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RESEARCH ARTICLE

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The inflammatory cellular feature in the peripheral blood of chronic subdural hematoma patients

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Abstract

Background: Chronic subdural hematoma (CSDH) is a common neurosurgical disease with an increasing incidence. The absorption route of CSDH is not clear. Whether inflammatory factors enter the peripheral blood and cause systemic reactions is unknown.

Methods: We screened 105 CSDH patients and 105 control individuals. Their clinical characteristics and blood routine results were collected and compared. The blood routine changes of CSDH patients before and after treatment were compared. Age-stratified analysis was performed due to age may affect the inflammatory markers.

Results: The white blood cell count, absolute neutrophil count, neutrophil percentage, neutrophil-lymphocyte count ratio (NLR), and platelet to lymphocyte count ratio (PLR) of CSDH patients before treatment were within the normal range, while were significantly higher than the control individuals ($p < 0.001$). The absolute lymphocyte count and lymphocyte percentage of control individuals were higher than those of patients ($p < 0.001$). The inflammatory cells in patients of different age groups were similar. After the patient was cured, the white blood cell count, the absolute value and percentage of neutrophils decreased ($p < 0.05$), while the number of monocytes increased.

Conclusions: CSDH caused slight systemic inflammatory responses in the peripheral blood, implying that there is a non-hematologic route for the absorption of hematoma.

KEYWORDS
absorption route, blood routine test, chronic subdural hematoma, local inflammation, systemic inflammatory responses

1 | INTRODUCTION

Chronic subdural hematoma (CSDH), characterized by pathological hematocele, is a common disease in neurosurgery. Its total incidence has reached 13.5–58.1/100,000 per year, and it is increasingly common in the elderly.[1,2] The Japan Neurosurgical Database showed that operation for CSDH is the most common neurosurgical management in 2018 and 2019(19.4–18.9%).[3] However, approximately 10–20% of surgically treated patients experience postoperative recurrence necessitating reoperation[4] which brings enormous economic, physical and mental burdens to patients.

The existing theoretical hypotheses for the mechanism of CSDH formation and development include osmotic imbalance theory, hyperfibrinolysis theory, local inflammatory response caused by blood exudation (bridging vein injury caused by minor brain injury), continuous exudation theory caused by angiogenesis disorder and meningeal lymphatic drainage dysfunction.[5,6] However, no consensus has been reached. More and more researches demonstrated that local inflammatory responses play important roles in the formation and development of CSDH. Inflammatory cells including neutrophils, lymphocytes, monocytes and eosinophils have also been observed on the outer membrane. High concentrations of inflammatory and pro-angiogenic cytokines were found in the hematomas compared with the serum of CSDH patients and have been correlated with recurrence,[7–11] which demonstrated the local inflammation in the hematoma. However, whether there was a systematic inflammation in the peripheral blood is still unknown.

To prompt the recovery of CSDH, it is necessary to reduce the hematoma production and meanwhile prompt its absorption. The recently reported technique of middle meningeal artery embolization for the treatment of CSDH has been confirmed to be safe and effective.[9,11] The technique is based on the mechanism that in the formation of CSDH, the middle meningeal artery continuously supplies nutrients to the CSDH capsule, so various cytokines are continuously generated in the hematoma cavity, resulting in the aggravated local inflammatory response and continuous oozing. Blocking this artery, that is, the nutrients of the CSDH capsule are broken and cytokine release is inhibited so that the hematoma absorption can be promoted.[10] However, there are few studies on the transformation and absorption of hematoma. In addition, spontaneous absorption of the hematoma without treatment was found in several pieces of research,[12,13] and some pharmacotherapy has been demonstrated to prompt the absorption.[6] These evoked the question: what was the absorption pathway of the hematoma fluids and how they were absorbed. If the hematoma was absorbed through the hematogenous route, systemic inflammation and fever should be incited since the hematoma fluids contain a huge number of inflammatory cytokines and even inflammatory cells. Actually, in clinical practice, fever was rare for CSDH patients on their first visit, and there was no report about abnormal WBC and neutrophil counts in the blood routine of CSDH patients. NLR and PLR, which are related to inflammatory diseases such as irritable bowel, diabetes and thyroiditis, are becoming new inflammatory markers in blood routine tests recently.[14–16] However, whether they are associated with CSDH is still unknown. Therefore, we retrospectively analyzed the characteristics of inflammatory cells in a group of CSDH patients to confirm whether CSDH triggered systemic inflammatory responses.

2 | METHODS

2.1 | Patients

A total of 129 CSDH patients who were admitted to the department of Neurosurgery in Tianjin Medical University General Hospital from 2019 to 2020 were screened, and 105 eligible patients were enrolled in this study. CSDH was diagnosed based on the combination of imaging data, clinical symptoms, and signs as well as the history of head trauma. Healthy controls were randomly recruited from the physical examination center according to the age and gender ratio of the patients. A total of 105 healthy controls were recruited.

The inclusion criteria were as follows: (a) age: ≥18 years; (b) patients did not experience severe trauma, inflammatory disease surgical therapy and fever within 3 months; (c) no other lesions except CSDH in the central nervous system. The exclusion criteria included administered glucocorticoids or anti-inflammation medicine within 3 months, pregnant women or parturients, previous inflammatory or infectious diseases.

2.2 | Laboratory test

The blood routine was measured with Sysmex XN (SYSMEX [Sysmex] Co., Ltd., Japan) for flow cytometry and calculation to obtain data. We calculated the NLR from the neutrophil-to-lymphocyte ratio and the PLR from the platelet-to-lymphocyte ratio. In the early morning of the second day after admission (without treatment), peripheral blood samples were collected for analysis. At the same time, blood routine examination data of healthy controls were collected. We follow up and collect data on cured patients (ct shows no hematoma and no clinical symptoms). Most of the patients have complete data at 6 months after discharge, and this part of blood routine data is collected.

2.3 | Statistical analysis

Data were collated and analyzed using Exceloffice365 and SPSS 25.0 (IBM Inc, Chicago, IL, USA). GraphPad (GraphPad Software, San Diego, CA, USA) was applied for data plotting. Data are presented as mean and standard deviation. We evaluated the data distribution using the Kolmogorov–Smirnov test. Normally distributed data were analyzed using Student's t test, while non-normally distributed data were analyzed using the Mann–Whitney U test, and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characterization of the enrolled patients and control individuals

The mean age of CSDH patients was 70.91 ± 11.89, and the control group was 70.90 ± 11.82. Blood glucose did not differ between groups. There was no difference in age, gender, history of cardiovascular disease and history of diabetes between the two groups (Table 1).

3.2 | Comparison of blood routine parameters between CSDH patients and control people

The blood routine parameters were compared between the CSDH patients and controls. The white blood cell count, absolute neutrophil count and neutrophil percentage were in the normal range in CSDH patients, but the white blood cell and neutrophil count, NLR and PLR were higher than those in control individuals ($p < 0.001$). The mean values of absolute lymphocyte count and percentage of lymphocytes in CSDH patients were lower than those in control individuals ($p < 0.001$). The absolute value of monocytes in patients with CSDH was higher than that in the normal population ($p = 0.059$), while the percentage of monocytes was lower than that in the normal population ($p = 0.259$), and there was no statistical difference between the two groups (Table 2 and Figure 1).

3.3 | Changes of inflammatory cells in peripheral blood of CSDH patient before and after treatment

Among the 105 enrolled CSDH patients, 11 patients were followed up in our hospital for another 6 months and completely cured, either with non-surgical or surgical treatment. Changes in blood routine inflammatory cells and related parameters before treatment and 6 months after cure were compared. The results which were analyzed by paired sample t test showed that inflammatory cells (absolute and percent white blood cells and neutrophils) were lower after the patients were cured than the baseline (Figure 2), but the monocyte counts were higher than the baseline. Compared with the values of the control group, inflammatory cells tend to be completely normal after the patients were cured (Table 3).

3.4 | Age stratification analysis

Due to age may affect the result of blood routine test, patients and control individuals were divided into five groups according to a 10-year-old group, and the inflammatory parameters in blood routine examination of patients and control individuals in each group were compared. There were significant differences in white blood cell count, absolute neutrophil count, absolute lymphocyte count, neutrophil percentage and lymphocyte percentage between patients over 70 years old and control people ($p < 0.05$), but there was no significant difference in absolute monocytes count and its percentage ($p > 0.05$; Table 4). This was inconsistent with the result when no age-stratified comparisons were made.

4 | DISCUSSION

Systemic inflammatory responses often have laboratory findings such as increased peripheral blood inflammatory cells and associated inflammatory protein expression. Many diseases involve inflammatory reactions, and most of these inflammatory reactions cause systemic reactions in patients. Crohn's disease is a chronic granulomatous disease that is more common in the terminal ileum and adjacent colon, also known as localized enteritis. Under inflammatory conditions, dysfunction of the intestinal epithelial barrier leads to the entry of luminal contents (e.g., food and intestinal flora) into the lamina propria of the affected bowel, resulting in the activation of helper T cells by dendritic cells and the production of proinflammatory cytokines. In addition, in response to luminal contents, macrophages produce proinflammatory cytokines (e.g., IL-12 and IL-23) that activate natural killer cells, resulting in the

TABLE 1 Characterization of the enrolled patients and control individuals.

Group	Patients ($n = 105$)	Controls ($n = 105$)	p-Value
Average age (years)	70.91 ± 11.89	70.90 ± 11.82	0.95
Gender (%)			
Male	80%	80%	1
Mean GCS score on admission	10.5	15	<0.01
History of cardiovascular disease (%)	20.9%	18.1%	0.29
History of diabetes (%)	9.50%	8.57%	0.63
Blood glucose	5.5 (4.8, 6)	5.4 (4.9, 5.9)	0.417
Trauma (%)			
Yes	16.19%	–	–
Symptoms (%)			
Headaches	50%	–	–
Dizziness	33.33%	–	–
Limb weakness	63.80%	–	–
CT (%)			
Unilateral hematoma	73.33%	–	–
Bilateral hematoma	26.67%	–	–

TABLE 2 Differences in inflammatory cell values and related parameters between patients and control individuals.

Indexes	Group	*n*	Mean	*SD*	*p*-Value
White blood cell count (10^9/L)	Patients	105	7.3992	3.1081	<0.001
	Controls	105	5.9464	1.13518	
Percentage of neutrophils (%)	Patients	105	67.876	12.2795	<0.001
	Controls	105	56.758	6.2004	
Percentage of monocytes (%)	Patients	105	7.27	2.801	0.259
	Controls	105	7.6	1.399	
Absolute value of monocytes (10^9/L)	Patients	105	0.5401	0.49048	0.059
	Controls	105	0.4476	0.09615	
Absolute value of neutrophils (10^9/L)	Patients	105	5.1382	2.64556	<0.001
	Controls	105	3.3786	0.7597	
Absolute value of lymphocyte (10^9/L)	Patients	105	1.5376	0.66515	<0.001
	Controls	105	1.9442	0.54339	
Percentage of lymphocyte (%)	Patients	105	22.428	9.7275	<0.001
	Controls	105	32.646	6.3587	
NLR	Patients	105	1.54	0.67	<0.001
	Controls	105	1.94	0.54	
PLR	Patients	105	170.5	102	<0.001
	Controls	105	118	37.31	

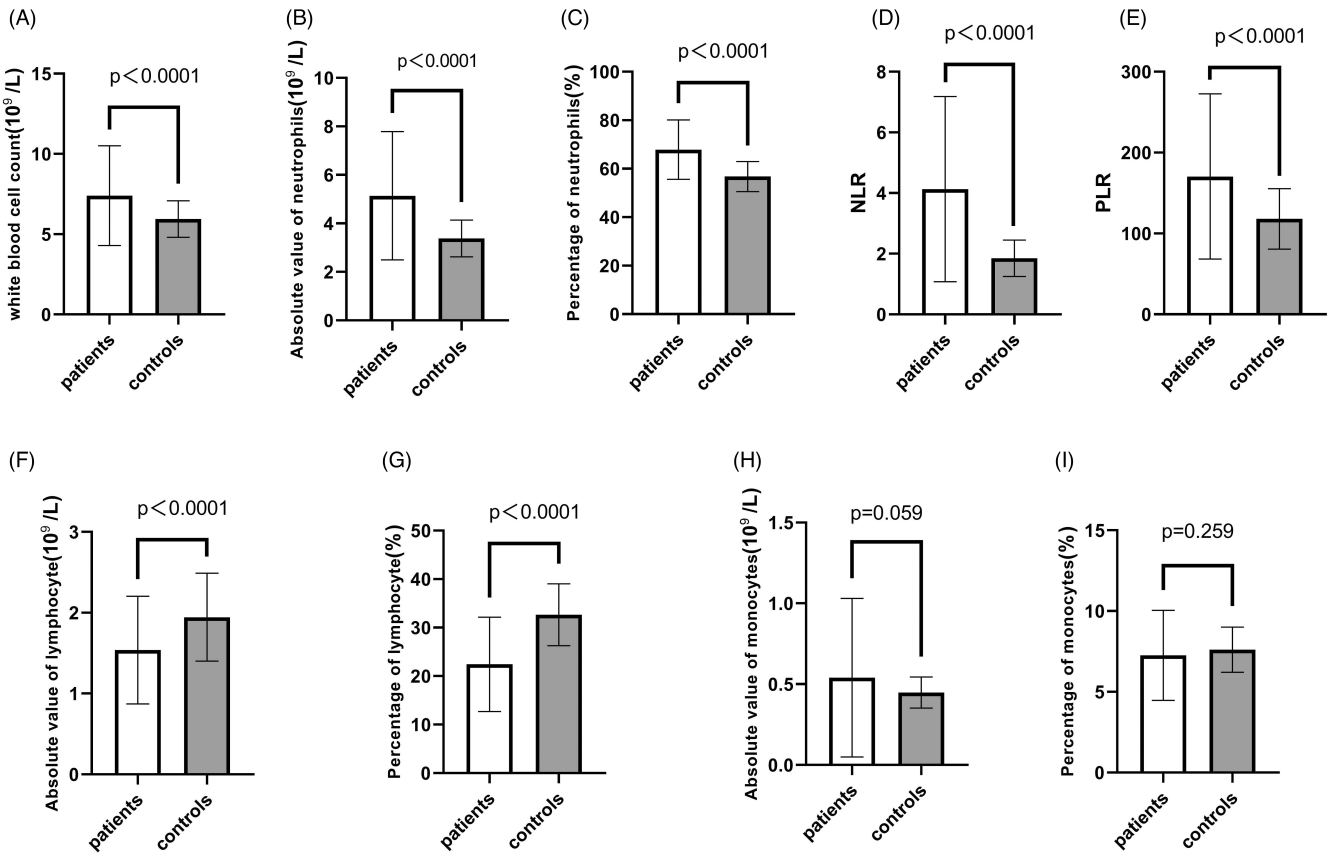

FIGURE 1 Comparison of routine blood parameters between patients and control individuals, (A) White blood cell count, (B) Absolute value of neutrophils, (C) Percentage of neutrophils, (D) NLR, (E) PLR, (F) Absolute value of lymphocyte, (G) Percentage of lymphocyte, (H) Absolute value of monocytes, (I) Percentage of monocytes.

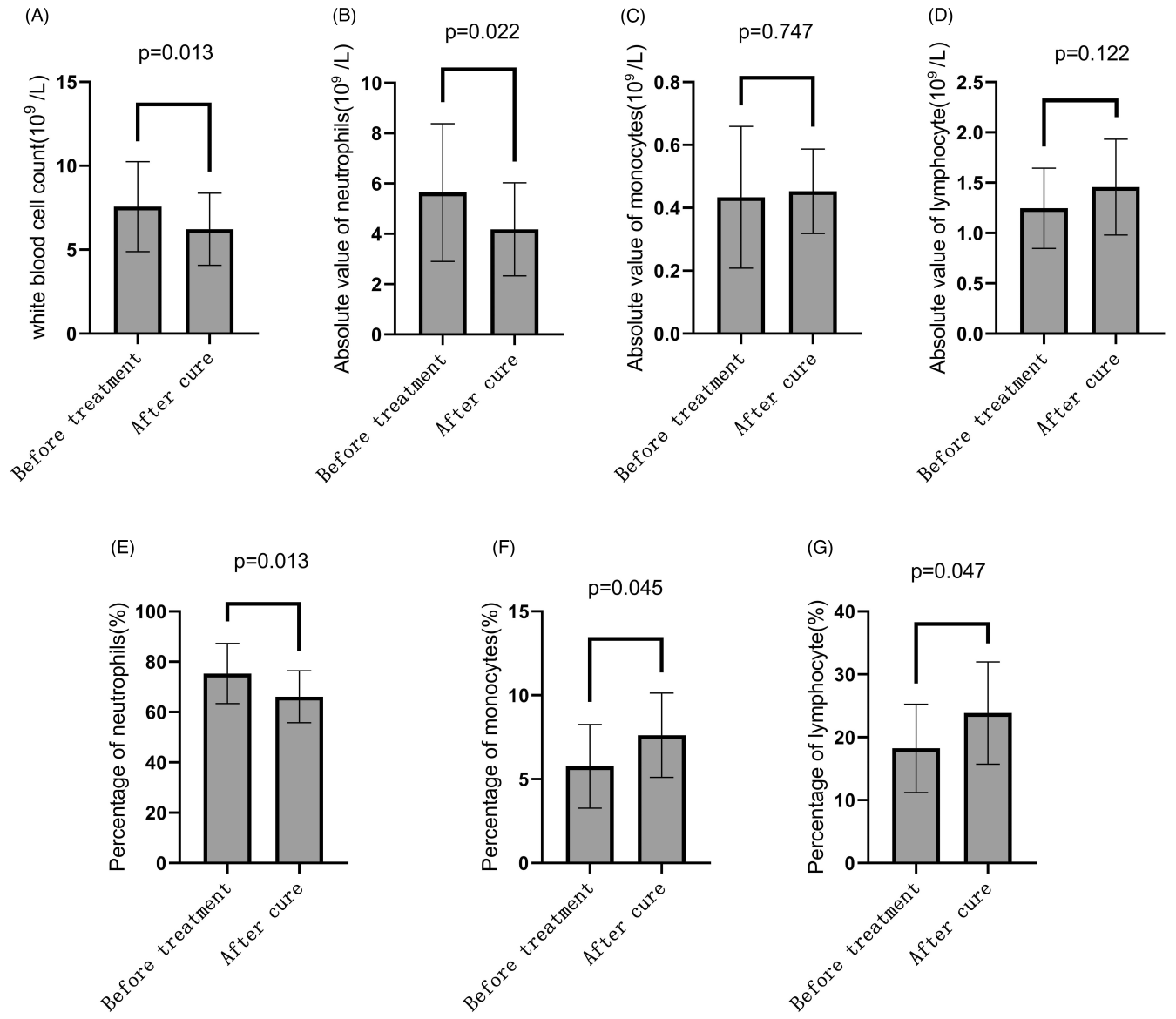

FIGURE 2 The blood routine inflammatory indexes of CSDH patients before and after the cure, the white blood cell count and the absolute neutrophil count of most patients after hematoma absorption decreased compared with the time when they were admitted to the hospital. (A) White blood cell count, (B) Absolute value of neutrophils, (C) Absolute value of monocytes, (D) Absolute value of lymphocyte, (E) Percentage of neutrophils, (F) Percentage of monocytes, (G) Percentage of lymphocyte.

persistence of intestinal inflammation, which in turn circulates. Patients may have systemic manifestations such as fever, night sweats and elevations of C-RP and ESR in peripheral blood.[17,18] Ulcerative colitis, which is also inflammatory bowel disease, has similar manifestations, and elevated C-RP has also been observed in patients. The diseases causing systemic reactions in patients include interstitial pneumonia, rheumatoid arthritis, COVID-19 infection, diabetic nephropathy, and patients may also have fever and other manifestations.[19–21] In contrast, systemic manifestations of inflammation do not appear to be observed in CSDH patients. In this study, we found that all the inflammatory indexes of blood routine examination obtained from peripheral blood of CSDH patients were within the normal range. However, the WBC count, neutrophil count and neutrophil percentage in the CSDH patients were higher than those of the comparable control individuals, which was in consistent with the age-stratified analysis. These results indicated that CSDH caused slight systemic inflammatory responses in the peripheral blood. There was no difference in blood glucose between the patient group and the control group, which basically ruled out the existence of stress reaction in patients.

Neutrophil-lymphocyte count ratio and PLR are important indicators of the inflammatory responses, and these two indicators have been applied as diagnostic criteria in many inflammatory responses

TABLE 3 Comparison of the mean values of routine blood parameters among patients, control individuals and cured patients.

Indexes	*n*	Group	Mean
White blood cell count (10^9/L)	105	Patients	7.40
	105	Controls	5.95
	11	Cured patients	6.22
Absolute value of monocytes (10^9/L)	105	Patients	0.54
	105	Controls	0.45
	11	Cured patients	0.45
Absolute value of neutrophils (10^9/L)	105	Patients	5.14
	105	Controls	3.38
	11	Cured patients	4.18
Absolute value of lymphocyte (10^9/L)	105	Patients	1.54
	105	Controls	1.94
	11	Cured patients	1.46
Percentage of neutrophils (%)	105	Patients	67.88
	105	Controls	56.76
	11	Cured patients	66.15
Percentage of monocytes (%)	105	Patients	7.27
	105	Controls	7.60
	11	Cured patients	7.62
Percentage of lymphocyte (%)	105	Patients	22.43
	105	Controls	32.65
	11	Cured patients	23.86

and immune diseases.[22-25] A retrospective study found that postoperative neutrophil count and NLR were higher in those who recurred, and postoperative NLR ratio was independently associated with recurrence.[26] In this study, we found both NLR and PLR of the CSDH patients were higher than those of healthy controls but lower than the upper limit of normal reference values indicated in the literature.[27] After the hematoma was absorbed and cured, these markers, which were significantly higher than those of blood routine in healthy controls, were also basically returned to normal. These results suggested that systematic inflammatory responses may also play important roles in CSDH.

CSDH has been demonstrated to be a cerebrovascular disease mediated by chronic inflammation and angiogenesis.[28] There were numerous newly formed capillaries with enlarged blood vessels and a lack of a basement membrane in the outer membrane of the hematoma. The newly formed capillaries tear easily and are highly permeable, which can result in re-bleeding and exudation.[29] Hemorrhage accounts for 0.2%–28.6% of hematoma content, suggesting that continuous or intermittent hemorrhage may play an important role in CDSH formation and progression.[30] However, the course of CSDH maybe 3 or more weeks, and the symptoms were always mild, which indicated that there was both the reabsorption and collection process during the formation of the hematoma. When the rate of accumulation of blood products outpaces physiological reabsorption, the hematoma gradually enlarges.[28] We have previously demonstrated that atorvastatin alone or atorvastatin combined with dexamethasone could prompt the absorption of the hematoma.[31,32] All these results demonstrated that the hematoma in the subdural space could be absorbed. But how the hematoma was absorbed and the absorption route was still unknown. In this study, we found CSDH only causes slight inflammatory responses, which suggested not all the components of hematoma were drained into the peripheral blood. With an acute SDH model, we have demonstrated that the hematoma in the subdural space was drained outside the skull via the meningeal and neck lymphatic vessels,[5] which suggested that the hematoma of CSDH patients was also absorbed through the meningeal and neck lymphatic vessels. This may be the reason why CSDH does not develop strong systemic inflammatory responses in the peripheral blood.

This study also has some limitations. Firstly, it is a retrospective study, and the follow-up data are incomplete to assess whether these markers are associated with the prognosis. Secondly, the mechanism that how the hematoma was absorbed is not studied in this research which needs further research.

In conclusion, the blood routine inflammatory cell characteristics showed that CSDH caused slight systemic inflammatory responses in the peripheral blood, implying that there is a non-hematologic route for the absorption of hematoma. Therefore, further study is necessary to clarify the absorption route of hematoma which may deepen our understanding of the pathophysiology of CSDH. This absorption pathway also helps to develop new treatments, which

TABLE 4 Comparison of blood routine results among different age groups.

Age (years)	Group	White blood cell count (10^9/L)	Absolute value of monocytes (10^9/L)	Absolute value of neutrophils (10^9/L)	Absolute value of lymphocyte (10^9/L)	Percentage of monocytes (%)	Percentage of neutrophils (%)	Percentage of lymphocyte (%)
41–50 (n = 7)	Patients	7.88^{-}	0.54^{-}	5.27^{-}	1.91^{-}	7.57^{-}	63.29^{-}	26.87^{-}
	Controls	6.04	0.48	3.38	2.04	8.03	55.61	33.94
51–60 (n = 12)	Patients	8.59^{-}	0.88^{-}	5.7^{-}	1.87^{-}	8.36^{-}	64.76^{++}	24.63^{++}
	Controls	5.74	0.41	3.15	2	7.37	54.93	34.7
61–70 (n = 32)	Patients	7.01^{+}	0.43^{-}	4.77^{++}	1.58^{++}	6.4^{+}	66.32^{++}	24.71^{++}
	Controls	5.99	0.45	3.39	1.99	7.46	56.56	33.3
71–80 (n = 29)	Patients	7.25^{++}	0.51^{-}	5.12^{++}	1.44^{++}	7.2^{-}	69.48^{++}	20.78^{++}
	Controls	5.96	0.42	3.42	1.95	7.12	57.36	32.69
>80 (n = 25)	Patients	7.36^{+}	0.56^{-}	5.33^{++}	1.33^{++}	7.85^{-}	70.79^{++}	19.12^{++}
	Controls	5.95	0.49	3.42	1.83	8.34	57.52	30.41

-p < 0.01; +p < 0.05; ++p > 0.05.

may bring less risk to patients who cannot be operated and improve the prognosis of patients.

AUTHOR CONTRIBUTIONS

J.R. and G.C. designed the study. F.Y. collected the data. G.C. and F.Y. analyzed the data. G.C. and F.Y. drafted and wrote the manuscript. J.R. revised the manuscript critically for intellectual content. The author(s) read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

PATIENT CONSENT STATEMENT

All persons gave their informed consent prior to their inclusion in the study.

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