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Changes in HALP Score After Interventional Therapy in Treatment-Resistant Chronic Migraine: A Retrospective Cohort of Responders

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ABSTRACT

Objective: Chronic migraine (CM) is a disabling neurovascular disorder often linked to systemic low-grade inflammation. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score has been proposed as an integrative biomarker of nutritional and inflammatory status; however, its role in migraine remains unclear. This study examined whether HALP improves after interventional therapy in treatment-resistant CM and whether changes correlate with clinical outcomes.

Materials and Methods: This retrospective study included 128 CM patients who were unresponsive to ≥3 months of pharmacological prophylaxis and subsequently achieved a ≥50% reduction in monthly headache frequency after interventional treatment were analyzed. Patients received either repetitive greater occipital nerve blocks or pulsed radiofrequency. Clinical outcomes (headache frequency, numerical rating scale (NRS), and analgesic consumption) and laboratory parameters (hemoglobin, albumin, lymphocyte, and platelet counts) were recorded at baseline and 6 months. HALP was calculated as (Hemoglobin (g/L) × Albumin (g/L) × Lymphocyte count ($\times 10^9$/L) / Platelet count ($\times 10^9$/L)). Associations were tested with Spearman's ρ.

Results: At 6 months, patients showed significant improvements: NRS decreased from 8.0 (7.0–9.0) to 3.0 (3.0–4.0), headache frequency from 19.0 (16.8–21.0) to 3.0 (2.0–4.0), and analgesic consumption from 8.0 (6.0–9.0) to 3.0 (2.0–4.0) tablets/month (all $p<0.001$). HALP increased from 49.3 (36.2–58.4) to 66.5 (56.0–75.7) ($p<0.001$). ΔHALP was weakly but statistically significantly correlated with reduced headache frequency ($\rho=0.195$, $p=0.027$), but not with ΔNRS ($\rho=0.091$, $p=0.308$) or Δanalgesic consumption ($\rho=0.103$, $p=0.246$).

Conclusion: Interventional treatments for CM were associated with significant increases in HALP scores, suggesting modulation of systemic inflammatory–nutritional status. As ΔHALP was only weakly related to reduced attack frequency and unrelated to pain intensity or analgesic use, HALP may reflect biological changes at the group level and could serve as a monitoring biomarker; however, its individual-level clinical relevance appears to be limited.

Keywords: Albumin, Chronic migraine, Hemoglobin, lymphocyte, Nerve block, Neuroinflammation, platelet score, Pulsed radiofrequency, Systemic biomarker

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INTRODUCTION

Chronic migraine (CM) is a disabling neurological disorder characterized by frequent headache episodes that significantly impair quality of life and daily functioning. It is estimated that approximately 1–2% of the global population is affected by CM, with a higher prevalence among women and individuals of working age.[1] According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), CM is defined as headache occurring on 15 or more days per month for more than 3 months, with features of migraine headache on at least 8 of those days.[2] Compared to episodic migraine, CM is associated with greater disease burden, including increased attack frequency, higher rates of medication overuse, psychiatric comorbidities, and a lower health-related quality of life.[3]

For patients with CM who do not respond to medical treatment, greater occipital nerve (GON) block and pulsed radiofrequency (PRF) therapy are two effective interventional methods. A GON block reduces neuronal stimulation by targeting the peripheral nerves, while PRF therapy provides long-term pain relief by modulating the nerve at low temperatures. Both methods have been reported to effectively reduce the frequency and intensity of pain.[4-7]

The pathophysiology of CM is complex and multifactorial, involving central sensitization, altered pain modulation, and potentially, sustained neuroinflammatory processes.[8]

Although the exact mechanisms are not fully understood, a body of evidence suggests that neurogenic inflammation and systemic immune dysregulation play a significant role in the development of migraines.[9,10]

Neuroinflammatory cascades involve the activation of the trigeminovascular system, the release of vasoactive neuropeptides such as calcitonin gene-related peptide, and the upregulation of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6.[11-13] These mediators promote the persistence and chronicity of migraine attacks by increasing the excitability of both peripheral and central nociceptors.[14] Alongside these mechanisms, several hematologic markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and C-reactive protein (CRP), have been investigated as peripheral indicators of systemic inflammation in migraine patients.[15-17] More recently, broader inflammatory indices have also been proposed, including systemic immune–inflammation-based scores[18] and composite biomarker approaches,[19] highlighting the increasing recognition of migraine as a disorder with systemic inflammatory underpinnings. However, these parameters only reflect individual components of the inflammatory response and may not fully capture the complexity of immune-nutritional interactions in chronic pain conditions.

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a composite biomarker initially developed in oncology to reflect the combined state of hematological, nutritional, and inflammatory pathways.[20] In contrast to unidimensional biomarkers, the HALP score integrates multiple physiological components: hemoglobin, reflecting oxygen transport capacity and anemia; albumin, representing nutritional status and hepatic synthetic function; lymphocytes, as markers of immune competence; and platelets, which participate in proinflammatory processes. Each of these parameters is known to be modulated by systemic inflammation, physiological stress, and chronic pain factors intrinsically linked to the pathophysiology of migraine.[14] Despite its theoretical relevance, the HALP score has not yet been explored in patients with migraine. In this study, we aimed to evaluate the changes in HALP scores from pre- to post-treatment among patients with CM who underwent a standardized interventional protocol involving either a GON block or PRF therapy. We hypothesized that a significant reduction in headache frequency would be associated with an improvement in HALP scores. Furthermore, we aimed to investigate whether HALP may serve as a novel integrative biomarker of systemic inflammation in the management of migraine. If validated, the HALP score could serve as a simple and cost-effective tool to monitor treatment response or stratify inflammatory burden in clinical practice.

MATERIALS AND METHODS

Ethical Considerations

The study was approved by the Local Ethics Committee (Approval No: 12/14; Date: July 17, 2025). This retrospective analysis of anonymized patient data was conducted in accordance with the principles of the Declaration of Helsinki. The committee waived the requirement for informed consent, as permitted by institutional and national regulations.

Study Design and Population

This retrospective observational study was conducted at the pain clinic of a tertiary education and research hospital between January 2023 and June 2025. Adult patients diagnosed with CM based on the ICHD-3 criteria, who had undergone at least 3 months of standard pharmacological prophylaxis without meaningful clinical response, were included. They were referred to our clinic for interventional treatment due to frequent and severe migraine attacks.

Only patients demonstrating a ≥50% reduction in monthly headache frequency at 6 months post-treatment were

included in the final analysis. Although a controlled group was initially considered, the small number of non-responders (*n*=7) precluded meaningful statistical comparison. Therefore, pre-treatment clinical status served as the internal control for within-subject comparisons.

Inclusion Criteria

Patients aged 18–65 years, diagnosed with CM per ICHD-3, receiving standard prophylactic therapy for at least 3 months without adequate control of attacks, with available pre- and post-treatment laboratory data (CBC and albumin), and who underwent standardized interventional treatment.

Exclusion Criteria

Medication overuse headache, acute or chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease, and vasculitis), autoimmune diseases, hematological disorders or malignancies, active infection or fever within 14 days before evaluation, chronic liver or renal failure, cachexia, corticosteroid or immunosuppressive use, pregnancy or breastfeeding, and incomplete medical records.

Treatment Protocol

Experienced pain physicians performed all procedures under sterile conditions.

GON Block

A 25-gauge needle was introduced at the level of the occipital protuberance using anatomical landmarks. After negative aspiration, 2 mL of a mixture containing 1 mL 0.5% bupivacaine and 1 mL 2% lidocaine was injected per side. No corticosteroids were used. Blocks were performed weekly for the first 4 weeks, and then every other week for a total of 8 sessions.

PRF of the GON

Following local anesthesia, a 22-gauge, 5-mm active tip radiofrequency cannula was advanced toward the GON guided by anatomical landmarks. Correct positioning was confirmed through sensory stimulation at 50 Hz (paresthesia at ≤0.5 V) and the absence of a motor response at 2 Hz. PRF was applied at 65 V, 42°C, 20 ms pulse width, 2 Hz frequency, for 240 s (2 cycles×120 s). The maximum tip temperature did not exceed 42°C.

Minor complications (bleeding, dizziness, local pain) were recorded immediately after the procedure and during follow-up; no serious adverse events occurred.

Data Collection

Data integrity was ensured through comprehensive clinical documentation. A successful treatment response was defined as a ≥50% reduction in monthly headache frequency, consistent with the International Headache Society and American Headache Society guidelines. Initially, medical records of patients diagnosed with CM who underwent either GON block or PRF between June 2023 and June 2025 were reviewed, identifying a total of 189 cases. Fifty-four patients were excluded due to missing baseline data (*n*=13), loss to follow-up (*n*=17), or unavailable laboratory values at the 6-month visit (*n*=24). Due to the limited number of non-responders (*n*=7), only responders were included in the final analysis. Ultimately, 128 responders were included in the final analysis (Fig. 1).

Extracted data comprised demographic variables (age, sex); clinical characteristics (disease duration in months, pain intensity using the numerical rating scale (NRS, 0–10), monthly headache frequency, and analgesic consumption); and laboratory parameters (hemoglobin, lymphocyte count, platelet count, and serum albumin), recorded at baseline and

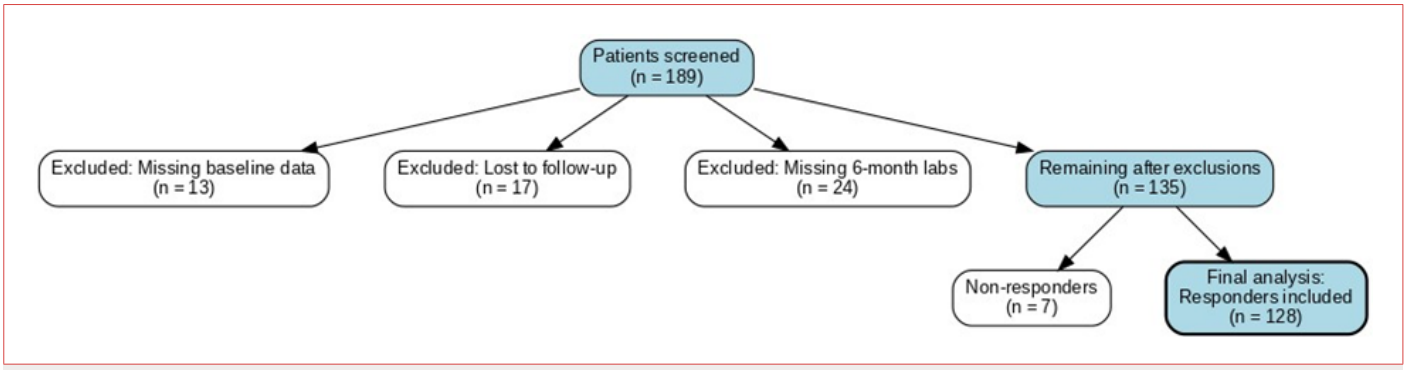

Figure 1. Flowchart of patient selection and inclusion process. A total of 189 patients with chronic migraine were initially screened. After exclusions for missing baseline data (*n*=13), loss to follow-up (*n*=17), and absence of 6-month laboratory values (*n*=24), 135 patients remained. Of these, 7 did not achieve the predefined treatment response and were excluded. The final analysis included 128 responders.

at the 6-month follow-up. To minimize bias, data extraction and screening were conducted by a researcher independent of the treating physician.

The primary outcome was the change in the HALP score, calculated as:

HALP=Hemoglobin (g/L)×Albumin (g/L)×Lymphocyte count ($\times 10^9$/L)/Platelet count ($\times 10^9$/L).

This composite index reflects systemic inflammatory and nutritional status; an increase is considered indicative of systemic improvement. Secondary analyses examined the correlation between HALP changes and clinical outcomes, including pain intensity (as measured by the NRS), attack frequency, and analgesic consumption.

Laboratory analyses were performed using standardized automated analyzers at the institutional central biochemistry and hematology laboratories, with both internal quality control and external accreditation procedures. Reference ranges were: hemoglobin 135–180 g/L (males) and 125–160 g/L (females); serum albumin 35–52 g/L; lymphocyte count 1.16–3.18 $\times 10^9$/L; and platelet count 150–450 $\times 10^9$/L.

Statistical Analysis

All statistical analyses were planned a priori, with distributional assumptions checked before inferential testing. Continuous variables were summarized as median (interquartile range, IQR), and categorical variables as *n* (%). Normality was assessed using the Shapiro–Wilk test and by visual inspection of distributions. Given that key outcomes (monthly attack frequency, NRS, and analgesic consumption) exhibited non-normal distributions and several laboratory variables did not consistently meet normality across subgroups, non-parametric methods were adopted for inference.

Within-subject changes from baseline to 6 months were tested using the Wilcoxon signed-rank test. Between-group comparisons (repetitive GON blocks vs. PRF, PRF) used the Mann–Whitney U-test for continuous variables and Pearson's χ^2 (or Fisher's exact when appropriate) for categorical variables.

Change scores (Δ) were coded so that higher values reflect clinical improvement: ΔNRS = baseline − month 6; Δanalgesic consumption = baseline − month 6; Δattack frequency = baseline − month 6; and ΔHALP = month 6 − baseline.

Associations between changes in HALP (ΔHALP) and clinical outcomes were examined with Spearman's rank correlation (ρ). For all primary analyses, effect sizes were reported ($r=z/\sqrt{N}$ for Wilcoxon) together with 95% confidence intervals for median differences (bootstrap, B=10,000) and for correlation coefficients (Fisher's z approximation). All p-values were two-sided with α=0.05; very small p-values are reported as p<0.001. All analyses were performed using IBM Statistical Package for the Social Sciences Statistics, version 25.

RESULTS

A total of 128 patients were included (110 females [85.9%], 18 males [14.1%]) with a mean age of 44.4±10.7 years and a mean disease duration of 8.1±2.6 months. Based on the interventional approach, 88 patients (68.8%) underwent repeated GON blocks, while 40 patients (31.2%) received PRF. Baseline distributions were comparable between groups, with no significant differences in age, sex, disease duration, baseline headache frequency, NRS, analgesic consumption, or HALP (all p>0.05).

At 6 months, patients demonstrated significant improvements in all clinical outcomes. Median NRS decreased from 8.0 (7.0–9.0) to 3.0 (3.0–4.0), with a median reduction of 5.0 (95% CI, 4.0–6.0; Wilcoxon r=0.82; p<0.001). Analgesic consumption declined from 8.0 (6.0–9.0) to 3.0 (2.0–4.0) tablets/month, corresponding to a median reduction of 5.0 (95% CI, 4.0–6.0; r=0.78; p<0.001). Monthly headache frequency decreased from 19.0 (16.8–21.0) to 3.0 (2.0–4.0), with a median reduction of 16.0 (95% CI, 15.0–17.0; r=0.89; p<0.001). Laboratory measures also improved, including increases in hemoglobin, albumin, and lymphocyte counts, decreases in platelet counts, and a marked rise in HALP (49.3 [36.2–58.4] to 66.5 [56.0–75.7]; median difference 16.0 [12.0–20.0]; r=0.71; p<0.001, Table 1).

Correlation analyses showed that ΔHALP was weakly but significantly associated with reductions in monthly headache frequency (ρ=0.195; 95% CI, 0.020–0.361; p=0.027), whereas correlations with ΔNRS (ρ=0.091; 95% CI, −0.084–0.261; p=0.308) and Δanalgesic consumption (ρ=0.103; 95% CI, −0.072–0.272; p=0.246) were not significant (ρ=0.195, p=0.027; Table 2 and Fig. 2).

Subgroup Analysis

Age distributions did not differ significantly between the block and PRF groups (Mann–Whitney U, p=0.140), and female predominance was similar (85.2% vs. 87.5%; χ^2, p=0.95).

Both treatment groups showed significant reductions in monthly migraine frequency at 6 months (Wilcoxon, both "p<0.001). In the block group, frequency decreased from 19.0 ([17.0–21.0] to 3.0 [2.0–4.0]; in the PRF group, from 19.0 [17.0–22.0] to 3.0 [2.0–4.0] (baseline in Table 1; 6-month distributions in Table 3).

Between-group comparisons showed no significant differences at baseline (age p=0.140; disease duration p=0.874; attack

Table 1. Change from Baseline to 6 Months (Wilcoxon, Effect Size, CI).

Variable	Baseline median (IQR)	6 mo median (IQR)	Median difference (6mo – Baseline)	Wilcoxon p	Effect size r	N
NRS	8.0 (7.0–9.0)	3.0 (3.0–4.0)	−5.0 (−6.0 to −4.0)	<0.001	−0.862	128
Analgesic consumption (tabs/mo)	8.0 (6.0–9.0)	3.0 (2.0–4.0)	−5.0 (−6.0 to −4.0)	<0.001	−0.853	128
Attack frequency (/mo)	19.0 (16.8–21.0)	3.0 (2.0–4.0)	−16.0 (−17.0 to −15.0)	<0.001	−0.869	128
Hemoglobin (g/L)	124.5 (121.0–132.0)	129.0 (124.0–135.0)	+4.0 (+3.0 to +5.0)	<0.001	+0.737	128
Albumin (g/L)	41.3 (39.8–44.3)	43.4 (41.4–46.7)	+2.1 (+1.4 to +2.5)	<0.001	+0.744	128
Lymphocyte ($\times10^9$/L)	2.1 (1.8–2.3)	2.3 (2.1–2.6)	+0.2 (+0.1 to +0.2)	<0.001	+0.408	128
Platelet ($\times10^9$/L)	228.5 (196.0–291.5)	198.0 (176.0–222.0)	−30.0 (−31.0 to −19.0)	<0.001	−0.725	128
HALP	49.3 (36.2–58.4)	67.1 (56.0–75.7)	+17.0 (+15.0 to +20.0)	<0.001	+0.830	128

Median difference was calculated as (6 months − Baseline). Accordingly, positive values denote an increase and negative values denote a decrease. Effect size r (Wilcoxon) is reported with its sign to indicate the direction of change. NRS: Numerical Rating Scale; mo: month; tabs: tablets; g/L: grams per liter; $\times10^9$/L: cells $\times10^9$ per liter; HALP: Hemoglobin×Albumin×Lymphocyte/Platelet.

Table 2. Correlations between ΔHALP and clinical improvements at 6 months.

Outcome (Δ, + = improvement)	Spearman ρ	95% CI	p-value	N
NRS (baseline – 6 months)	0.091	(-0.084, 0.261)	0.308	128
Analgesic consumption (baseline – 6 months)	0.103	(-0.072, 0.272)	0.246	128
Attack frequency (baseline – 6 months)	0.195	(0.020, 0.361)	0.027*	128

Notes: Δ values coded so that positive numbers reflect clinical improvement (e.g., ΔNRS=baseline – 6 months; ΔHALP=6 months – baseline). 95% CI: confidence interval. *p<0.05.

frequency p=0.690; NRS p=0.359; analgesic consumption p=0.681; HALP p=0.748; Table 1) or at 6 months (attack frequency p=0.504; NRS p=0.222; analgesic consumption p=0.484; HALP p=0.464; Table 3).

In subgroup analyses, HALP scores increased from baseline to 6 months in both groups. In the PRF group, ΔHALP was not significantly correlated with changes in headache frequency (ρ=0.16, p=0.31), NRS (ρ=−0.14, p=0.39), or analgesic consumption (ρ=0.13, p=0.44). In the block group, a weak but statistically significant positive correlation was observed between ΔHALP and reduction in monthly headache frequency (ρ=0.22, p=0.038). In contrast, correlations with ΔNRS (ρ=0.20, p=0.066) and Δanalgesic consumption (ρ=0.07, p=0.54) were not significant (Table 4).

Table 3. Six-month outcomes by treatment group (Block vs PRF).

Variable	Block	PRF	p-value
NRS at 6 Months	3.00 (3.00–4.00)	3.00 (2.75–4.00)	0.222
Analgesic consumption at 6 Months (tablets/mo)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	0.484
Attack Frequency at 6 Months (episodes/mo)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	0.504
Hemoglobin 6 Months (g/L)	130.00 (124.00–134.25)	129.00 (124.75–135.00)	0.971
Albumin 6 Months (g/L)	43.55 (41.38–46.40)	43.25 (41.38–47.62)	0.992
Lymphocyte 6 Months ($\times10^9$/L)	2.32 (2.08–2.59)	2.31 (2.06–2.54)	0.616
Platelet 6 Months ($\times10^9$/L)	198.00 (176.00–217.25)	204.50 (177.50–250.75)	0.275
HALP 6 Months	67.52 (58.41–75.57)	64.55 (50.35–76.02)	0.464

Notes: Six-month clinical and laboratory outcomes are summarised as median (IQR). Between-group comparisons used the Mann–Whitney U test (two-sided, α=0.05). PRF, pulsed radiofrequency; IQR: Interquartile range; NRS: Numerical rating scale; HALP, hemoglobin×albumin×lymphocyte/platelet.

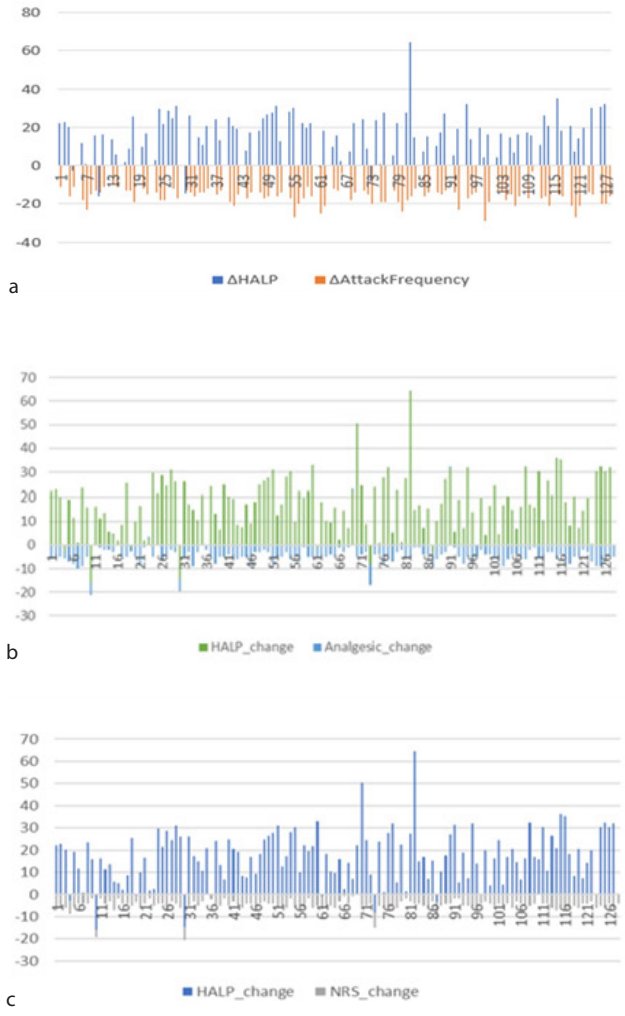

Figure 2. Associations between Δ hemoglobin, albumin, lymphocyte, and platelet (HALP) and clinical parameters at 6 months: Attack frequency, pain intensity (numerical rating scale [NRS]), and analgesic consumption. **(a)** ΔHALP versus reduction in monthly headache frequency. **(b)** ΔHALP versus reduction in analgesic consumption. **(c)** ΔHALP versus reduction in NRS.

DISCUSSION

In our study, patients who underwent either repetitive GON blocks or PRF treatment showed a significant increase in HALP scores after treatment (from 48.78±14.39 to 65.37±14.29, p<0.001). To the best of our knowledge, this is the first study to longitudinally evaluate the HALP score in treatment-resistant CM following GON blocks or PRF, and to relate the change in HALP score (ΔHALP) to clinical outcomes. This improvement may reflect not only clinical recovery but also a modulation of systemic inflammatory and nutritional status. However, since only responders were included in the analysis, the limited variability should be considered when interpreting biomarker–outcome associations. The increase in HALP showed a statistically significant but weak association with reductions in monthly attack frequency, indicating a limited link between systemic biological changes and clinical response. Given the responder-only design and the limited variability, HALP should be viewed as a biological trend at the group level for now. It does not seem to be a reliable predictor for individual patients.

Table 4. Subgroup correlations of ΔHALP with clinical improvement (Block and PRF analysed separately).

Clinical Parameter	Spearman's ρ	p-value
PRF Group		
Change in headache frequency	0.1632	0.314
Change in NRS	-0.1403	0.388
Change in analgesic consumption	0.1267	0.436
Block Group		
Change in headache frequency	0.2219	0.038
Change in NRS	0.1972	0.066
Change in analgesic consumption	0.0662	0.540

Notes: Within-group associations between ΔHALP and changes in monthly headache frequency, NRS, and monthly analgesic consumption were assessed using Spearman's rank correlation (ρ) (two-sided, α=0.05). Results are presented separately for the Block and PRF subgroups. Abbreviations: PRF, pulsed radiofrequency; NRS: Numerical Rating Scale; Δ, change from baseline to 6 months.

No significant correlations were found with pain intensity (NRS) or analgesic consumption. This dissociation aligns with prior observations that systemic inflammatory indices correlate more closely with disease activity than with subjective pain perception.

NLR, CRP, and cytokine levels, which are often correlated with migraine burden but not consistently with pain intensity.[9,15,21] Accordingly, HALP is best positioned as a monitoring biomarker of biological disease activity rather than a surrogate for pain severity. While the subgroup signal looked more evident in the nerve block cohort, single-session PRF is generally considered clinically comparable to repeated blocks, and our analysis was not powered to test between-modality differences. Therefore, we think this difference is preliminary and likely due to the small sample size, rather than a real biological difference between the treatments.

In recent years, the HALP score has emerged as a comprehensive biomarker of systemic inflammatory and nutritional status,

particularly in oncology. Studies have demonstrated that low HALP values are associated with a poor prognosis. At the same time, higher scores are linked to better survival and improved treatment responses in cancers such as stomach, colon, lung, and bladder.[20,22] Moreover, large-scale cohort studies have suggested a non-linear association between HALP and mortality.[23] Beyond oncology, the HALP score has also been evaluated as a systemic predictor of outcomes in ischemic stroke, cardiovascular disease, and diabetic complications.[24,25] Low HALP scores have been associated with a poor prognosis in several neuroinflammatory and metabolic disorders.[26] Beyond oncology, the role of HALP in chronic pain and migraine is largely unexplored. Given reports of non-linear (e.g., thresholded or J-shaped) associations in other populations,[23] future studies should explicitly test for non-linearity (e.g., using restricted cubic splines) rather than assume linear effects.

At a component level, the overall HALP rise in our cohort appears to be driven primarily by platelet deactivation and lymphocyte recovery, with albumin and hemoglobin contributing more modestly—an immune-hematologic pattern compatible with attenuation of attack-related neuroinflammation and platelet hyperactivation. These patterns align with reports of platelet hyperactivation and immune dysregulation during migraine attacks.[27-31] Among the HALP components, albumin is a negative acute-phase reactant that tends to increase with suppression of inflammation.[32] In our cohort, the rise in albumin was a key factor driving HALP improvement, which may reflect a reduced inflammatory burden. Control of migraine attacks may have led to lower cytokine levels (e.g., IL-6, TNF-α), which normally inhibit hepatic albumin synthesis, alongside improvements in nutritional status and oral intake. The increase in hemoglobin levels is also noteworthy. Hemoglobin reflects both erythropoiesis and systemic health; iron deficiency anemia is frequently reported in migraine patients and may be associated with an increased frequency of attacks.[33,34] Thus, the post-treatment increase in hemoglobin may represent systemic recovery, although its direct effect on migraine outcomes remains uncertain.

The observed rise in lymphocyte counts supports the concept that migraine is not solely a vascular disease but also involves immune-mediated neuroinflammation. Elevated NLR during acute migraine, driven by neutrophilia and lymphocytopenia, is considered an inflammatory marker.[27] Therefore, an increase in lymphocyte levels following treatment could indicate regression of systemic inflammation and rebalancing of immune function. In parallel, the reduction in platelet counts after treatment is consistent with reports of platelet hyperactivation during migraine attacks.[28-31] This hematologic response may reflect control of systemic inflammation and contribute to the overall HALP increase. Standardizing preanalytical conditions for blood sampling (fasting status, time of day, and interictal timing) would further reduce biological and circadian variability in HALP and its components. Standardization would also facilitate between-study comparability and reduce preanalytical bias in composite scores such as HALP.

This study has several limitations. First, the retrospective and non-randomized design without a control group precludes causal inference. Importantly, patients served as their own internal controls through within-subject pre–post comparisons, which partially mitigates the absence of an external control group. Although a comparative group of non-responders was initially considered, the minimal number of such cases (n=7) prevented meaningful analysis. All interventions were performed by a single-experienced pain specialist using standardized protocols, while data collection was conducted independently by a blinded investigator, reducing bias. Nevertheless, unmeasured confounders such as nutritional intake, albumin kinetics, iron repletion, body weight change, intercurrent infection or inflammation, menstrual phase, hydration, and adjustments in preventive pharmacotherapy may have influenced HALP independently of the procedures. Given multiple endpoints and subgroup analyses, correlation findings should be regarded as exploratory; confirmatory work should prespecify outcomes and control for multiplicity. Finally, the responder-only frame restricts variability and likely attenuates biomarker–outcome coupling; inclusion of non-responders in prospective cohorts is essential.

CONCLUSION

The significant increase in HALP scores observed after interventional therapy may represent a systemic biological response in CM. Given the chronic low-grade neuroinflammation underlying migraine, HALP may provide indirect insights into inflammatory activity and treatment response in this population. While HALP has been widely studied in oncology and cardiometabolic conditions, to our knowledge, this is the first report on its potential relevance in treatment-resistant CM. Overall, HALP currently appears to be more suited for monitoring biological activity than for predicting individual clinical responses. These results are hypothesis-generating, and further prospective, randomized, large-scale studies are warranted to validate HALP as a monitoring biomarker in migraine management.

DECLARATIONS

Ethics Committee Approval: The study was approved by Antalya Training and Research Hospital Ethics Committee (No: 12/14 Date: 17/07/2025).

Informed Consent: The committee waived the requirement for informed consent, as permitted by institutional and national regulations.

Conflict of Interest: The authors declare that there is no conflict of interest.

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