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Prediction of Postoperative Recurrence of Chronic Subdural Hematoma Using Preoperative Systemic Immune Inflammation Index and Eosinophils

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Abstract

Objective Chronic subdural hematoma (CSDH) is a common neurological problem with significant recurrence after surgery. Risk considerations can vary, ranging from patient-related factors to those related to the surgical procedure. This study explores the association between preoperative eosinophil count and systemic immune inflammation (SII) with CSDH recurrence.

Materials and Methods We conducted a prospective analysis of 105 patients with equal numbers of CSDHs who underwent surgery for CSDH between January 2023 and January 2024. The preoperative eosinophil counts, along with other differential leukocyte counts, were measured. The SII index was calculated using the standard formula (SII = neutrophil count × platelet count/lymphocyte count). Multivariate and univariate regression analyses were performed to assess the association between risk factors and CSDH recurrence.

Results The preoperative eosinophil count showed a significant correlation with recurrence ($p < 0.001$). The SII index was significantly higher in patients with recurrent CSDH ($p = 0.003$). Neutrophils were found to be significantly associated with CSDH recurrence ($p = 0.038$). Age ($p < 0.001$) and SII ($p = 0.005$) were found to be independent predictors of CSDH recurrence, whereas hematoma volume ($p < 0.001$) and the antiplatelet regimen were a significant predictor of CSDH recurrence ($p = 0.047$). Variables like male gender, diabetes mellitus, anticoagulants, and hematoma volume were associated with eosinophil-rich or eosinophil-poor status.

Conclusion Preoperative eosinophil count, neutrophils, and the SII index may serve as potential predictors of CSDH recurrence. Further studies with larger sample sizes are needed to validate these findings.

Keywords
- chronic subdural hematoma
- recurrence
- eosinophils
- systemic immune inflammation
- predictors

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Introduction

Chronic subdural hematoma (CSDH) is a prevalent neurosurgical condition characterized by the accumulation of blood between the dura mater and the arachnoid membrane surrounding the brain.[1,2] It mainly affects older adults, with an incidence that increases significantly with age, peaking between 60 and 80 years of age.[3] Although the precise etiology of CSDH is still unknown, it is usually accepted to be the consequence of bridging vein rupture in the subdural region, frequently as a result of mild head trauma.[4] This causes blood to gradually accumulate and cause brain tissue damage underneath, resulting in a range of neurological symptoms.[5]

The mainstay of treatment for symptomatic CSDH is surgical hematoma evacuation, with burr hole craniotomy and drainage being the most often sought technique.[6] Up to 20% of cases experience CSDH recurrence, which poses a considerable clinical issue even with the typically positive outcomes of surgery.[7] In addition to requiring more surgical procedures, recurrence increases the risk of complications and worsen long-term neurological effects. Therefore, determining credible preoperative indicators for CSDH recurrence is crucial to enhancing patient care and achieving better outcomes. Peripheral blood indicators may play a role in anticipating the return of CSDH, according to recent studies.[8–11] Promising choices among these measures include eosinophil levels and the systemic immunological inflammation (SII) index.[12,13]

Eosinophils are a subset of white blood cells that are involved in inflammation reactions as well as allergy and parasite disorders.[14,15] Research has shown that eosinophils are present in both the surrounding membrane and the hematoma fluid, suggesting that they may play a role in the pathophysiology of CSDH.[16–18] According to certain theories, eosinophils could be involved in the persistent inflammation and neovascularization that are seen in CSDH, which could affect the likelihood of recurrence.[19] Increased preoperative eosinophil levels have been linked to a higher chance of CSDH recurrence.[20] However, the precise processes behind this correlation are yet unknown.

Apart from eosinophils, another new marker that has been utilized to predict outcomes in a variety of medical illnesses such as cancer, cardiovascular disease, and inflammatory disorders is the SII.[21] The SII index reflects the balance between systemic inflammation and immune response and is dependent on the levels of neutrophils, platelets, and lymphocytes in the peripheral blood. Blood measures, such as the absolute counts of neutrophils, lymphocytes, and platelets, are used to compute the SII.[22] Leukocyte counts around the brain's membranes have been linked to alterations in most investigations,[23] suggesting that they could be a valuable diagnostic sign that affects the SII index. It offers a thorough assessment of immune function and systemic inflammation, indicating the ratio of pro- to anti-inflammatory reactions. Therefore, the present study was undertaken to investigate the association between preoperative eosinophil levels, SII, and the risk of postoperative CSDH recurrence.

Materials and Methods

The sample size was calculated and resulted in a sample size of 119 patients. The 119 recruited patients had CSDHs in 123 cerebral hemispheres. The prospective study was conducted from January 2023 to January 2024 at the Department of Neurosurgery, Institute of Medical Sciences, Banaras Hindu University. The study received approval from the institute's ethical board. The presumptive diagnosis of CSDH was made using noninvasive methods, like magnetic resonance imaging (MRI) or computed tomography (CT) scans. The inclusion and exclusion criteria were followed to recruit the patients. Patients diagnosed with CSDH, confirmed by neuroimaging such as CT or MRI, and exhibiting neurological symptoms attributable to CSDH, who underwent burr hole drainage or craniotomy, and were able to attend follow-up visits, were included in the study. Patients with a history of previous neurosurgical procedures unrelated to the current CSDH, those with other significant intracranial pathologies such as brain tumors or arteriovenous malformations, and patients with severe systemic diseases that might confound the study results, such as active malignancy, were excluded from the study. Informed consent was obtained from all participants, and thorough discussions were held regarding any potential discomfort, disadvantages, and outcomes of the study with the participants.

Baseline clinical and demographic characteristics of the patients were recorded. Clinical characteristics were defined as follows. A diastolic blood pressure of 90 mm Hg or higher, a systolic blood pressure of 140 mm Hg or higher, or the use of antihypertensive medication were the markers of hypertension. The usage of hypoglycemic medications or a hemoglobin A1c value greater than 6.5% were used to characterize diabetes mellitus. A platelet counts of less than $100 \times 10^3/\mu L$ was defined as thrombocytopenia. At presentation, patients were classified as either H1 blocker, steroid, oral antiplatelet, or anticoagulant users.

Ten days before surgery, the preoperative differential leukocyte count (DLC) was measured using peripheral blood. The SII was calculated using the following formula: SII = neutrophil count $\times$ platelet count/lymphocyte count.[24] The standard surgical protocol was followed for doing the burr hole surgery. The surgical procedure was outlined as follows: burr hole craniotomy was performed under local anesthesia, followed by evacuation and irrigation of the hematoma. Only in the cases where the initial burr hole proved challenging for irrigation and evacuation of hematoma was a second burr hole created. For irrigation, normal saline was utilized.[25] A closed drainage system was usually left in the hematoma cavity for 12 to 48 hours after surgery. Following surgery, the patients were monitored for a minimum of 3 months or until the CSDH disappeared, indicating resolution. Any future recurrence of postoperative CSDH was documented. A symptomatic ipsilateral growth of the CSDH on postoperative day 7 or later, indicating the necessity for repeat surgery, was considered a recurrence of CSDH. Severe headaches, dementia, decreased consciousness, and neurological deficits, including limb weakness or aberrant gait, were

considered indicative of CSDH recurrence. Early subdural hemorrhage after surgery that happened before postoperative day 6 was regarded as a surgical complication rather than a recurrence.

Data Analysis

The data were anonymously coded and recorded in Microsoft Excel 2021 (Microsoft., Inc). Statistical analysis was conducted using SPSS software version 29 (SPSS Inc., Chicago, IL). Descriptive statistical analysis was employed to present the data in percentages and frequencies. Logistic regression analysis was carried to investigate the risk factors for CSDH recurrence. A p-value less than 0.05 was considered statistically significant. The data were presented with the mean ± standard deviation. Missing data were addressed using several imputation strategies. This method involved creating several complete datasets by filling in missing values with plausible estimates based on observable data patterns. Each imputed dataset was then analyzed independently. The results from these analyses were pooled to produce the final estimates, thus accounting for the uncertainty associated with the missing data.

To control confounders, we ran multivariate regression analyses, which allowed us to analyze the independent relationship between the variables of interest and the result while correcting for any confounding factors.

Results

Initially, we identified 119 patients who underwent 123 surgeries for CSDH. Among these, 12 patients were excluded from the study due to insufficient data regarding their medical history, and 2 patients with four CSDH surgeries did not attend the follow-up. Finally, 105 patients participated in the study (►**Fig. 1**). Out of the 105 patients, CSDH recurrence was observed in 11 patients, accounting for approximately 10.5% of the recruited patients. The demographic variables, along with the presence of certain comorbidities and medications involved, are shown in ►**Table 1**.

Preoperative DLC was evaluated to explore any association with CSDH recurrence. The distribution revealed that eosinophil count was significantly higher in patients who experienced a recurrence of CSDH ($p < 0.001$; ►**Fig. 2**), while other white blood cell indices, except neutrophils ($p = 0.038$), did not show any significant relation with CSDH recurrence (►**Table 2**). However, the SII index was significantly higher in patients who experienced recurrence of CSDH compared with nonrecurrent patients ($p = 0.003$; ►**Fig. 3**).

We found a direct correlation between the recurrence rate of CSDH and preoperative eosinophil count. To determine if a patient is eosinophil rich or eosinophil poor and to correlate eosinophil-rich/eosinophil-poor status with other independent variables, we calculated a cutoff value for eosinophils. A receiver operating characteristic (ROC) curve with an area under the curve (AUC) of 0.902 (95% confidence interval [CI]: 0.73–2.53; $p = 0.041$) was obtained (►**Supplementary Fig. S1**, available in the online version). We identified 100/µL as the cutoff value. Thus, eosinophil count ≥100/µL was considered rich, and lower than these counts were considered eosinophil poor. Among the 105 patients, 11 were found to be eosinophil rich and 94 were eosinophil poor. Certain demographic variables such as male gender, diabetes mellitus, and hematoma

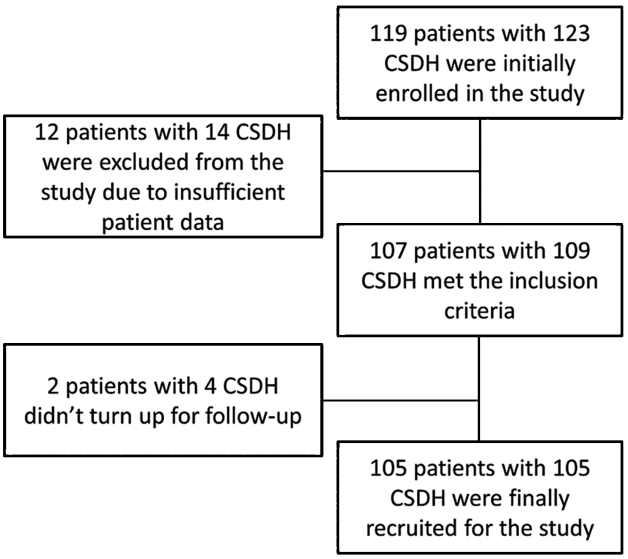

Fig. 1 Flowchart showing the selection of patients. CSDH, chronic subdural hematoma.

Table 1 Demographic variables of the patients ($n = 105$)

Variable	n[a]
Age	61.8 ± 8.4
Gender	
Male	94 (89.5)
Female	11 (10.5)
Days of admission	5.45 ± 1.6
Comorbidity	
Hypertension	30 (28.6)
Asthma	9 (8.6)
Thrombocytopenia	5 (4.8)
Diabetes Mellitus	32 (30.5)
Medication	
Antiplatelets	16 (15.2)
Anticoagulants	4 (3.8)
Steroids	10 (9.5)
Histamine H1-receptor antagonist	15 (14.3)
Bilateral Operation	4 (3.8)
Hematoma (vol, mL)	87.3 ± 15.5
Recurrence of CSDH	11 (10.5)

Abbreviation: CSDH, chronic subdural hematoma.
[a]The values are represented as frequency and in round brackets as a percentage. Age, days of admission, hematoma volume, and recurrence of CSDH are presented as mean ± standard deviation.

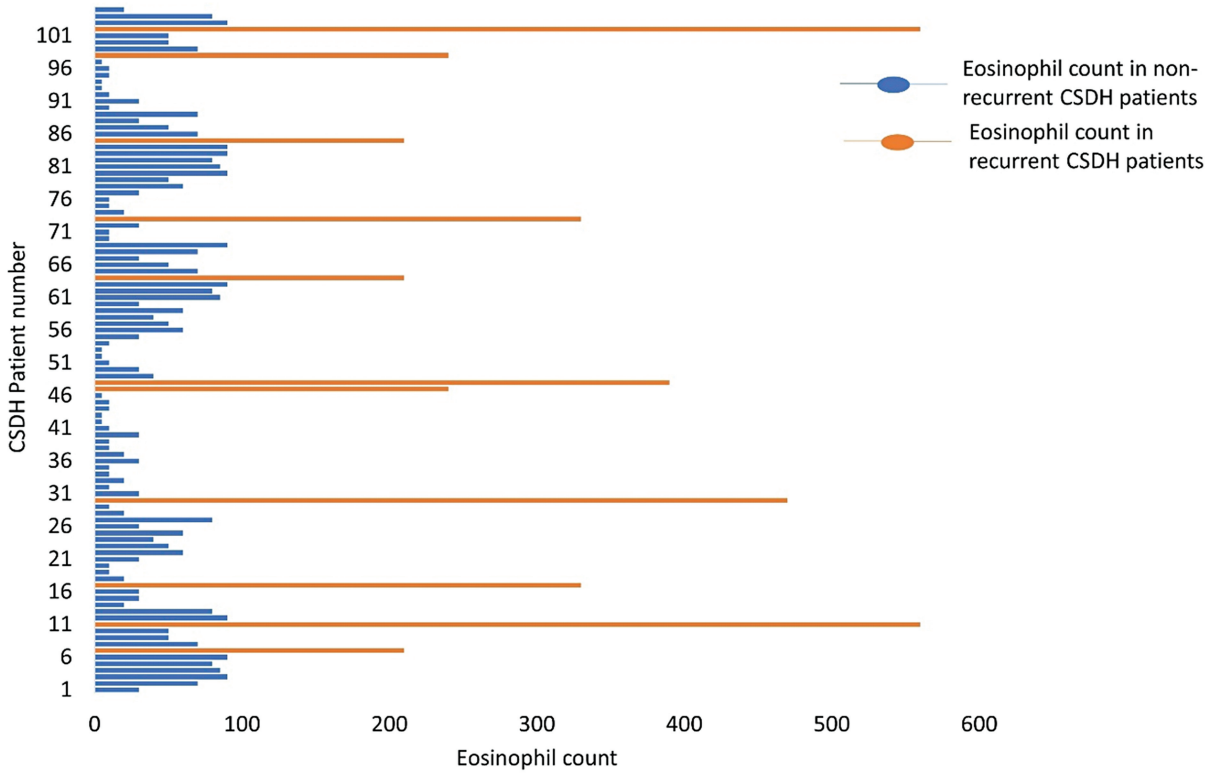

Fig. 2 Distribution of eosinophil count in chronic subdural hematoma (CSDH) patients.

Table 2 Preoperative differential leukocyte count in CSDH patients ($n = 105$)

Differential leukocyte count (/μL)	CSDH recurrence		*p*-Value
	No ($n = 94$)	Yes ($n = 11$)	
Neutrophils	7,053 ± 489	8,822 ± 149	0.038
Lymphocytes	3,031 ± 447	1,143 ± 93	0.317
Monocytes	333 ± 186	210 ± 106	0.106
Eosinophils	40 ± 29	340 ± 136	< 0.001
Basophils	5 ± 6	3 ± 2	> 1.0
Platelets	225,834 ± 131,286	264,000 ± 17,395	0.981
SII	535,926 ± 310,318	2,046,900 ± 197,283	0.003

Abbreviation: SII, systemic immunological inflammation.

volume showed significant associations with eosinophil-rich and eosinophil-poor status (►**Table 3**). The relationship between anticoagulant medication use was found significantly associated with the eosinophil status ($p = 0.05$); however, comorbidities like asthma, hypertension, thrombocytopenia, and other medication were found insignificant with the eosinophil status (►**Table 3**).

Multivariate and univariate regression analyses were conducted to check the association of various risk factors with CSDH recurrences (►**Table 4**). In the univariate analysis, age (adjusted odds ratio [AOR] 0.23; 95% CI: 0.11–0.37; $p < 0.001$), hypertension (AOR: 0.31; 95% CI: 0.22–0.53; $p = 0.05$), diabetes mellitus (AOR: 0.37; 95% CI: 0.17–0.51; $p = 0.005$), SII (AOR: 1.94; 95% CI: 1.51–2.39; $p = 0.005$), and hematoma volume (AOR: 2.14; 95% CI: 1.17–3.15; $p < 0.001$) were found to be independent predictors of CSDH recurrence, along with thrombocytopenia (AOR: 0.58; 95% CI: 0.41–0.67; $p < 0.001$) and the use of anticoagulant and antiplatelet drugs, with an AOR of 0.76 (95% CI: 0.17–1.86; $p = 0.002$) and an AOR of 1.17 (95% CI: 0.87–2.01; $p < 0.001$), respectively (►**Table 4**). The multivariate analysis showed hematoma volume AOR of 3.10 (95% CI: 2.47–5.62; $p < 0.001$), thrombocytopenia (AOR: 3.67; 95% CI: 2.26–7.81; $p = 0.019$), and antiplatelet regimen as significant predictors of CSDH recurrence (AOR: 1.73; 95% CI: 0.94–5.91; $p = 0.047$; ►**Table 4**).

Table 3 Eosinophil rich/poor status in CSDH patients

Factor	Total	Eosinophil status		*p*-Value
		Rich	Poor	
No. of CSDH	105	11 (10.5)	94 (89.5)	
Mean age	105	74 ± 3	60 ± 7	0.081
Male	94	11 (12)	33 (88)	0.031
Medical history				
Hypertension	30	10 (34)	20 (66)	0.791
Diabetes mellitus	32	9 (29)	23 (71)	0.051
Thrombocytopenia	5	0	5 (100)	–
Asthma	9	0	9 (100)	–
Drugs used				
Antiplatelets	16	11 (68)	5 (32)	0.052
Anticoagulants	4	3 (75)	1 (25)	0.050
Steroids	10	3 (30)	7 (70)	0.059
Histamine h1-receptor antagonist	15	2 (13)	13 (87)	0.503
Bilateral Operation	4	0	4 (100)	–
Hematoma (vol, mL)	105	122.5 ± 8	83.2 ± 10	0.048

Abbreviation: CSDH, chronic subdural hematoma.

Table 4 Univariable and multivariable logistic regression analysis of predictors of CSDH recurrence

Variable	Univariate		Multivariate	
	AOR (95% CI)	*p*-Value	AOR (95% CI)	*p*-Value
Age	0.23 (0.11–0.37)	<0.001	–	–
Gender	0.13 (0.08–5.17)	0.394	–	–
Medical condition				
Hypertension	0.31 (0.22–0.53)	0.050	0.48 (0.44–4.69)	0.327
Asthma	0.13 (0.10–1.99)	0.364	Ref	
Diabetes mellitus	0.37 (0.17–0.51)	0.005	0.43 (0.23–5.30)	0.052
Thrombocytopenia	0.58 (0.41–0.67)	<0.001	3.67 (2.26–7.81)	0.019
Drugs used				
Histamine	0.18 (0.09–0.61)	0.301	Ref	
Steroids	1.24 (0.03–3.71)	0.104	0.48 (0.21–3.86)	0.061
Anticoagulants	0.76 (0.17–1.86)	0.002	1.84 (0.38–8.25)	0.138
Antiplatelets	1.17 (0.87–2.01)	<0.001	1.73 (0.94–5.91)	0.047
Bilateral Operation	−0.12 (−0.6 to 0.35)	>0.999	0	
Hematoma (vol, mL)	2.14 (1.17–3.15)	<0.001	3.10 (2.47–5.62)	<0.001
SII	1.94 (1.51–2.39)	0.005	–	–

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; CSDH, chronic subdural hematoma; SII, systemic immune inflammation.

Discussion

Preoperative eosinophil count and CSDH recurrence have a strong correlation ($p < 0.001$), suggesting that eosinophils may play a role in the pathophysiology of recurrence. Eosinophils are well known for their roles in inflammatory processes such as tissue healing, allergic reactions, and parasite infections.[12,14,15] Numerous mechanisms could account for their contribution to recurrence in the setting of CSDH. For instance, eosinophils release proinflammatory mediators like cytokines, chemokines, and growth factors that have the ability to intensify the inflammatory cascade,

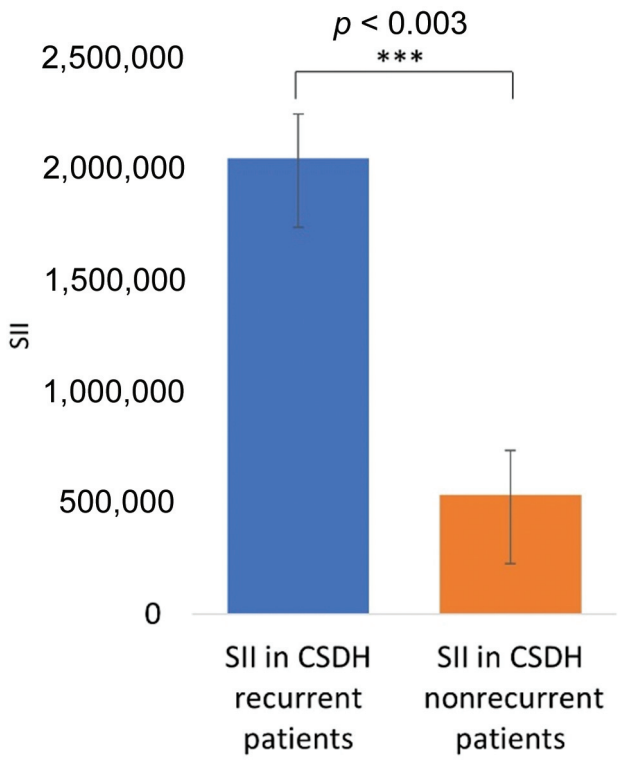

Fig. 3 Systemic immunological inflammation (SII) index in chronic subdural hematoma (CSDH) recurrent and nonrecurrent patients. *** signifies that *P*-Value of data is significant.

increasing vascular permeability and drawing additional immune cells to the site of damage in the subdural region, encouraging hematoma growth and recurrence.[26,27] Furthermore, eosinophils produce proteins and enzymes, such as major basic protein and eosinophil peroxidase, which causes fibrosis and tissue damage.[28] Fibrosis and chronic inflammation are the defining characteristics of chronic systemic inflammatory diseases like CSDH. The presence of prolonged eosinophil has also been linked to the creation of a fibrous, thick capsule around the hematoma, which may facilitate recurrence.[29,30] Likewise, vascular endothelial growth factor, which is formed by eosinophils, has the ability to induce angiogenesis, which may facilitate the growth and recurrence of hematomas.[31]

Previous investigations support the fact that patients with recurrent CSDH have increased eosinophil levels. For instance, Matsubara et al showed that preoperative eosinophils have a rich predictive power in predicting the recurrence of CSDH.[20] This implies eosinophils penetrate the hematoma membrane and release inflammatory cytokines that aid in the genesis of the immune response. Likewise, Davidson et al observed a correlation between increased eosinophil-to-lymphocyte ratio and recurrence of CSDH,[12] implying a possible function of eosinophils in the advancement or recurrence of the disease.

Neutrophils ($p = 0.047$) were the only white blood cell index that showed a significant correlation with CSDH recurrence, indicating a distinct function for neutrophils in the pathophysiology of recurrence. As the first immune system cells to respond to tissue damage and infection, neutrophils are essential to the acute inflammatory response.[32] Patients with recurrent CSDH may have high levels of these substances, which could indicate persistent inflammation and tissue damage in the subdural region. The lack of association between other leukocyte cell types and CSDH recurrence suggests that chronic inflammation and immune dysregulation, rather than an acute immune response, may drive disease progression.[33]

Conflicting reports exist regarding the association of various DLCs in identifying CSDH recurrence. For instance, Zhang et al suggested higher numbers of neutrophils and platelets in recurrent CSDH patients compared with control groups.[10] Similarly, another study found that lymphocytes play a nonsignificant role in predicting CSDH recurrence.[34] Additionally, a study identified the neutrophil-to-lymphocyte ratio as an independent predictor associated with CSDH, although it could not conclusively determine if this ratio is a significant predictive factor for CSDH recurrence.[35]

Individuals with a recurrence of CSDH were shown to have a considerably higher SII index than individuals without a recurrence. The SII is a composite indicator of the immunological state and systemic inflammation that takes platelet, lymphocyte, and neutrophil numbers into account.[24,36] A proinflammatory condition is evident by elevated SII levels, which show an imbalance in the immune response with more neutrophils and fewer lymphocytes. Patients with recurrent CSDH may have a more prominent inflammatory response, as indicated by their increased SII. Reduced lymphocytes and elevated neutrophil counts could indicate persistent subdural space inflammation that encourages hematoma recurrence. Studies investigating the SII index are more prevalent in the context of traumatic brain injury, with only a few studies evaluating its use in predicting brain hemorrhage.[37–39] Our results are consistent with these findings, indicating that the SII index, derived from a ratio of two fitted parameters, is likely more reliable than other parameters.

Male gender, thrombocytopenia, and hematoma volume strongly correlated with the eosinophil-rich and eosinophil-poor status.[40,41] The eosinophil-rich status was found to be significantly correlated with male gender, which is in line with other studies showing a higher prevalence of CSDH in men.[42] This suggests that there may be a gender-specific susceptibility to CSDH recurrence, which could be brought on by differences in hormonal profiles or inherited tendencies. Furthermore, a strong association was found between thrombocytopenia and the presence of eosinophils. Although we did not assess these characteristics in our study, low platelet counts in thrombocytopenia may indicate underlying systemic disorders or hematologic issues that could impact the inflammatory response and cause a recurrence of CSDH. The strong association between hematoma volume and eosinophil-rich status suggests that larger hematomas are associated with eosinophil-rich inflammatory responses.[43]

Our findings have significant clinical implications that could influence patient management and clinical practice in treating CSDH. The identification of preoperative eosinophil counts and the SII index as predictive markers for CSDH recurrence can provide clinicians with valuable tools for risk

stratification. Patients identified as high risk based on these biomarkers could benefit from more aggressive management strategies, such as enhanced surgical precision, extended postoperative observation, and early intervention protocols for recurrence. Additionally, routine preoperative screening for these markers could become a standard part of the clinical workflow, thereby enabling personalized treatment plans that improve patient outcomes and reduce the likelihood of recurrence. By incorporating these predictive markers into clinical protocols, we can enhance the overall quality of care for patients with CSDH, leading to better prognostic assessments and optimized therapeutic interventions.

Limitations

Although our study provided insightful information, there is a certain limitation associated with this study. The limited number of 105 patients in the sample may not accurately reflect the heterogeneous group of people with CSDH, which could impact how broadly applicable our results are. Second, selection bias may have been introduced and impacted the accuracy of our results due to the exclusion of some patients and the loss of others to follow-up. Third, our research did not fully account for other potential confounding factors, such as underlying systemic disorders, surgical procedures, and postoperative treatment, even though we did find significant relationships between these variables and CSDH recurrence. Finally, only preoperative characteristics were examined in this investigation; postoperative variables and long-term outcomes may offer a more complete knowledge of CSDH recurrence.

Conclusion

This study confirms the relationship between preoperative variables and chronic subdural CSDH recurrence. We observed that eosinophil count is a strong predictor of recurrence of CSDH, along with a few demographic and clinical factors. The significant relationship between eosinophil count and recurrence raises the possibility that eosinophils have a role in the pathogenesis of CSDH and its recurrence, presumably via promoting tissue damage and fibrosis and inducing proinflammatory responses. Furthermore, a more marked systemic inflammatory response is shown by a higher SII index in patients with recurrent CSDH, which may be a factor in the recurrence of hematomas. The incorporation of eosinophil count and SII index as biomarkers into clinical protocols can greatly enhance the management of CSDH by enabling precise risk stratification and personalized patient care strategies. Future clinical protocols that include routine assessment of these markers may lead to more effective prevention of CSDH recurrence. Although our study was limited by a small sample size, further research is warranted to confirm and validate our findings.

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Conflict of Interest
None declared.

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