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ORIGINAL ARTICLE

Analysis of Correlation between Blood Inflammation Indicators in Peripheral Blood and Prognosis of Patients with Multiple Myeloma

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SUMMARY

Background: **This study aimed to investigate the value of the peripheral blood neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) in the prognosis of patients with multiple myeloma (MM).**
Methods: **Before treatment, the NLR and LMR and all clinical indicators of 168 patients, diagnosed with MM at the Affiliated Hospital of Southwest Medical University from April 2013 to April 2022, were retrospectively analyzed, and the patients were grouped according to their median NLR counts and median LMR counts. Differences between the groups were compared by using the chi-squared (χ^2) test, the Kaplan-Meier survival curve and Log-rank test were used for survival analysis and difference comparison, and the COX proportional risk model was constructed to analyze the factors affecting the prognosis of the MM patients. The test level was $\alpha = 0.05$.**
Results: **The groups were divided into high NLR group (> 2.19) and low NLR group (≤ 2.19) and high LMR group (> 3.45) and low LMR group (≤ 3.45), according to the median NLR and LMR values. The clinical stage, blood β_2 microglobulin, and serum creatinine levels in the high NLR group were higher than in the low NLR group, and the differences between the groups were statistically significant ($p < 0.05$). The clinical stage and blood β_2 microglobulin in the low LMR group were higher than in the high LMR group, and the differences between the groups were statistically significant ($p < 0.05$). The Cox univariate and multivariate analyses showed that peripheral blood NLR < 2.19 and LMR ≤ 3.45 were independent risk factors for the prognosis in patients with MM ($p < 0.05$).**
Conclusions: **High NLR and low LMR counts of peripheral blood suggest a poor prognosis; NLR and LMR may be prognostic indicators in MM patients.**
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KEYWORDS

neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, multiple myeloma, prognosis

INTRODUCTION

Multiple myeloma (MM) accounts for 13% of hematological malignancies and 1 - 1.4% of all tumors [1]. It has the characteristics of an abnormal proliferation of clonal plasma cells in bone marrow, and excessive monoclonal immunoglobulin or its light or heavy chain fragments can appear in serum or urine [2]. MM can lead to a series of clinical manifestations such as anemia, osteolytic destruction, hypercalcemia, and renal

function damage [3]. In the past 15 years, with the emergence of anti-tumor drugs [4-6], the overall survival rate (OS) of MM patient has significantly improved. In recent years, Kafezomi, Pomadomide, and Daretozumab have further improved the treatment effect [7-8]. Indeed, MM patients have an increasing life expectancy [9]. However, relapse occurs in almost all MM patients. There is an urgent need to find valuable indicators to evaluate the patient prognosis to guide a more aggressive treatment and delay the progression of the disease. At present, the commonly used clinical DS stage, International Staging System (ISS) stage, and RISS stage involve prognostic indicators, including hemoglobin (Hb), serum calcium (Ca), osteolytic disease, M protein level in blood or urine, renal function, blood β_2 microglobulin (β_2-MG), and cytogenetic changes. With the continuous deepening of research on tumor inflammation microenvironment, it is found that inflammation plays a crucial role in the initiation, growth, proliferation, metastasis, and diffusion of a tumor [10]. At present, it is known that inflammatory cells are involved in the regulation of the MM bone marrow microenvironment to varying degrees [11]. In solid and other hematological malignancies, relevant studies have shown that the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) can be used as valuable prognostic indicators, both of which can comprehensively reflect the inflammatory level and immune status of tumor patients [12-15]. However, the application of NLR and LMR in patients with MM is still unclear, and there are few literature reports regarding LMR as a prognostic indicator of MM. Therefore, the relationship between NLR and LMR counts and the clinical characteristics of MM patients and their significance in the prognosis of MM patients were explored in this study.

MATERIALS AND METHODS

Subjects

From April 2013 to April 2022, 168 patients were initially diagnosed as MM in the Affiliated Hospital of Southwest Medical University. Inclusion criteria: The diagnosis of all patients met the criteria for diagnosis and efficacy of hematological diseases. Exclusion criteria: 1) if previously diagnosed or accompanied by other malignant tumors; 2) presence of primary or secondary immune diseases; 3) all patients with acute infection and acquired immunodeficiency syndrome (AIDS). Out of 168 patients, 88 were male and 80 were female, with a median age of 63 (37 - 80) years. According to the ISS stage, there were 79 cases in stage I and II, and 89 cases in stage III. Classification according to the type of immunoglobulin with abnormal proliferation: 47 cases of IgG-lambda-type, 45 cases of IgG-kappa-type, 17 cases of IgA-lambda-type, 23 cases of IgA-kappa-type, 7 cases of IgD-lambda-type, 14 cases of light chain lambda-type, 14 cases of light chain kappa-type, and 1 case of non-secretory type.

Data source

The absolute neutrophil count (ANC), monocyte count (MONO), and absolute lymphocyte count (ALC) of the newly diagnosed MM patients were collected before treatment to calculate the NLR and LMR values. The age, gender, Hb, serum Ca, serum albumin (ALB), serum lactate dehydrogenase (LDH), serum creatinine (Cr), and β_2-MG, proportion of plasma cells, and ISS stage (stage I: ALB $\geq$ 35 g/L, β_2-MG < 3.50 mg/L; stage II: all patients who do not meet the requirements of stage I and III; stage III: β_2-MG $\geq$ 5.50 mg/L) of patients were collected.

Judgment of curative effect

According to the unified standard formulated by the International Myeloma Working Group in 2016 [16], the curative effect is divided into stringent complete remission (sCR), complete remission (CR), very good partial remission (VGPR), partial remission (PR), moderate remission (MR), stable disease (SD), progressive (PD), clinical recurrence, and post-CR recurrence. In this study, patients with sCR + CR + VGPR were defined as $\geq$ VGPR, and other patients were defined as < VGPR.

Follow-up

The follow-up method was telephone and outpatient follow-up. The follow-up time lasted up to May 2022. The patient's disease progression, recurrence, and death were recorded in detail. The data of all patients who lost to follow-up were treated as truncated data, and their survival time was calculated until their last follow-up time. Progression-free survival (PFS) was defined as the time from the date of diagnosis to the date of disease progression or death.

Statistical analysis

The patients were divided into high NLR group (> 2.19, H-NLR group), low NLR group ($\leq$ 2.19, L-NLR group), high LMR group (> 3.45, H-LMR group), and low LMR group ($\leq$ 3.45, L-LMR group), with the median NLR of 2.19 and 3.45 as the critical values. SPSS 25.0 software was used for analysis. The chi-squared (χ^2) test was used for comparison between the groups. The Kaplan-Meier survival curve and Log-rank test were used for survival analysis. A single-factor Cox proportional risk regression model was constructed to study factors with prognostic values. The assignment of relevant variables is shown in Table 1. The COX proportional risk model was constructed to analyze the factors affecting the prognosis of the MM patients. Test level was α = 0.05.

RESULTS

Clinical data

The clinical stage, levels of blood β_2-MG, and serum Cr of the high NLR group were higher than those of the low NLR group ($p < 0.05$). The clinical stage and levels

Table 1. Variable assignment of the Cox proportional risk regression model.

Variables	Assignment
Gender	0 = female, 1 = male
Age (years)	0 = < 65, 1 = ≥ 65
Hb (g/L)	0 = < 100, 1 = ≥ 100
ALB (g/L)	0 = < 35, 1 = ≥ 35
Ca (mmol/L)	0 = < 2.75, 1 = ≥ 2.75
Cr (μmol/L)	0 = < 177, 1 = ≥ 177
β_2-MG (mg/L)	0 = < 5.5, 1 = ≥ 5.5
LDH (U/L)	0 = < 240, 1 = ≥ 240
NLR	0 = ≤ 2.19, 1 = > 2.19
LMR	0 = ≤ 3.45, 1 = > 3.45
Clinical stage	0 = stage I and stage II, 1 = stage III
Proportion of plasma cells (%)	0 = < 30, 1 = ≥ 30
Whether there is disease progression or death	0 = truncation, 1 = disease progression or death
PFS (month)	Continuous variables

of blood β_2-MG of the low LMR group were higher than those of the high LMR group ($p < 0.05$). However, no matter whether in the NLR group or LMR group, there was no statistically significant difference in the proportion of patients receiving ≥ VGPR ($p = 0.447$), and there was no statistically significant difference in other general clinical data between the groups ($p > 0.05$) (Table 2).

Correlation between NLR, LMR, and PFS in MM patients

The median PFS of the 168 patients was 14.50 (9.08 - 24.68) months; 17.55 (12.83 - 30.57) months in the L-NLR group, and 12.03 (6.11 - 2.33) months in the high NLR group ($p = 0.001$), as is shown in Figure 1. The median PFS of patients in the L-LMR group was 13.47 (8.00 - 23.10) months, lower than of the patients in the H-LMR group with 16.37 (9.77 - 30.40) months ($p = 0.046$) (Figure 2).

Univariate and multivariate analysis for variables affecting PFS of MM patients

The results of the univariate analysis showed that NLR, LMR, and Cr were prognostic factors affecting the survival of MM ($p < 0.05$), as shown in Table 3. Age, serum Ca, serum Cr, blood β_2-MG, and proportion of plasma cells were included in the multi-factor Cox proportional risk model. The effect of NLR on PFS time was statistically significant (HR = 1.529, 95% CI: 1.050 - 2.228, $p = 0.027$). The influence of LMR on PFS time was also statistically significant (HR = 0.622, 95% CI: 0.420 - 0.922, $p = 0.018$). NLR and LMR counts were independent factors affecting the prognosis of MM, while the effects of other variables on PFS time were not statistically significant ($p > 0.05$) (Table 4).

DISCUSSION

Combination therapy (proteasome inhibitors and immunomodulatory drugs combined with autologous stem cell transplantation) significantly improves the outcome of MM patients [17]. It is a need to accurately and effectively evaluate potential indicators that can be used to predict prognosis in MM patients.

At present, the commonly used prognostic evaluation methods in clinics include DS stage, ISS stage, RISS stage, and MSMART stratification. In recent decades, the DS stage method has been widely used, but its application is complex, involves many parameters, and ignores the important prognostic indicator of β_2-MG. Although ISS staging is simple and convenient, the factors related to the prognosis of MM are complex, and it is not perfect to use just the two indicators of β_2-MG and ALB. RISS staging and MSMART stratification involve cytogenetic examination. They require high laboratory conditions, and the cost and convenience of prediction limit their clinical application. Therefore, domestic and foreign scholars continue to explore more convenient and economical prognostic indicators in order to develop a more reasonable staging standard.

Whole blood cell count (WBCC) is a cheap and easy diagnostic test, which is widely used in the daily clinical practice. It is of great significance in the diagnosis and monitoring of blood diseases. Although it has been used for many years, new applications of WBCC are still being discovered. In recent years, research has focused on the proportion of different types of white blood cells under different disease conditions, of which the NLR and LMR are the most valuable parameters [18].

MM strongly depends on the bone marrow microenvi-

Table 2. Analysis of the relationship between NLR, LMR, and the clinical characteristics of MM patients.

Variables	n	NLR ≤ 2.19 (n = 84)	NLR > 2.19 (n = 84)	χ^2	p	LMR ≤ 3.45 (n = 87)	LMR > 3.45 (n = 81)	χ^2	p
Gender				0.382	0.537			1.124	0.289
Male	88	46	42			49	39		
Female	80	38	42			38	42		
Age (years)				1.187	0.276			3.725	0.054
< 65	95	44	51			43	52		
≥ 65	73	40	33			44	29		
Hb (g/L)				1.971	0.160			0.006	0.940
< 100	124	66	58			64	60		
≥ 100	44	18	26			23	21		
ALB (g/L)				1.581	0.209			1.022	0.312
< 35	68	38	30			32	36		
≥ 35	100	46	54			55	45		
Ca (mmol/L)				2.043	0.153			1.588	0.208
< 2.75	148	77	71			74	74		
≥ 2.75	20	7	13			13	7		
Cr (μmol/L)				6.685	0.010			1.375	0.241
< 177	137	75	62			68	69		
≥ 177	31	9	22			19	12		
LDH (U/L)				0.290	0.590			0.217	0.641
< 240	127	62	65			65	63		
≥ 240	41	22	19			22	18		
β2MG (mg/L)				10.622	0.001			4.512	0.034
< 5.5	75	48	27			32	43		
≥ 5.5	93	36	57			55	38		
Clinical stage				6.905	0.009			4.570	0.033
I, II	79	48	31			34	45		
III	89	36	53			53	36		
Curative effect				0.095	0.758			0.579	0.447
< VGPR	82	40	42			40	42		
≥ VGPR	86	44	42			47	39		
Proportion of plasma cells (%)				0.104	0.747			0.446	0.504
< 30	60	29	31			29	31		
≥ 30	108	55	53			58	50		

ronment, which can support cell proliferation and survival [19]. In the 19th century, Rudolf Virchow first discovered white blood cells in the tumor microenvironment, which suggests the possible relationship between inflammation and cancer. Inflammatory cells in the tumor microenvironment produce a variety of inflammatory mediators and cytokines (such as the most important interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), which promote the invasion of cancer cells [20]. Further study showed that reactive oxygen species and nitrogen in inflammatory cells lead to mutations of some tumor suppressor genes, and inflammatory factors, such as IL-6 and prostaglandin E2, lead to DNA methylation, which plays an important role in the tumorigenesis [21]. Neutrophils are complex cells with a variety of special functions, which can regulate many processes such as acute injury and repair, cancer, autoimmune, and chronic inflammation [22]. Generally

Table 3. Univariate analysis of the variables affecting the prognosis for MM patients.

Variables	B	Wald χ^2	HR (95% CI)	p
Male	0.137	0.571	1.146 (0.805 - 1.633)	0.450
Age ≥ 65 years	0.014	2.019	1.014 (0.995 - 1.033)	0.155
Hb < 100 g/L	-0.188	0.841	0.829 (0.555 - 1.238)	0.359
ALB < 35 g/L	0.164	0.790	1.179 (0.820 - 1.693)	0.374
LDH ≥ 240 U/L	0.200	0.918	1.221 (0.812 - 1.863)	0.338
Ca ≥ 2.75 mmol/L	0.489	3.434	1.631 (0.972 - 2.737)	0.064
Cr ≥ 177 μmol/L	0.482	4.358	1.620 (1.030 - 2.547)	0.037
β_2-MG ≥ 5.5 mg/L	0.244	1.798	1.277 (0.893 - 1.825)	0.180
NLR > 2.19	0.461	6.516	1.586 (1.113 - 2.259)	0.011
LMR ≤ 3.45	-0.503	7.570	0.605 (0.423 - 0.865)	0.006
III stage	0.179	0.978	1.196 (0.839 - 1.706)	0.323
Proportion of plasma cells ≥ 30%	0.381	3.736	1.464 (0.995 - 2.156)	0.053

Table 4. Multivariate analysis of the variables affecting the prognosis for MM patients.

Variables	B	Wald χ^2	HR (95% CI)	p
Age ≥ 65 years	0.011	1.312	1.011 (0.992 - 1.031)	0.252
Ca ≥ 2.75 mmol/L	0.246	0.777	1.279 (0.740 - 2.211)	0.378
Cr ≥ 177 μmol/L	0.268	1.032	1.307 (0.780 - 2.192)	0.310
β_2-MG ≥ 5.5 mg/L	-0.016	0.006	0.984 (0.657 - 1.472)	0.937
NLR > 2.19	0.425	4.894	1.529 (1.050 - 2.228)	0.027
LMR ≤ 3.45	-0.475	5.597	0.622 (0.420 - 0.922)	0.018
Proportion of plasma cells ≥ 30%	0.347	2.812	1.414 (0.943 - 2.121)	0.094

speaking, neutrophils play a central role in tumor inflammation. Reactive oxygen species, reactive nitrogen, or protease released by neutrophils can promote the occurrence of a tumor. Neutrophils reflect inflammatory states and can be involved in the tumorigenesis, growth, proliferation, metastasis, and spread [23]. Circulating monocytes can produce a class of tumor-related macrophages (TAMs), an important component of tumor-associated inflammatory cells [24]. TAMs are associated with a poor prognosis in classical Hodgkin lymphoma, follicular lymphoma, and MM [25]. TAMs recruited to the tumor site by tumor-derived chemokines can affect the number of peripheral blood mononuclear cells. Therefore, the absolute value of peripheral blood mononuclear cells can reflect the recruitment degree of TAM to a certain extent [26]. On the other hand, monocytic cells are also important for innate immune responses. Many genes expressed by peripheral blood monocytes participate in immune response, and their expression level is related to tumor prognosis. In addition, monocytes also secrete TNF α and IL-1 [27]. Lymphocytes can kill and inhibit the proliferation and metastasis of tumor cells. No single lymphocyte subgroup is responsible for tumor immune control. On the contrary, the location, aggregation, interaction, and co-stimulation of all lymphocyte subgroups are necessary for a successful anti-tumor immune response [28]. Therefore, the NLR and LMR are consistent with the theories supported by many studies and can provide an accurate prediction of cancer prognosis. As new indicators, NLR and LMR have obvious changes in many tumors and may play an important role in the occurrence, proliferation, and metastasis of tumors. The studies about NLR, LMR, and MM were searched. Some reports have considered differences about the effect of NLR on OS in patients with hematological malignancies. High NLR is associated with OS in MM patients (cut-off point of NLR was 2.59) [29], and the survival time of MM patients is prolonged with NLR < 2.0 [30]. Our results showed that the 5-year PFS and OS estimates of patients with NLR > 2.0 were 18.2 and 36.4 months, respectively, while the 5-year PFS and OS estimates of

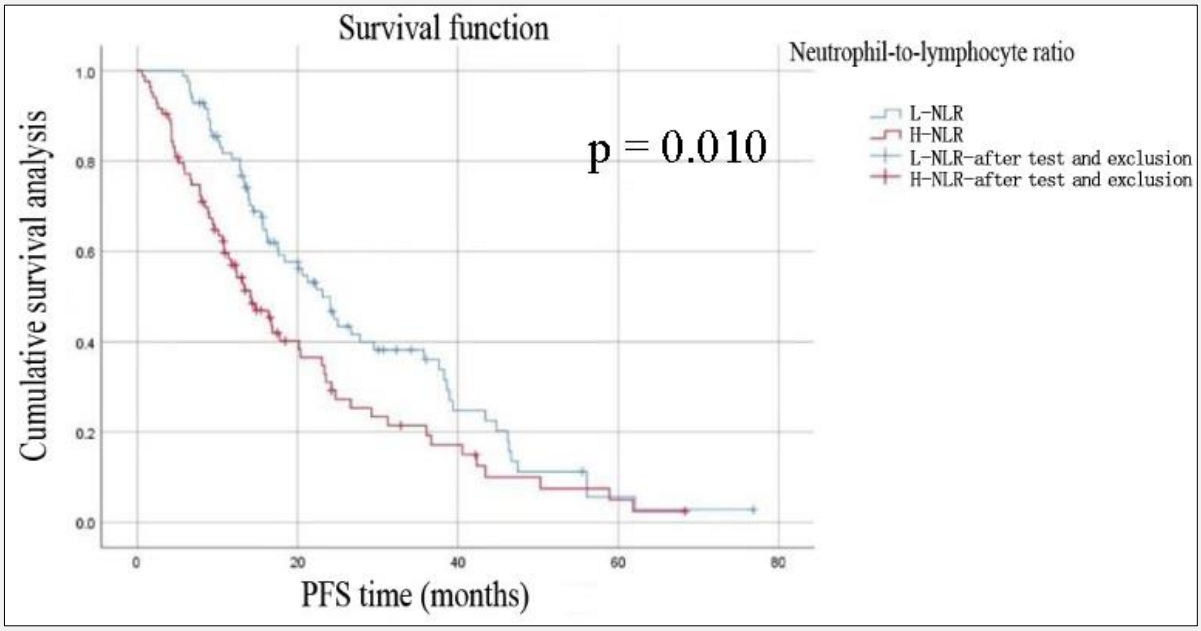

Figure 1. PFS curves of MM patients in the low NLR group and the high NLR group.

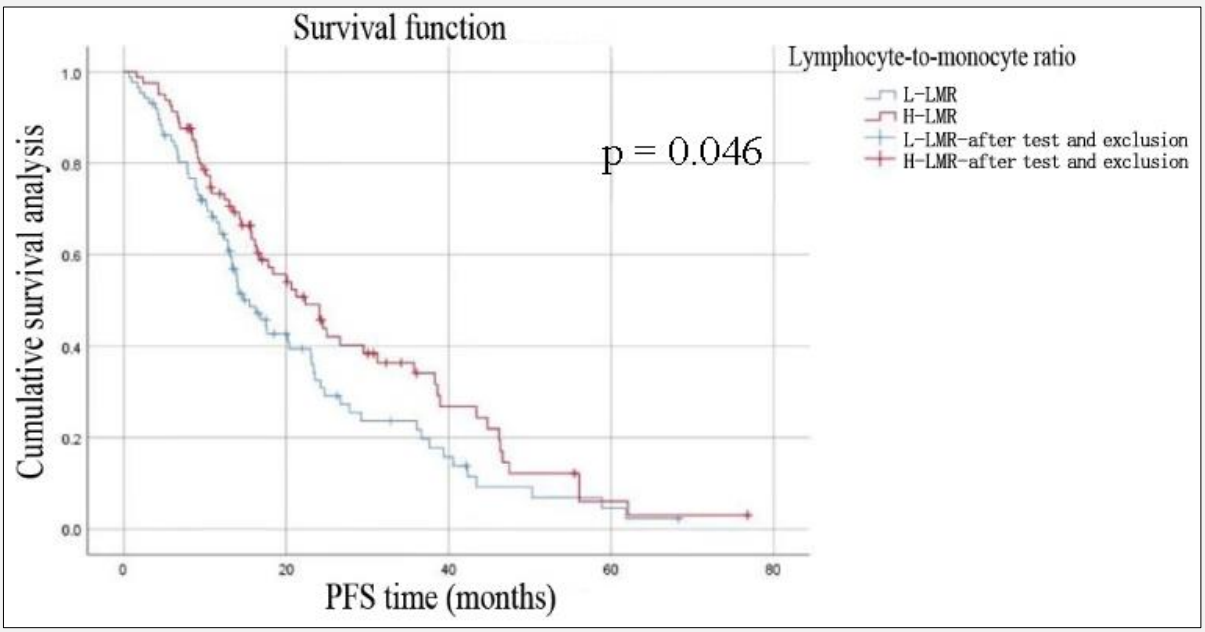

Figure 2. PFS curves of MM patients in the low LMR group and the high LMR group.

patients with NLR < 2.0 were 25.5 and 66.6 months, respectively. The prognostic relevance of NLR was more prominent among young patients who received autologous stem cell transplantation in the early stage [31]. However, there are few studies on the relationship between LMR and the prognosis of MM patients [32]. It is unclear whether NLR and LMR can be used as biomarkers for the prognosis of MM.

This study found that the PFS time of high NLR and low LMR groups were shorter. NLR, LMR, and Cr were prognostic factors affecting the survival of MM. The clinical stage, levels of β_2-MG, and blood Cr in the high NLR group were higher than those of the low NLR group. The clinical stage and level of β_2-MG in the low LMR group were higher than those of the high LMR group. In patients with high or low NLR and LMR, the proportion of plasma cells, LDH, ALB, and the prognosis of MM patients were not statistically significant ($p > 0.05$). It is believed that this may be due to the limitations of our study. First, this study was a retrospective study, and the quality of evidence was lower compared with other types of research. Secondly, the patients included in this study were not grouped according to their treatment plan. Third, the number of patients included was small, and the clinical indicators did not include changes in cytogenetics. It is hoped that more well-designed, high-quality, multi-center studies will be reported in the future to enrich our findings.

In conclusion, NLR and LMR were related to the prognosis of MM patients. NLR and LMR can be used as independent prognostic risk factors for MM. High NLR and low LMR indicated a poor prognosis of MM patients. Whether it can be introduced into DS stage or ISS stage standards to develop a more reasonable staging standard needs further in-depth study and discussion. As the first-hand laboratory data of MM patients, blood routine examination is of great significance in evaluating the progress of patients' disease and early intervention by paying attention to the influence of its blood inflammatory markers on the prognosis of patients.

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Availability of Data and Materials:
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate:
The present study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University, and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki, and its later amendments or comparable ethical standards.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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