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Impact of splenectomy on prognosis in lymphoma with splenic involvement

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Abstract

Background Lymphoma presenting splenic invasion as the primary manifestation poses unique diagnostic and therapeutic challenges. This study aims to systematically analyze the clinical features, prognostic factors, and outcomes of patients with splenic involvement as the initial presentation of lymphoma.

Methods A retrospective analysis was conducted on lymphoma patients diagnosed with splenic involvement confirmed by histopathological examination at our hospital from March 2011 to February 2023. A total of 113 patients were included based on predefined inclusion and exclusion criteria. The collected data encompassed clinical presentations, diagnostic methods, histopathological features, treatment regimens, and outcomes. Kaplan–Meier survival analysis was performed to generate survival curves for overall survival (OS) and progression-free survival (PFS), with statistical significance assessed using the log-rank test. Additionally, univariate and multivariate analyses utilizing Cox regression analyses were conducted to identify potential prognostic factors.

Results According to the pathological results, there were 6 types of lymphoma: indolent lymphoma ($n=23.18$ of splenic marginal zone lymphoma (SMZL), 4 of follicular lymphoma (FL), 1 of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Aggressive lymphoma ($n=90.74$ of diffuse large B cell lymphoma (DLBCL), 10 of NK/T cell lymphoma, 4 of mantle cell lymphoma (MCL), 1 of T lymphoblastic lymphoma, 1 of EBV-positive T cell lymphoma). Diagnosis was confirmed by hollow needle biopsy in 42 patients and through diagnostic splenectomy in 71 patients. 12 patients underwent splenectomy alone while 59 received chemotherapy following splenectomy. The median follow-up time was 37.53 months (range 0 to 162.33 months). The overall 5 year survival (OS) rate for the entire cohort was 62.39% and the 5 year progression-free survival (PFS) rate was 53.98%. Among those who underwent splenectomy, the 5 year OS rate and 5 year PFS rate were 68.06 and 62.50%, which were superior to 52.44 and 37.80% for non-splenectomy patients ($P=0.009$ and $P<0.001$, respectively). These differences were also observed in the aggressive lymphoma subgroup ($n=90$), the 5 year OS rate and 5 year PFS rate were 62.96 and 57.41%, which were also superior to 48.61 and 37.50% for non-splenectomy patients ($P=0.042$ and $P=0.017$, respectively). In the whole group ($n=110$), multivariate model shows prolonged APTT ($P=0.024$), virous treatments ($P=0.016$) and elevated ferritin ($P=0.017$) were independent predicted OS parameters. In aggressive lymphoma subtype ($n=87$), treatment ($P=0.021$) and prolonged APTT ($P=0.016$) emerged as independent risk factors. In indolent lymphomas, no significant differences were found.

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Conclusion In this group of lymphoma patients presenting with splenic invasion as the first manifestation, the pathological type was almost aggressive lymphoma, with DLBCL being the main subtype. Common clinical symptoms include elevated ferritin, prolonged APTT and high LDH levels. This study suggests that splenectomy should be considered for these patients when their overall condition allows for safe intervention. Splenectomy combined with chemotherapy can significantly improve the survival time of patients.

Keywords Splenic lymphoma, Prognosis, PET–CT, Splenectomy, Liver function

Introduction

In recent years, due to the popularity of sensitive imaging techniques, flow cytometry and biomolecular analysis, the incidence of lymphoma is on the rise. Alterations in NK-cell function are commonly observed in various lymphomas, including aggressive forms like DLBCL and Hodgkin lymphoma (HL) [1]. The incidence of lymphoma is about 5–7 per 100,000 people [2], the median age is 60 to 65 years [3], which is a heterogeneous group of malignant diseases originating from lymphatic systems, includes lymph nodes, spleen, bone marrow or other lymphoid tissues. The spleen may be involved as a part of systemic lymphoma or as the main site of the lymphoma. The former is a common clinical manifestation ranging from indolent diseases such as SMZL and FL to aggressive diseases like DLBCL or MCL [4, 5]. The latter is defined as PSL, usually limited mainly to the spleen or splenic hilar lymph nodes, with no evidence of involvement except in the bone marrow and possibly the liver or secondary splenic lymphoma, with a prevalence of 30–40%. From the literature review, the initial diagnosis of lymphoma appears to be made only occasionally during splenectomy [6]. Despite clinical experience, the prognostic value of therapeutic splenectomy in patients with splenic infiltrating lymphoma remains unclear. Consequently, we reviewed a group of patients with lymphoma diagnosed for the first time by splenocentesis or splenectomy and analyzed the clinical presentation and treatments of lymphoma with spleen invasion as the main manifestation.

Materials and methods

Study participants and clinical data

At the First Affiliated Hospital of Zhejiang University School of Medicine, we retrospectively enrolled 113 cases diagnosed as lymphoma by pathological specimen of spleen from March 2011 to February 2023.The pathological subtypes were determined according to the 2016 revised World Health Organization classification. Concrete inclusion and exclusion criteria were as follows: Inclusion criteria: (1) no suitable lymph nodes for biopsy; (2) lymphoma was confirmed by splenectomy or biopsy from spleen; (3) older than 18 years; (4) initial treatment in our hospital. Exclusion criteria: (1) lymphoma was previously diagnosed; (2) missing the most clinical data. Demographic, laboratory results, diagnostic procedure, treatments, relapse and date of death or last follow-up were obtained for all patients. The last follow-up time was September 1st, 2024. This study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Zhejiang University. All methods are carried out in accordance with the Declaration of Helsinki (WMA General Assembly, Helsinki, Finland, October 2024).

Endpoint and definitions

The primary assessments of this study encompassed PFS and OS. PFS is characterized as the duration from the date of diagnosis to treatment failure, which incorporates instances of disease recurrence, progression, mortality, or deletion the follow-up due to various reasons. OS is delineated as the time span from the initial diagnosis of the disease to death from any cause or patients' data were lost during follow-up for various reasons.

Statistical analysis

Data were analyzed using GraphPad Prism 9.0 and SPSS 27. For the statistical analysis, patients were categorized into two subgroups: (1) aggressive lymphoma or indolent lymphoma; (2) DLBCL or other types lymphoma. Chi-square test was used for classified data analysis, Mann–Whitney U test was used for continuous or grouped data that are not normally distributed. T-test was employed for data conforming to a normal distribution with homogeneous variances and Wilcoxon rank sum test was used for non-normally distributed data. The median follow-up time was estimated with Kaplan–Meier method. The clinically accepted normal upper limits were utilized as the optimal cut-off thresholds for ferritin, APTT and LDH. Kaplan–Meier survival analysis and the Cox proportional hazards model were used to generate survival curves. The impact of various variables on survival were assessed through Cox multivariate survival analysis. All statistical tests were two-tailed with a significance level set at the P-value of 0.05.

Result

Baseline characteristics

Ultimately, 113 patients meeting the inclusion criteria were included in this study. The characteristics of these enrolled patients are presented in Table 1. The median age of these 113 cases was 59 years (range 18–82 years). The ratio of male to female was 1.09 to 1. The specific performance is shown in Table 1. The most common symptom was abdominal discomfort included bloating and abdominal pain 59 patients (52.21%), B symptoms were presented in 54 patients (47.79%). Spleen occupying was found in 25 patients during physical examination, 83 of 113 (73.5%) patients had enlarged spleen. Core needle biopsy was performed in 41 patients and splenectomy was performed in 72 patients. Bone marrow involvement was found in 54 of 108 patients (50%), liver involvement was found in 5 patients (4.42%). Other involved extranodal sites were the adrenal and pancreas (3 patients each); jaw, lung, stomach and pharynx (1 patient each). According to Ann Arbor staging, most patients, 102 cases (98.24%) were at stage III and IV. IPI was used to evaluate the prognosis of invasive lymphoma (n = 90), a low IPI (0–2) was documented in 50 cases (55.5%) and a high IPI (3–5) was documented in 40 cases (44.5%). In the DLBCL group, there were 54 patients with non-GCB, 20 patients with GCB subtype, 32 patients with MYC rearrangement, and 26 patients with overexpression of double MYC and BCL proteins expression. In all cases, the presence of spleen lesions was confirmed by biopsy or excision of the spleen after routine physical examination or PET examination. 58 patients underwent 18F-FDG scanning prior to splenic puncture or surgery due to economic conditions and disease situation. The specific SUV value of the 6 patients were unknown due to data from other hospitals and other reasons. In those 52 patients, the median of SUV value was 7.75 (IQR 4.58–16.15). The mean Ki-67 proliferative index of patients was 70% (40–80%). Hemophagocytic syndrome (HLH) was presented in 10 patients.

Treatment and outcome

Treatment modalities

We divided the treatment into three groups: (1) monosplenectomy (S); (2) splenectomy followed by chemotherapy (SC); (3) mono-chemotherapy(C). 12 of 113 patients received S, 60 cases received SC, 41 cases received C. Specifically, among 18 cases of SMZL, 7 patients underwent S, 6 received SC and 5 were treated with C alone. The chemotherapy regimens were either rituximab (R) combined with or without CHOP. In 74 cases of DLBCL, 3 patients underwent S, 44 underwent SC and 27 only received C. The chemotherapy regimen was 67 patients included CHOP, 62 of them receiving in combination with R. 5 patients did not receive R, but 3 of them were treated with POLA or MINE. In addition, among the 4 other patients who underwent chemotherapy, 2 were treated with ruxolitinib and steroids due to early onset HLH, while the remaining 2 received ECOP or GCOP regimens. Among 10 cases of NK/T lymphoma, 2 patients underwent SC while 8 patients received C alone. The chemotherapy regimens indicated that 7 patients received ECHOP, including 2 with HLH who were treated with ruxolitinib, while 3 patients received CHOP or pegaspargase, gemcitabine and oxaliplatin (P-Gemox) regimen. In 4 cases of FL, 1 patient underwent S, 2 underwent SC and 1 received C alone. The chemotherapy regimen based on the patient's general condition was either R combined with or without CHOP. Among 4 cases of MZL, 1 patient received S alone, 2 received SC and 1 was treated with C alone. All chemotherapy regimens were CHOP combined with R. The chemotherapy-only patient later relapsed and was treated with obinutuzumab and orelabrutinib. One patient with T-cell lymphoma was treated with chidamide combined with L-asparaginase and received HSCT. One EBV-positive T-cell and NK-cell lymphoproliferative disorder patient received R and steroids because of HLH and followed by splenectomy. The subsequent chemotherapy included P-Gemox. One patient with CLL/SLL received splenectomy combined with R-CHOP, later switching to rituximab with cyclophosphamide, doxorubicin, and dexamethasone (Hyper-CAVD-A). Furthermore, 10 patients developed HLH during the treatment and 9 patients subsequently received HSCT (5 of them underwent autologous hematopoietic stem cell transplantation and 4 cases were got allogeneic hematopoietic stem cell transplantation).

Treatment outcome

The median duration of follow-up was 37.53 months (range, 0–162.33 months). During this time, 46 patients (40.71%) died; 43 cases (38.05%) were due to progression or recurrence of the primary disease, 3 patients died from pulmonary infection and the remaining died from lymphoma recurrence or progression. 3 cases (2.65%) died early after splenectomy due to bleeding or severe infection. A complete response (CR) was achieved in 48 patients (42.48%) and a partial response (PR) was achieved in 47 patients (41.59%). 18 patients (15.93%) progressed after treatment. Relapse occurred in 18 patients (15.30%), and 2 of these had central nervous system relapse. In the DLBCL subgroup ($n = 74$), 10 patients did not respond to treatment, 31 cases achieved PR, 33 cases achieved CR. In the aggressive lymphoma subgroup ($n = 90$), 16 patients did not respond to treatment, 36 cases achieved PR, 38 cases achieved CR.

Table 1 Patients baseline characteristic

Characteristic	All ($n=113$)	DLBCL ($n=74$)	Non-DLBCL ($n=39$)	*P* value
Age, years, *n* (%)				
Median (range)	59 (18–82)	61 (25–82)	55 (18–74)	
≥60	52 (46.01)	42 (56.75)	13 (33.33)	0.018*
<60	61 (53.98)	34 (45.95)	26 (66.67)	
Male/female, *n* (ratio)	59/54,1.09	39/35,1.11	20/19,1.05	0.886
Laboratory tests, median (IQR)				
WBC, $\times 10^9$/L	4.60 (3.00–7.25)	4.80 (3.68–6.97)	3.35 (2.40–7.70)	0.519
N, $\times 10^9$/L	2.70 (1.80–4.10)	3.13 (2.15–4.20)	2.00 (1.20–3.20)	0.141
L, $\times 10^9$/L	1.01 (0.71–1.65)	1.08 (0.69–1.52)	0.98 (0.78–2.30)	0.517
Platelets, $\times 10^9$/L	116.00 (73.50–187.00)	124.00 (81.75–216.25)	87.00 (67.00–150.00)	0.458
LDH, U/L	303.00 (208.00–683.00)	338.00 (214.25–684.50)	238.00 (198.00–569.00)	0.477
ALT	16.00 (11.00–27.00)	16.50 (12.00–26.25)	15.00 (10.00–35.00)	0.355
Cr,	64.00 (55.00–79.5)	63.50 (54.75–78.00)	69.00 (55.00–89.00)	0.624
Ferritin	376.9 (154.6–1071.7)	632.49 (254.60–1202.90)	177.50 (71.84–464.39)	0.455
APTT	29.5 (26.75–34.60)	29.65 (26.70–34.73)	29.40 (26.90–34.70)	0.468
PT	12.20 (11.40–13.15)	12.15 (11.40–13.30)	12.20 (11.10–13.00)	0.255
Ki-67	70.00 (40.00–80.00)	80.00 (70.00–80.00)	27.50 (10.00–57.50)	<0.001***
Laboratory tests, mean ± SD				
HB, g/L	106.96 ± 27.80	105.51 ± 28.76	107 ± 26.00	0.268
Albumin, g/L	37.46 ± 7.63	36.48 ± 7.93	41.50 ± 6.71	0.262
Globulin, g/L	25.45 ± 6.46	25.69 ± 6.19	22.90 ± 7.00	0.556
Fibrinogen	3.78 ± 4.93	3.70 ± 1.11	2.54 ± 8.32	0.342
Thickness of spleen, cm, median (IQR)	5.70 (4.57–6.83)	5.40 (4.50–6.50)	6.60 (5.10–8.10)	0.337
HLH, *n* (%)	10 (8.85)	7 (9.45)	3 (7.69)	0.753
Bone marrow involvement, *n* (%)	54 (47.79)	29 (39.19)	25 (64.10)	0.028
B syndrome, *n* (%)	54 (47.79)	34 (45.95)	20 (51.28)	0.589
Ann Arbor stage, *n* (%)				
IS	1 (0.88)	1 (1.35)	0	
II	1 (0.88)	0	1 (2.56)	
III	24 (21.24)	15 (20.27)	9 (23.08)	
IV	87 (76.99)	58 (78.38)	29 (74.36)	0.462
Pathological classification, *n* (%)				
SMZL,	18 (15.93)			
DLBCL	74 (65.49)			
T/NK cell lymphoma*	10 (8.85)			
FL	4 (3.54)			
MCL	4 (3.54)			
Others#	3 (2.65)			
SUV, median, (IQR)	7.75 (4.51–16.65)	12.00 (5.42–22.45)	5.07 (3.55–6.38)	0.400
Treatments, *n* (%)				
Splenectomy	12 (10.62)	3 (4.05)	9 (23.08)	
Splenectomy followed by chemotherapy	59 (52.21)	44 (59.46)	16 (41.02)	
Treatments, *n* (%)				
Chemotherapy	42 (37.17)	27 (36.49)	14(35.90)	0.006**
CD3	101 (89.3%)	67 (90.5%)	34 (87.2%)	0.54
CD5	30 (26.5%)	20 (27.05)	19 (48.7%)	0.53
CD19	25 (22.1%)	11 (14.9%)	5 (12.8%)	0.87
CD20	101 (89.3%)	68 (91.9%)	34 (87.2%)	0.93
CD22	6 (5.3%)	2 (2.7%)	0	0<0.001***

Table 1 (continued)

Others# refers to: EBV-positive T cell lymphoma, chronic lymphocytic leukemia/Small lymphocytic lymphoma, T lymphoblastic lymphoma

WBC white blood cell, *HGB* hemoglobin, *LDH* lactate dehydrogenase, *SMZL* splenic marginal zone lymphoma, *DLBCL* diffuse large B cell lymphoma, *MCL* mantle cell lymphoma, *FL* follicular lymphoma

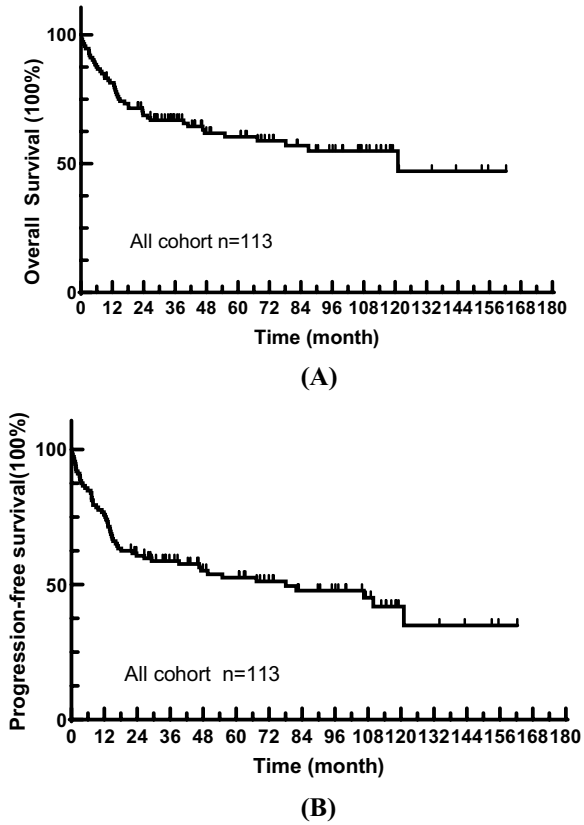

Fig. 1 A Overall survival and B progression-free survival for 113 patients with lymphoma infiltrating spleen

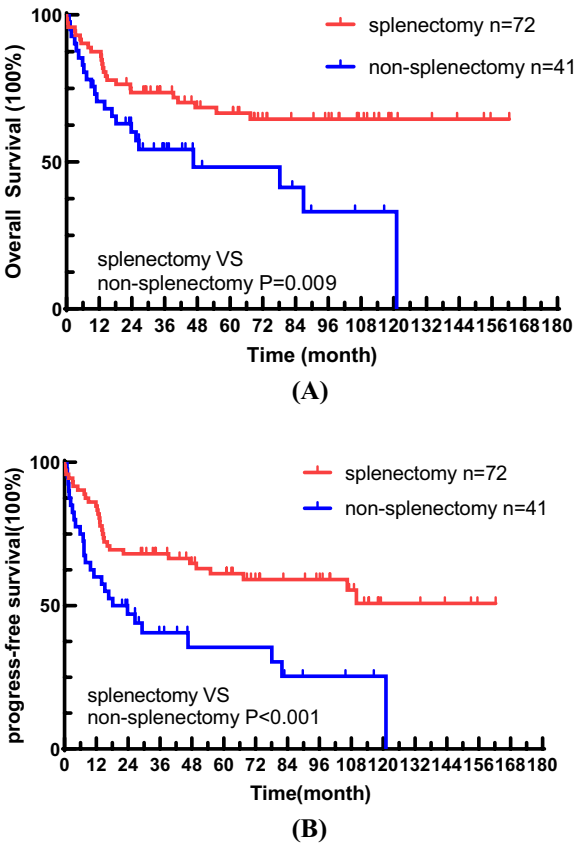

Fig. 2 A Overall survival and B progression-free survival for patients with lymphoma infiltrating spleen who did or did not undergo splenectomy at diagnosis

Survival analysis

The OS and PFS values for the whole cohort are shown in Fig. 1. For the entire cohort, the 5 year OS was 62.39% and 5 year PFS rate was 53.98%. Figure 2 plots the OS and PFS values, according to the splenectomy status at diagnosis, 5 year OS was 68.06% for the splenectomized patients and 52.44% for the non-splenectomy patients ($P=0.009$); the corresponding values of PFS were 62.50 and 37.80%. ($P<0.001$). These differences were also apparent in aggressive lymphoma group ($n=90$), 5 year OS was 62.96% for the splenectomy patients and 48.61% for the non-splenectomy patients ($P=0.042$; Fig. 3A), and the PFS values were 57.41 and 37.5%, respectively ($P=0.017$; Fig. 3B). No significant findings were noted in indolent lymphoma subgroup as the indication for splenectomy. Because there were 3 cases died early after splenectomy due to bleeding or severe infection, these were excluded from the survival factor analysis. In Table 2 univariate analyses of the relationship between clinical features and survival across the whole cohort ($n=110$), we found that the presence of B symptoms ($P<0.001$), elevated LDH ($P=0.024$), prolonged APTT ($P=0.003$), elevated ferritin ($P<0.001$), GC ($P=0.013$) and different treatments ($P=0.004$) were associated with survival outcomes while male, presence or absence of double expression, abdominal discomfort symptoms, and presence or absence of bone marrow infiltration were all negative. When these data were fed into a multivariate model, prolonged APTT ($P=0.024$), virous treatments ($P=0.016$) and elevated ferritin ($P=0.017$) were independent predicted OS parameters Table 3.

Aggressive lymphoma subtype In a univariate analysis that only analyzed the relationship between clinical features and survival in the aggressive lymphoma

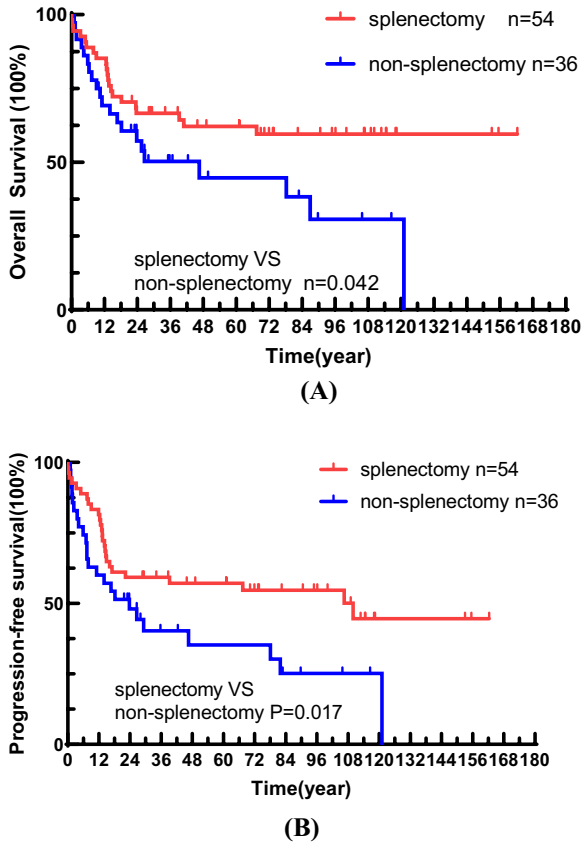

Fig. 3 A Overall survival and B progression-free survival for patients with aggressive lymphoma who did or did not undergo splenectomy at diagnosis

($n=87$) cohort in Table 4, we found that with B syndrome ($P=0.001$), male ($P=0.008$), prolonged APTT ($P=0.005$), different treatments ($P=0.029$) and elevated ferritin ($P=0.021$) were linked to shorter survival but not with age, bone marrow infiltration and elevated LDH. In multifactorial analysis, treatment ($P=0.021$) and prolonged APTT ($P=0.016$) emerged as independent risk factors.

DLBCL subtype In the diffuse large B cell subgroup ($n=74$), through univariate analysis, we found that age > 60 years old ($P=0.016$), B syndrome ($P=0.013$), APTT > 33S ($P=0.009$), ferritin > 330 ng/ml ($P=0.012$) NON-GCB ($P=0.021$), and non-GCB ($P=0.021$). Splenectomy alone was associated with shorter survival, independent of gender, bone marrow infiltration, and elevated LDH. In multivariate analysis, simple splenectomy and APTT > 33S (HR 2.522, 95% CI 1.068–5.973, $P=0.035$) were independent risk factors. (Table 4).

Discussion

Lymphoma encompasses a wide range of hematologic malignancies, with splenic involvement is often a challenge to diagnose and treat. Although splenic infiltration in lymphoma is commonly seen in advanced or disseminated disease, there is growing recognition of its role as a primary site of involvement in certain lymphoma subtypes. This study is the first clinical retrospective analysis of lymphoma patients with splenic invasion as the initial presentation. It analyzed 113 patients, allowing for a thorough evaluation of clinical clinical, laboratory, and imaging features and providing sufficient statistical certainty to determine the important therapeutic role of splenectomy in diagnosis. The average age of our patients was 59 years, which is notably younger than the typical age of diagnosis for all forms all DLBCL types which was approximately 70 years. However, this age is comparable to the reported for patients with PS-DLBCL patients at diagnosis as 56.6 years [7]. Our patients had B symptoms, prolonged APTT and elevated ferritin. But interestingly, while elevated LDH levels have been suggested

Table 2 All cohort: univariate analysis and multivariate analysis for overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
B syndrome	2.878 (1.526–5.427)	< 0.001***		
Elevated LDH	2.182 (1.108–4.298)	0.024*		
prolonged APTT	2.395 (1.312–4.371)	0.003**	2.030 (1.098–3.750)	0.024*
Elevated ferritin	3.148 (1.609–6.161)	< 0.001***	2.338 (1.163–4.699)	0.017*
Treatment	2.412 (1.423–4.088)	0.004**	2.006 (1.138–3.534)	0.016*
GC	0.215 (0.050–0.920)	0.023*		
Bone infiltration	1.374 (0.737–2.562)	0.316		

The one asterisk *corresponds to $P<0.05$

The two asterisks **correspond to $P<0.01$

The three asterisks ***correspond to $P<0.001$

Table 3 Subgroup aggressive lymphoma: univariate analysis and multivariate analysis for overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male	0.556 (0.286–1.083)	0.008**		
Age > 60 years	1.638 (0.880–3.049)	0.120		
B syndrome	2.911 (1.488–5.696)	0.001***	1.452 (0.687–3.072)	0.329
Elevated ferritin	2.351 (1.112–4.971)	0.021*		
Elevated LDH	1.812 (0.873–3.760)	0.105		
prolonged APTT	2.436 (1.285–4.620)	0.005**	2.493 (1.270–4.893)	0.008**
Treatment				
SC VS S	0.012 (0.001–0.200)	0.002***	0.007 (0–0.129)	< 0.001***
C VS S	0.023 (0.001–0.385)	0.009**	0.009 (0–0.165)	0.002***

Table 4 Subgroup aggressive lymphoma: Univariate analysis and multivariate analysis for DLBCL

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male	0.456 (0.253–1.169)	0.119		
Age > 60 years	2.723 (1.205–6.152)	0.016*	1.471 (0.592–3.652)	0.406
B syndrome	2.611 (1.228–5.553)	0.013*	1.536 (0.619–3.811)	0.355
Elevated ferritin	3.462 (1.319–9.088)	0.012*	1.658 (0.588–4.672)	0.339
Elevated LDH	1.567 (0.681–3.606)	0.291		
Prolonged APTT	2.726 (1.285–5.779)	0.009**	2.525 (1.068–5.973)	0.035*
NON-GCB	0.183 (0.043–0.777)	0.021*	0.353 (0.077–1.611)	0.179
Treatment				
SC VS S	0.014 (0.001–0.244)	0.003**	0.015 (0.001–0.291)	0.006***
C VS S	0.029 (0.002–0.492)	0.014*	0.019 (0.001–0.373)	0.009***

as a key tumor biomarker, our study found that high LDH did not play a significant role in prognosis, which contrasts with the findings of Jurisic et al. who emphasized LDH as an important biomarker for early diagnosis in NHL [8]. Jurisic V's data highlight the potential of LDH as a tumor biomarker, with measurements in serum, cultured cells, and tumor tissues playing a crucial role in early diagnosis. Furthermore, their study compared spontaneous LDH release from circulating PBMCs with serum LDH activity in 53 NHL patients across various subtypes. Results show that serum LDH was significantly elevated only in advanced stages (III and IV), while spontaneous LDH release was elevated in both early and advanced stages, suggesting that microassay measurement of spontaneous LDH release may aid in the early diagnosis of NHL, even before serum LDH levels increase. In Park' s study LDH is one of the prognostic factors in most patients [9–11]. Ferritin, a protein involved in iron storage, is a well-established marker of inflammation and can be elevated in various malignancies, including lymphoma. Previous studies have found that elevated ferritin levels in lymphoma patients are often associated with tumor burden, advanced disease stage, and poor prognosis. For example, a study by Koch et al. [12] found that elevated ferritin levels in patients with DLBCL were linked to an increased risk of disease progression and relapse. The findings in this paper align with these observations, suggesting that ferritin may be an important biomarker for monitoring lymphoma progression in patients with splenic involvement. TNF-α, a multifunctional cytokine produced by NK cells and cytotoxic T lymphocytes, plays a critical role in inflammation, immune responses, and lymphoid tissue function. While its ability to induce apoptosis is vital for cellular homeostasis, its use in therapy is limited due to side effects. Elevated TNF-α levels in lymphoma patients modulate immune responses and may influence tumor growth [13, 14]. Our study also reports a prolonged APTT which is a critical finding, as disseminated intravascular coagulation (DIC) and HLH are known complications of high-grade lymphomas, particularly those with splenic involvement [15]. The prolonged APTT in lymphoma patients can indicate severe coagulopathy, which requires prompt attention and management. Previous literature [16] highlights the difficulty in distinguishing between HLH and lymphoma-related symptoms, which often overlap. These clinical findings emphasize the need for early detection and management of these

complications in lymphoma patients. Among our patients, abdominal pain was found in 45 cases, and splenomegaly was found in 83 cases, among which 25 cases had no discomfort, so they revealed splenomegaly by chance. The average weight of the normal spleen is 135 g [11], the major axis is 10–12 cm, and the thickness is about 3.5 mm, while the average thickness of the spleen in our study is 5.70 mm. The incidence of splenic mass (73.45%) in our patients was significantly higher than that reported by Shimizu-Kohno et al. (60%), which may be due to the fact that our patients initially presented with primary splenic infiltration. Also in Shimizu-Kohno et al. study, 115 Japanese patients with splenic malignant lymphoma, 46 of whom were DLBCL, 97% of whom had splenomegaly. Splenomegaly can also lead to hypersplenia, which is characterized by a reduction in cells, including anemia, thrombocytopenia, and neutropenia, due to the isolation and destruction of blood cells within the splenomegaly. In clinical diagnosis and treatment, it is important to distinguish not only between lymphoma and benign splenic lesions, but also the type of lymphoma in order to proceed with appropriate treatment. From the literature review, the initial diagnosis of lymphoma appears to be made only occasionally during splenectomy [5]. Bone marrow damage was rare in both studies (7 and 10%, respectively). In our study 54 patients (50%) of our patients had B symptom and 54 patients (50%) of our patients had bone marrow infiltration.The prognostic value of Ki-67 in DLBCL was recently summarized in a meta-analysis and a large prospective study [17]. The results showed that a high Ki-67 index predicted poor survival, and the number of Ki-67 positive cells in our study was high (70% on average), so overall our study demonstrated a 5 year PFS rate of only about 53.98%. In addition, there have been studies on patients with lymphoma with splenic invasion as the initial manifestation, so the diagnosis and treatment of this type of patients have not been fully studied, and relevant studies have included a mixed population of patients with intolerance and aggressive splenic lymphoma. In their article, "How I Diagnose and Treat Splenic lymphoma" [4], Iannitto and Tripodo supported the use of diagnostic splenectomy, but do not make specific recommendations for cases of aggressive lymphoma other than to emphasize the importance of correct pathological diagnosis. Anyway, previous research on the role of splenectomy in lymphoma treatment is mixed. Appel et al. [18] reported that splenectomy can improve survival in patients with SMZL, while Chihara et al. [19] found that splenectomy combined with chemotherapy in patients with PSL resulted in improved survival outcomes. However, there is a lack of robust evidence supporting the routine use of splenectomy in aggressive lymphomas such as DLBCL. Miyaoka et al. [20] emphasized that splenectomy in high-grade lymphomas should be considered only in carefully selected cases due to the risk of disease progression, especially in patients with advanced stage disease or extra-nodal involvement. In our study, splenectomy was also recommended for patients with aggressive lymphoma. Morel et al. [21] described 59 patients with splenic lymphoma, 16 of whom had moderate or aggressive disease. Although the results of their analysis were favorable for splenectomy, the authors did not distinguish between pathological subtypes. In our study, 41 patients (36.28% of the cohort) were diagnosed by core needle biopsy. This method has been in use since the early 1980s. The main concern is the risk of bleeding because the spleen is a vascular organ. In a review, Lieberman et al. [22] reported a high diagnostic success rate (90%) for core puncture biopsies and a 0–8% incidence of bleeding complications. In general, no intervention is required, indicating that bleeding is minimal and surgery is safe; diagnostic splenectomy has been reported to have an incidence of 12% and a mortality of 1%. Although laparoscopic splenectomy is rare in number and can be performed safely in cases of large splenomegalysis, doctors and patients tend to avoid it for diagnostic purposes. In our case, 72 patients (63.72% of the cohort) were diagnosed by splenectomy, and 3 patients (2.7%) died early due to infection and bleeding after splenectomy. Mortality rates were similar to those previously reported. Splenectomy itself carries risks of short-term thromboembolism (portal and deep vein thrombosis) and long-term infection (pneumonia, meningitis, and septicaemia) [23]. In conclusion, most lymphoma patients with splenic infiltration as the primary manifestation present with aggressive disease, with DLBCL being the predominant subtype. Common clinical symptoms include B symptoms, elevated ferritin, and prolonged APTT. Our study indicates that splenectomy should be considered to effectively extend the survival of patients when their overall condition allows.

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Author contributions
XJY and JSH conceived the study, MQX, LL and LLW collated and analyzed the data and draft the article. LXZ and LL collected and selected the references, LJW and KZ screened patients, LL and LXZ revised the manuscript. All the authors have read and approved the manuscript. All the authors have contributed to conceiving, drafting, or revising the manuscript, have agreed on the journal to which the article will be submitted, have provided final approval of

the version to be published, and have agreed to be accountable for all aspects of the work.

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Availability of data and materials
If necessary, data may be provided with the consent of the corresponding author.

Declarations

Ethics approval and consent to participate
Informed written consent was obtained from all subjects and/or their legal guardian(s) for participation in the study. This study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Zhejiang University. All methods were carried out in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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