective clearance of large-molecule coagulation factors by DFPP is the direct physical cause of the precipitous drop in FIB. With a molecular weight of approximately 340 kDa, the sieving coefficient of FIB during the secondary filtration phase of DFPP is significantly higher than that of pathogenic IgG (150 kDa) and similar to that of IgM (900 kDa)[7]. Previous studies have shown that DFPP has a highly efficient clearance rate for large-molecule coagulation factors, with the single-session clearance of circulating FIB reaching 63% to 69%[8]. Our data corroborate this phenomenon and further indicate that

the baseline FIB level is an independent predictor of the absolute decline after the first session. This conforms to a first-order kinetics clearance model: the higher the initial plasma concentration, the greater the absolute clearance per session.

Through continuous dynamic monitoring, this study found that FIB and IgG exhibited highly parallel consumption trajectories during DFPP therapy (Fig. 1). This visually confirms that while DFPP effectively removes large pathogenic antibodies, it inevitably causes a massive non-selective loss of physiological coagulation factors with similar molecular weights. Notably, after the fourth session, their consumption trajectories diverged. IgG continued to decline, whereas FIB levels showed a slight rebound. This reflects the differences in their in vivo synthetic and metabolic kinetics. As an acute-phase reactant synthesized by the liver, FIB has a rapid compensatory synthesis rate, whereas the resynthesis of IgG is relatively slow. This rapid hepatic compensatory mechanism partially prevents an unrestricted drop in FIB but also suggests that the patient's baseline liver function status may play a critical role in determining the dynamic balance between FIB consumption and recovery.

This study identified a seemingly paradoxical phenomenon between baseline ALT levels and the dynamic consumption trajectories of FIB. We observed that a higher baseline ALT was independently associated with a smaller initial decline in FIB, yet following serial treatments, the high-ALT group was more prone to severe hypofibrinogenemia. It must be emphasized that this study excluded patients with severe liver disease, and the baseline ALT of most of the cohort fell within the normal reference range. Therefore, "high ALT" in this context primarily represents higher levels within the normal range, rather than substantive liver failure. This indicates that even subtle differences in baseline liver function within the normal range can serve as sensitive indicators for predicting the FIB consumption trajectory during DFPP. We hypothesize that this phenomenon may be related to the hepatic compensatory synthesis mechanism and the potential depletion of its reserve capacity. FIB is a typical acute-phase reactant almost exclusively synthesized by the liver. Stimulated by the acute changes in blood volume and osmotic pressure during the initial DFPP session, a high-normal or mildly elevated ALT may reflect hepatocytes in a state of stress or mild inflammatory activation. At this stage, the liver may be more sensitive to acute-phase stimuli. Previous studies suggest it might upregulate FIB transcription and synthesis via pathways such as interleukin-6 (IL-6)[9] to partially compensate for the initial loss, thus phenomenologically presenting as a smaller net decline in FIB after the first session.

However, with continuous replacement therapy, particularly after switching to the EC-20W secondary filter with a smaller pore size from the second session onwards, the reduced filter pore size is the primary physical reason for the subsequent precipitous drop in FIB. Meanwhile, potential differences in hepatic compensatory synthesis reserve may be one of the biological mechanisms causing different patients to exhibit distinct decline trajectories when facing the same physical sieving pressure. Under this dual pressure, maintaining plasma FIB levels relies heavily on the continuous synthetic reserve of the liver. A higher baseline ALT often indicates potential subclinical micro-injury or metabolic burden in hepatocytes[10]. In this high-load state, the liver may struggle to sustain supraphysiologic levels of FIB synthesis over a prolonged period. When the clearance rate of serial plasmapheresis exceeds the

maximum synthetic rate of the liver, the compensatory mechanism may fail to keep pace. This may explain why patients with high-normal baseline ALT experience a more pronounced drop in FIB levels during subsequent sessions and manifest severe hypofibrinogenemia. As this is a retrospective study without dynamic monitoring of inflammatory factors like IL-6 and hepatic synthesis markers, the mechanisms remain theoretical hypotheses and require further validation in future prospective studies.

Regarding safety, although the incidence of severe hypofibrinogenemia in the high-ALT group reached 68.2%, no severe major bleeding events occurred in this cohort; only a few patients experienced mild oozing at the puncture site (5 in the high-ALT group, 3 in the low-ALT group). This finding holds profound clinical significance. The underlying mechanism may be akin to the "rebalanced hemostasis" observed in patients with chronic liver disease[11]. We postulate that while DFPP substantially clears FIB and procoagulant factors, it simultaneously removes anticoagulant and fibrinolytic proteins such as antithrombin and plasminogen, thereby achieving a new "coagulation-anticoagulation balance" at extremely low levels of coagulation factors. This iatrogenic hypofibrinogenemia is transient; once the treatment interval is extended or plasmapheresis is halted, the liver can typically restore FIB levels rapidly within a few days. Therefore, our data strongly support the adoption of a conservative blood product management strategy during DFPP therapy. For patients without active bleeding or with only puncture site oozing, simple local physical compression is sufficient for effective control, without the need for routine prophylactic infusion of exogenous fibrinogen or cryoprecipitate. This not only conserves precious blood resources but also fundamentally circumvents the risks of infection and allergy associated with blood products.

This study has several limitations. As a single-center retrospective study with a relatively small sample size, selection bias may exist, limiting the statistical power to detect rare severe major bleeding events. There may be a Type II error (false negative) when comparing the incidence of severe hypofibrinogenemia between the two groups. Furthermore, this study only utilized ALT as a surrogate marker for liver function and failed to comprehensively evaluate other indicators reflecting hepatic synthetic function, such as albumin and prealbumin, nor did it dynamically monitor real-time changes in liver enzymes before and after each session. Future studies should consider synchronously monitoring inflammatory factors like IL-6 to further validate the potential mechanism of hepatic compensatory depletion.

In conclusion, while effectively treating neuroimmunological diseases, DFPP induces significant consumption of FIB. Baseline liver function status is a critical indicator for predicting the dynamic trajectory of FIB during serial treatments. For patients with elevated baseline ALT, vigilance is warranted regarding the potential risk of developing severe hypofibrinogenemia during the middle and late stages of serial therapy. Nevertheless, this severe hypofibrinogenemia generally exhibits excellent clinical tolerance. Future prospective, large-sample studies should incorporate comprehensive molecular markers of coagulation and fibrinolysis to further validate the regulatory role of liver function on hemostatic homeostasis during extracorporeal blood purification therapies.

Declarations

Author contributions

T.J. drafted the manuscript. Y.M. performed the statistical analysis. X.Z., Shi.Z., F.Y were responsible for the data collection. J.S., Q.Z., Lu.W., and Shu.Z. performed the DFPP procedures. Y.G. secured the funding and critically reviewed the manuscript. All authors read and approved the final manuscript.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request, subject to institutional data protection regulations.

Declaration of conflicting interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent to participate

The requirement for written informed consent was waived by the Ethics Committee of Shanghai Punan Hospital due to the retrospective nature of the study.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai Punan Hospital (Approval No: KS2025-022). The study was conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards. The requirement for written informed consent was waived by the Ethics Committee of Shanghai Punan Hospital due to the retrospective nature of the study. All data were strictly de-identified before analysis to ensure patient confidentiality.

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Figures

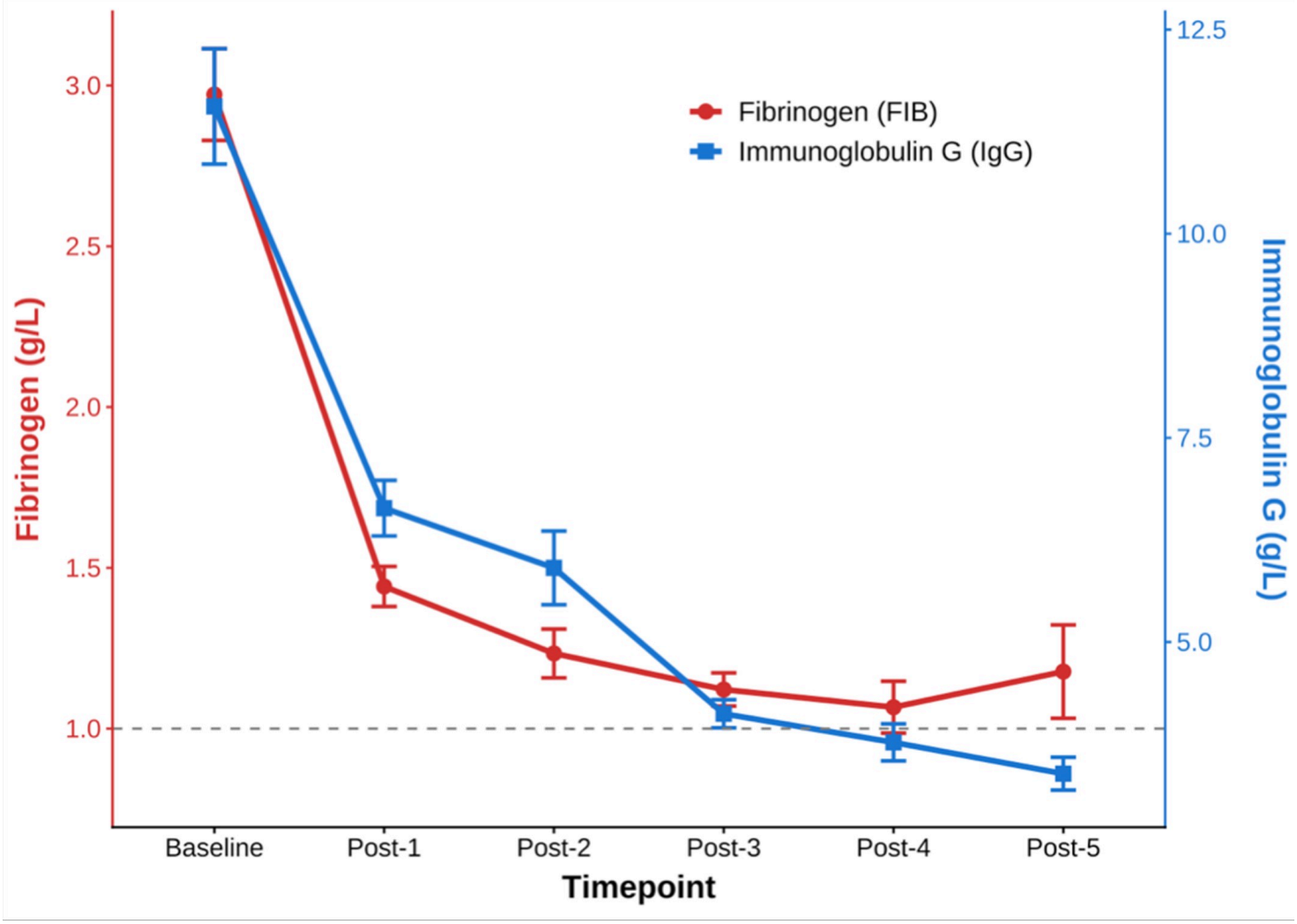


Figure 1

Dynamic trajectories of fibrinogen and immunoglobulin G during serial DFPP sessions.

The red solid line with circles and the blue solid line with squares represent the mean concentrations of FIB and IgG, respectively. Error bars indicate the standard error of the mean (SEM). The gray dashed line denotes the clinical threshold for severe hypofibrinogenemia (FIB = 1.0 g/L).

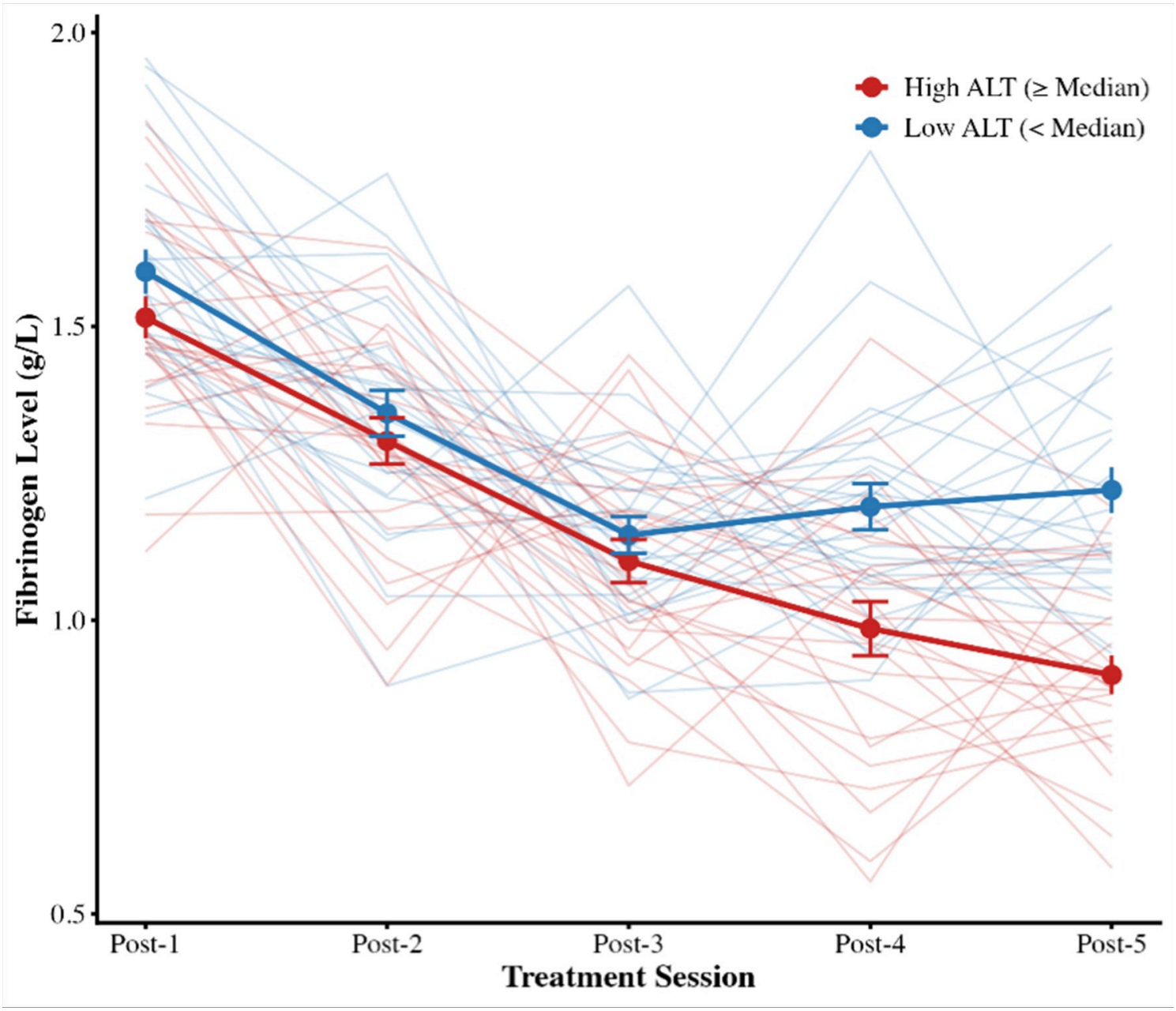


Figure 2

Dynamic trajectories of fibrinogen during DFPP therapy stratified by baseline ALT levels.

Note: The plot illustrates the dynamic changes in FIB levels during alternate-day DFPP therapy across five post-treatment time points (Post-1 to Post-5). Semi-transparent thin lines represent individual patient trajectories, while thick solid lines with error bars indicate the group means and standard errors of the mean (SEM) at each corresponding time point. Linear mixed-effects model analysis revealed a significant divergence in the trajectories between the two groups (*P*for interaction = 0.002). ALT, alanine aminotransferase.

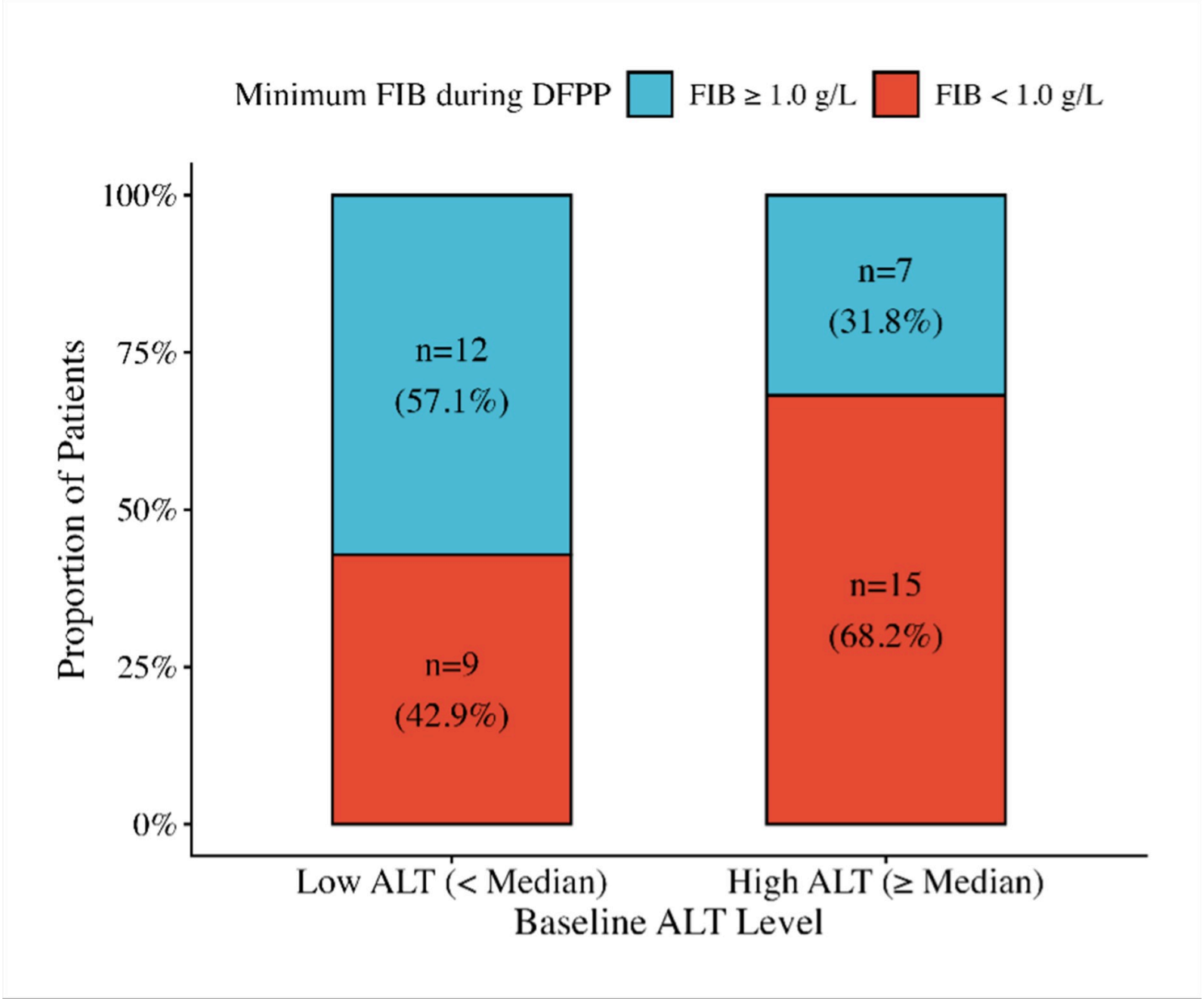


Figure 3

Incidence of severe hypofibrinogenemia during DFPP therapy stratified by baseline ALT levels.

Note: The stacked bar chart illustrates the proportions of patients with a nadir FIB < 1.0 g/L versus ≥ 1.0 g/L during serial DFPP sessions. Patients were stratified into high- and low-ALT groups based on the median baseline ALT level. Data labels within the bars indicate the number of cases (n) and percentages (%). DFPP, double-filtration plasmapheresis; FIB, fibrinogen; ALT, alanine aminotransferase.

Supplementary Files

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