Original Article

Prognostic significance of diffuse increased fluorine-18-fluorodeoxyglucose (^{18}F-FDG) uptake within the reticuloendothelial system in lymphoma patients

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Background: As constituents of the reticuloendothelial system, the spleen and bone marrow (BM) have been recognized as integral components of the systemic inflammatory response in cancer contexts, thereby serving as predictive indicators for assessing cancer prognosis. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) has attained widespread utilization for staging, assessing treatment response, and prognostication in lymphoma patients. Several investigations have proposed that focal increased ^{18}F-FDG uptake in the BM or spleen may correlate with malignant involvement in lymphoma. However, scant data exist regarding the implications of diffuse BM and splenic uptake. This study aimed to explore the relationships between metabolic parameters of the spleen and BM on ^{18}F-FDG PET/CT and inflammatory markers, and to assess their prognostic value in patients with lymphoma.

Methods: A retrospective analysis was conducted on 118 patients newly diagnosed with malignant lymphoma, who underwent ^{18}F-FDG PET/CT and exhibited diffuse increased splenic or BM uptake in ^{18}F-FDG PET/CT imaging. The mean standardized uptake value (SUV) of the spleen, BM, and liver was calculated. The association between metabolic variables and systemic inflammatory markers was investigated, and the prognostic significance of clinicopathological and PET parameters was assessed using overall survival (OS) and progression-free survival (PFS).

Results: A statistically significant correlation was found between the spleen-to-liver SUV ratio (SLR) and inflammatory markers such as C-reactive protein (r=0.264, P=0.007) and platelet-to-lymphocyte ratio (r=0.227, P=0.021). No significant correlation was observed between BM-to-liver SUV ratio (BLR) and

hematologic parameters, while concordance analysis revealed a fair agreement between BLR and bone marrow biopsy (BMB) (Cohen's Kappa-κ =0.271, P=0.002). In patients with aggressive non-Hodgkin lymphoma, both SLR [P=0.017, HR 2.715, 95% confidence interval (CI): 0.875–8.428] and BLR (P=0.044, HR 0.795, 95% CI: 0.348–1.813) were significantly linked to OS, while SLR (P=0.019, HR 2.223, 95% CI: 1.139–4.342) emerged as a significant prognostic factor for PFS.

Conclusions: This study highlighted that diffuse increased splenic ^{18}F-FDG uptake in lymphoma patients was closely associated with inflammation, whereas diffuse BM uptake was likely attributable to BM infiltration rather than inflammatory changes. Furthermore, both parameters held promise as prognostic indicators for patients with aggressive lymphoma.

Keywords: Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT); lymphoma; spleen; bone marrow (BM)

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Introduction

Over recent decades, the incidence of malignant lymphoma has dramatically increased worldwide. Lymphomas are traditionally classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). More recently, increasing attention has been paid to the correlation between inflammation, innate immune response, and cancer. Inflammatory cells, as well as some of the signaling molecules of the innate immune system, are essential components of the tumor microenvironment (TME), which play an important part in promoting tumor proliferation, survival, and migration (1). This is also relevant in lymphomas. Accumulating evidence suggests that TME and host immunity may play a significant role in the pathogenesis and progression of human lymphomas (2,3).

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) has attained widespread utilization for staging, assessing treatment response, and prognostication in lymphoma patients (4). Given that ^{18}F-FDG uptake not only reflects glycolytic activity within tumorous contexts but also in inflammatory settings, systemic inflammatory responses can be discerned and evaluated through ^{18}F-FDG PET/CT images (5). The reticuloendothelial system (RES), also referred to as the mononuclear phagocyte system (MPS), constitutes a facet of the immune system implicated in eliciting and modulating immune responses (6). As constituents of the RES, the spleen, bone marrow (BM), and liver have been recognized as integral components of the systemic inflammatory response in cancer contexts (7,8). Consequently, diffuse increased ^{18}F-FDG uptake observed in the liver, spleen, and BM may signify systemic inflammatory responses or immune system activation pertinent to cancer, thereby serving as predictive indicators for assessing cancer prognosis (9).

Several investigations have proposed that focal increased ^{18}F-FDG uptake in the BM or spleen may correlate with malignant involvement in lymphoma (10). However, scant data exist regarding the implications of diffuse BM and splenic uptake. Hence, our objective was to explore the associations between diffuse ^{18}F-FDG uptake of the RES on ^{18}F-FDG PET/CT and inflammatory markers, and to assess the prognostic utility of RES in lymphoma patients. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-180/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (No. 2021-157), with a waiver of informed consent. The study was registered in Chinese Clinical Trial Registry with registration number ChiCTR2100047592.

Patients histopathologically diagnosed with malignant lymphoma and who underwent ^{18}F-FDG PET/CT between March 2013 and November 2023 were retrospectively

reviewed for inclusion in this study. The inclusion criteria were: (I) newly diagnosed lymphoma; and (II) exhibiting diffuse increased uptake in the liver, spleen, or BM on ^{18}F-FDG PET/CT imaging. Exclusion criteria were defined as follows: (I) patients with primary diseases affecting the liver, spleen, or BM, or those with other primary cancers. (II) Patients who had undergone granulocyte colony-stimulating factor (G-CSF) therapy, chemotherapy, or stem cell transplantation within 1 month before the PET/CT scan, or who had other conditions potentially influencing liver, spleen, or BM metabolism (e.g., anemia, infectious diseases, or invasive procedures). (III) Patients with focal increased uptake in the liver, spleen, and BM. (IV) Inability to retrospectively analyze digital image data. (V) Patients lost to follow-up within 6 months. Follow-up data were obtained through clinical visits or telephone communication.

Clinicopathological and survival data

Clinical pathology data relevant to prognosis were extracted from electronic medical records. This encompassed clinical information (such as age, sex, pathological type, Ann Arbor stage, and presence of B symptoms), as well as hematological data [including lactate dehydrogenase (LDH), serum C-reactive protein (CRP), white blood cell (WBC) count, monocyte count (Mono), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)], obtained from laboratory studies conducted within 7 days before or after the ^{18}F-FDG PET/CT examination.

For survival analysis, overall survival (OS) was defined as the duration from the date of diagnosis to the date of death or last follow-up. Progression-free survival (PFS) was defined as the period from the date of diagnosis to any evidence of disease progression, death, or last follow-up.

Acquisition of ^{18}F-FDG PET/CT

^{18}F-FDG PET/CT imaging was conducted using a Discovery STE PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA). Patients fasted for a minimum of 4 hours prior to the examination, with blood glucose levels maintained below 11.1 mmol/L. Approximately 60 minutes following the injection of ^{18}F-FDG (dose: 4.07–5.55 MBq/kg), imaging encompassing the skull base to mid-thigh was performed. This included a low-dose CT scan (parameters: 140 kV, 120 mA, pitch 1.75, transaxial field of view 70 cm, rotation time 0.8 s, slice thickness 3.75 mm) and a PET scan (duration: 2–3 minutes per bed position, covering 5–7 positions). Reconstruction of coronal, axial, and sagittal slices of PET/CT fusion images was accomplished using the Xeleris workstation software (GE Healthcare; ADW4.1), employing a standard iterative algorithm that included corrections for scatter and attenuation based on the CT data.

Analysis of ^{18}F-FDG PET/CT imaging

^{18}F-FDG PET/CT images were independently assessed by two experienced nuclear medicine physicians who were blinded to the clinical details of all subjects. Diagnosis was based on visual assessment of the distribution of ^{18}F-FDG uptake, with efforts made to minimize the influence of physiological, pathological, and technical factors on uptake. In cases of discrepancy in visual assessment between the two readers, a consensus was reached with a third nuclear medicine physician present. Mean standardized ^{18}F-FDG uptake values (SUV_{mean}) of the spleen and liver were calculated using regions of interest (ROIs) placed at the center of the spleen and the right hepatic lobe, respectively. SUV_{mean} of the BM was determined using ROIs at the vertebral bodies of T10–12 and L3–5, and then averaged. The liver served as a reference organ for ^{18}F-FDG uptake in the BM and spleen, thus allowing calculation of the BM-to-liver SUV ratio (BLR) and spleen-to-liver SUV ratio (SLR).

Statistical analysis

All statistical analyses were conducted using the SPSS software package (Version27.0, Chicago, IL, USA) and GraphPad software (Version9.3.0, San Diego, CA, USA). Spearman's rank correlation analyses were employed to evaluate relationships between spleen, BM, or liver metabolism and clinicopathological parameters. The agreement between bone marrow biopsy (BMB) and visual PET assessment was assessed using Cohen's kappa (κ), with values interpreted as follows: slight agreement (0.0–0.2), fair agreement (0.21–0.4), moderate agreement (0.41–0.6), substantial agreement (0.61–0.8), and almost perfect agreement (0.81–1.0). Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve (AUC) was calculated to determine specific cut-off values for all continuous variables in survival analysis. If the AUC was less than 0.5, the median was utilized as the cut-off value. Survival analysis was performed using the Kaplan-Meier method, with between-group differences

Table 1 Characteristics of the study subjects

Variables	Total (n=118)
Age (years)	51.67±14.03
Gender	
Male	66 (55.9)
Female	52 (44.1)
Ann Arbor stage	
I + II	19 (16.1)
III + IV	99 (83.9)
With B symptoms	81 (68.6)
CRP (mg/L)	11.82 [3.56–17.33]
LDH (U/L)	232.00 [171.8–304.1]
WBC ($\times10^9$/L)	7.60 [5.56–10.89]
NLR	2.69 [1.32–5.57]
PLR	124.75 [68.25–207.14]
Mono ($\times10^9$/L)	0.53 [0.35–0.74]
Spleen SUV_{mean}	2.94 [2.07–3.75]
BM SUV_{mean}	2.35 [1.75–3.17]
Liver SUV_{mean}	1.84 [1.62–2.07]
SLR	1.60 [1.07–2.05]
BLR	1.26 [0.93–1.86]

Data are presented as mean ± standard deviation, n (%) or median [interquartile range] as appropriate. CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Mono, monocyte counts; SUV_{mean}, mean standardized uptake value; BM, bone marrow; SLR, spleen-to-liver SUV ratios; BLR, bone marrow-to-liver SUV ratios.

assessed via the log-rank test. Univariate Cox regression analysis was conducted for each parameter, and those with a p-value less than 0.05 were included in the multivariable analysis. Statistical significance was defined as P<0.05 using a two-tailed test.

Results

Patients' characteristics

A total of 118 patients were included in the study based on the aforementioned inclusion and exclusion criteria, comprising 66 males (55.9%) and 52 females (44.1%), with a mean age of 51.67±14.03 years. The median follow-up period was 33 months. Detailed patient characteristics are summarized in *Table 1*. Among the cohort, 11 patients (9.3%) were diagnosed with HL, while the remaining 107 patients (90.7%) were diagnosed with NHL. NHL was further classified into aggressive and indolent subtypes. The aggressive NHL group included 83 patients, encompassing diffuse large B-cell lymphoma (DLBCL, n=43), high-risk mantle cell lymphoma (n=9), Burkitt's lymphoma (n=2) and other highly aggressive B-cell lymphomas (n=10), peripheral T-cell lymphoma (n=6), angioimmunoblastic T-cell lymphoma (n=3), T lymphoblastic lymphoma (n=3), anaplastic large cell lymphoma (n=1), and NK/T-cell lymphoma (n=6). Additionally, 24 patients were classified as having indolent NHL, consisting of follicular cell lymphoma (FL, n=17), and marginal zone B-cell lymphoma (n=7).

Furthermore, 81 patients (68.6%) presented with B symptoms at diagnosis, and 99 patients (83.9%) were diagnosed at an advanced stage of disease (Ann Arbor stage III or IV).

The median spleen SUV_{mean} was 2.94 (range, 2.07–3.75), with a median SLR of 1.60 (range, 1.07–2.05) across all patients. Notably, 86 patients exhibited diffuse increased ^{18}F-FDG uptake in the spleen (SLR >1). The median BM SUV_{mean} was 2.35 (range, 1.75–3.17), with a median BLR of 1.26 (range, 0.93–1.86). Moreover, 79 patients displayed diffuse increased ^{18}F-FDG uptake in the BM (BLR >1). Notably, 57 patients demonstrated simultaneous diffuse increased ^{18}F-FDG uptake in both the spleen and BM.

Correlations between BM, spleen, or liver metabolism and clinicopathologic parameters

To elucidate the relationship between BM, spleen, or liver metabolism and systemic inflammatory markers, we examined the SLR, BLR, and various hematologic parameters (*Table 2*). We observed a significant correlation between SLR and CRP (r=0.264, P=0.007), as well as PLR (r=0.227, P=0.021) (*Figure 1*). Furthermore, no significant correlation was observed between BM and liver metabolism and hematologic parameters.

Diagnostic efficacy of BMB and PET/CT

All 118 newly diagnosed lymphoma patients underwent BMB, with 63 showing positive results for lymphoma cell involvement in the BM. On ^{18}F-FDG PET/CT images, 79 of the 118 patients exhibited BLR >1, while 39 displayed

Table 2 Correlation between metabolism and hematologic parameters

Parameters	SLR		BLR		Liver SUV	
	r	P	r	P	r	P
CRP	0.264	0.007*	0.049	0.622	–0.050	0.613
WBC	–0.016	0.870	0.044	0.659	–0.092	0.354
Mono	0.173	0.081	0.092	0.356	–0.027	0.790
NLR	0.021	0.834	0.166	0.094	0.026	0.792
PLR	0.227	0.021*	–0.109	0.275	–0.186	0.060

*, P<0.05. SLR, spleen-to-liver SUV ratios; BLR, bone marrow-to-liver SUV ratios; SUV, standardized uptake value; CRP, C-reactive protein; WBC, white blood cell; Mono, monocyte counts; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

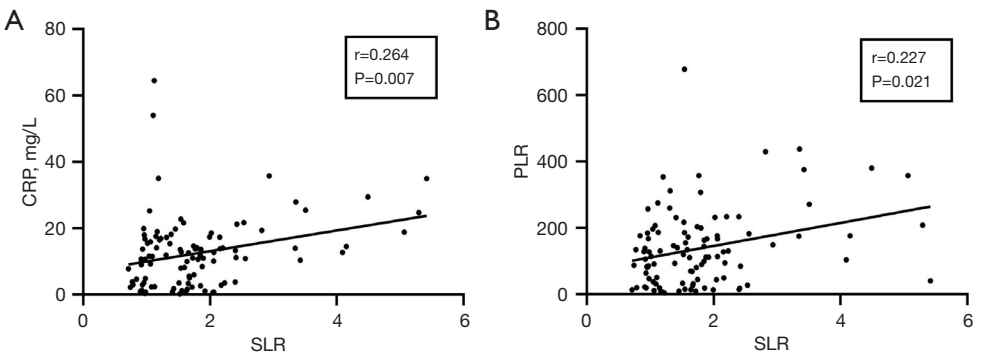

Figure 1 Correlations between SLR and CRP (A), SLR and PLR (B). Correlation coefficient (r) is 0.264 (P=0.007) and 0.227 (P=0.021), respectively. CRP, C-reactive protein; SLR, spleen-to-liver standardized uptake value ratios; PLR, platelet-to-lymphocyte ratio.

Table 3 BLR and BMB results

BLR	BMB		Total
	(+)	(–)	
>1	50	29	79
≤1	13	26	39
Total	63	55	118

BLR, bone marrow-to-liver standardized uptake value ratios; BMB, bone marrow biopsy; BMB (+), lymphoma cell involvement into bone marrow; BMB (–), a negative bone marrow biopsy result.

BLR ≤1. Concordance analysis revealed a fair agreement between BLR and BMB in this study population (Cohen's Kappa-κ =0.271, P=0.002) (*Table 3*).

ROC curve analysis

The AUC values were 0.686, 0.620 and 0.545 for SLR, BLR and liver SUV_{mean}, respectively.

For OS, the optimal cutoff values determined via ROC curve analysis were as follows: 10.885 mg/L for CRP, 315.5 U/L for LDH, 10.025×10^9/L for WBC, 0.71×10^9/L for Mono, 4.702 for NLR, 124.752 for PLR, 2.085 for liver SUV_{mean}, 1.528 for SLR, and 1.096 for BLR.

For PFS, the optimal cutoff values were as follows: 10.885 mg/L for CRP, 220.0 U/L for LDH, 7.6×10^9/L for WBC, 0.615×10^9/L for Mono, 1.467 for NLR, 124.752 for PLR, 1.84 for liver SUV_{mean}, 1.745 for SLR, and 1.263 for BLR.

Survival analysis

Univariate Cox regression analysis was conducted to assess the prognostic potential of clinicopathological and PET parameters for both OS and PFS.

For the 11 patients diagnosed with HL, there was no significant association between clinicopathology or PET parameters and OS as well as PFS due to the limited number of cases (*Table 4*).

Among 83 patients with aggressive NHL, B symptoms

Table 4 Univariate analyses of OS and PFS of HL patients

Parameters	OS		PFS	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age, >51 years	2.200 (0.1106–43.75)	0.5316	Undefined	0.5315
Gender, male *vs.* female	Undefined	0.4386	0.3172 (0.0543–1.854)	0.2722
Ann Arbor stage, III + IV *vs.* I + II	Undefined	0.1573	4.497 (0.7767–26.04)	0.1305
With/without B symptoms	1.286 (0.0786–21.01)	0.3173	1.504 (0.2606–8.682)	0.6439
CRP, >10.885 mg/L	0.7778 (0.0476–12.71)	0.8575	0.6515 (0.0967–4.389)	0.6333
LDH, >315.5 U/L	Undefined	0.5637	0.4376 (0.0729–2.627)	0.3035
WBC, >10.025×10^9/L	2.200 (0.1106–43.75)	0.4386	2.166 (0.3453–13.59)	0.4466
Mono, >0.71×10^9/L	0.7725 (0.0462–12.91)	0.6171	1.293 (0.2229–7.501)	0.7740
NLR, >4.702	Undefined	0.2568	0.4134 (0.0491–3.478)	0.3116
PLR, >124.752	0.4545 (0.0228–9.039)	0.5316	0.8523 (0.0851–8.531)	0.8831
Liver SUV, >2.085	Undefined	0.5637	0.4675 (0.0787–2.774)	0.3917
SLR, >1.528	Undefined	0.1967	0.7818 (0.1347–4.538)	0.7766
BLR, >1.096	Undefined	0.0588	0.7223 (0.1112–4.693)	0.7191

OS, overall survival; PFS, progression-free survival; HL, Hodgkin lymphoma; CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; Mono, monocyte counts; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SUV, standardized uptake value; SLR, spleen-to-liver SUV ratios; BLR, bone marrow-to-liver SUV ratios.

(P=0.0395), LDH levels (P=0.0026), Mono (P=0.0002), SLR (P=0.0141), and BLR (P=0.0493) exhibited significant associations with OS. Multivariate analysis identified both SLR [P=0.017, HR 2.715, 95% confidence interval (CI): 0.875–8.428] and BLR (P=0.044, HR 0.795, 95% CI: 0.348–1.813) were significant predictors for OS (*Table 5*). Additionally, B symptoms (P=0.0078), CRP (P=0.0400) and SLR (P=0.0002) emerged as statistically significant predictors for PFS. In the multivariate analysis, only SLR (P=0.019, HR 2.223, 95% CI: 1.139–4.342) remained a significant independent predictor for PFS (*Table 6*). Kaplan-Meier analysis revealed that patients with SLR >1.528 and BLR >1.096 exhibited shorter OS compared to those with SLR ≤1.528 and BLR ≤1.096, and patients with SLR >1.745 experienced shorter PFS (*Figure 2*).

For the indolent NHL subgroup, where all except one of the 24 patients survived, OS did not yield statistically significant results. LDH level (P=0.0454) was associated with PFS (*Table 7*).

Discussion

Diffuse increased ^{18}F-FDG uptake in the spleen and/or BM of patients with lymphoma is frequently observed. However, few studies have investigated its prognostic value. In this study, we identified a significant association between the SLR and systemic inflammatory markers, including CRP and PLR. Furthermore, SLR and BLR could serve as independent predictors of OS. Additionally, SLR was identified as an independent prognostic factor for PFS in patients with aggressive NHL.

The spleen, the largest secondary lymphoid organ in the human body, plays a crucial role in mechanical filtration, red blood cell production, and active immune responses to inflammation (11,12). Since the ^{18}F-FDG uptake in the spleen is generally lower than that in the liver, a higher uptake than the liver is considered unusual (13). The diffuse increased ^{18}F-FDG uptake in the spleen may reflect either an inflammatory process or lymphoma infiltration (14-16). Because the spleen SUV_{mean} can be influenced by various technical and physiological factors, while liver ^{18}F-FDG uptake is typically more stable and repeatable, it serves as a useful internal reference in clinical diagnostic settings. Therefore, we calculated the SLR by dividing the spleen SUV_{mean} by the liver SUV_{mean} (17-19). Previous studies have shown a significant

Table 5 Univariate and multivariate analyses of OS of aggressive NHL

Parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age, >51 years	1.168 (0.4491–3.036)	0.7525	–	–
Gender, male *vs.* female	0.6305 (0.2503–1.588)	0.3195	–	–
Ann Arbor stage, III + IV *vs.* I + II	1.655 (0.4814–5.693)	0.4979	–	–
With/without B symptoms	6.284 (2.185–18.97)	0.0395*	0.577 (0.215–1.546)	0.274
CRP, >10.885 mg/L	2.591 (0.9951–6.745)	0.0832	–	–
LDH, >315.5 U/L	3.877 (1.242–12.10)	0.0026*	1.822 (0.750–4.430)	0.185
WBC, >10.025×10^9/L	1.847 (0.5949–5.736)	0.2178	–	–
Mono, >0.71×10^9/L	5.457 (1.824–16.32)	0.0002*	2.006 (0.779–5.165)	0.149
NLR, >4.702	1.225 (0.4376–3.430)	0.6882	–	–
PLR, >124.752	0.9275 (0.3584–2.401)	0.8767	–	–
Liver SUV, >2.085	3.074 (0.9574–1.105)	0.0660		
SLR, >1.528	3.455 (1.550–7.698)	0.0141*	2.715 (0.875–8.428)	0.017*
BLR, >1.096	2.645 (1.076–6.505)	0.0493*	0.795 (0.348–1.813)	0.044*

*, P<0.05. OS, overall survival; NHL, non-Hodgkin lymphoma; CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; Mono, monocyte counts; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SUV, standardized uptake value; SLR, spleen-to-liver SUV ratios; BLR, bone marrow-to-liver SUV ratios.

Table 6 Univariate and multivariate analyses of PFS of aggressive NHL

Parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age, >51 years	0.9007 (0.4668–1.738)	0.7522	–	–
Gender, male *vs.* female	0.7520 (0.3912–1.446)	0.3852	–	–
Ann Arbor stage, III + IV *vs.* I + II	1.540 (0.7724–3.070)	0.2517	–	–
With/without B symptoms	3.322 (1.1517–0.5973)	0.0078*	1.637 (0.729–3.675)	0.232
CRP, >10.885 mg/L	2.055 (1.068–3.953)	0.0400*	1.755 (0.877–3.511)	0.112
LDH, >220 U/L	1.797 (0.9339–3.456)	0.0882	–	–
WBC, >7.6×10^9/L	0.6919 (0.3598–1.331)	0.2749	–	–
Mono, >0.615×10^9/L	1.454 (0.7256–2.913)	0.2605	–	–
NLR, >1.467	1.676 (0.8338–3.368)	0.1877	–	–
PLR, >124.752	1.118 (0.5811–2.151)	0.7361	–	–
Liver SUV, >1.84	1.315 (0.6798–2.542)	0.4062		
SLR, >1.745	3.272 (1.628–6.574)	0.0002*	2.223 (1.139–4.342)	0.019*
BLR, >1.263	0.6239 (0.3230–1.205)	0.1518	–	–

*, P<0.05. PFS, progression-free survival; NHL, non-Hodgkin lymphoma; CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; Mono, monocyte counts; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SUV, standardized uptake value; SLR, spleen-to-liver SUV ratios; BLR, bone marrow-to-liver SUV ratios.

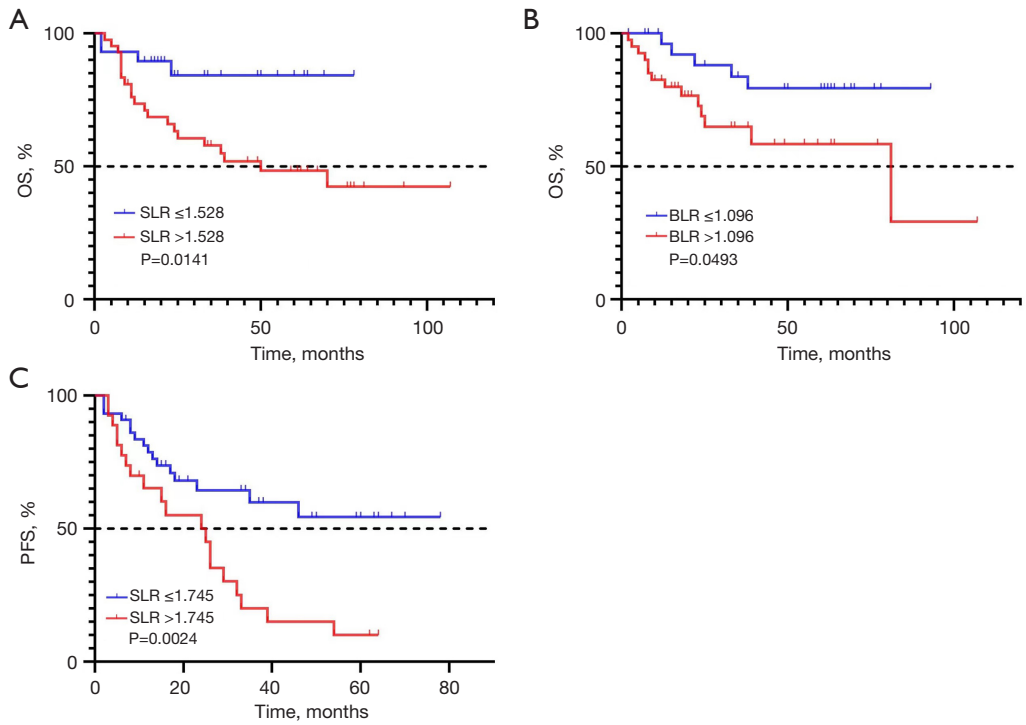

Figure 2 Kaplan-Meier survival curves for the OS and PFS of aggressive NHL. SLR (A) and BLR (B) were associated with OS, and SLR (C) was associated with PFS. OS, overall survival; SLR, spleen-to-liver standardized uptake value ratios; PFS, progression-free survival; BLR, bone marrow-to-liver standardized uptake value ratios; NHL, non-Hodgkin lymphoma.

Table 7 Univariate and multivariate analyses of PFS of indolent NHL

PFS parameters	Hazard ratio (95% CI)	P
Age, >51 years	3.508 (1.066–11.54)	0.0768
Gender, male *vs.* female	1.372 (0.3750–5.019)	0.6001
Ann Arbor stage, III + IV *vs.* I + II	0.6439 (0.0539–7.680)	0.6672
With/without B symptoms	1.819 (0.5577–5.943)	0.3194
CRP, >10.885 mg/L	0.8778 (0.2620–2.942)	0.8306
LDH, >220 U/L	3.159 (0.9198–10.85)	0.0454*
WBC, >7.6×10^9/L	0.8295 (0.2544–2.705)	0.7511
Mono, >0.615×10^9/L	2.932 (0.4547–18.90)	0.0835
NLR, >1.467	1.496 (0.4367–5.127)	0.5327
PLR, >124.752	1.270 (0.3792–4.250)	0.6834
Liver SUV, >1.84	0.5491 (0.1684–1.791)	0.3172
SLR, >1.745	1.111 (0.3405–3.626)	0.8582
BLR, >1.263	1.417 (0.3840–5.232)	0.5648

*, P<0.05. PFS, progression-free survival; NHL, non-Hodgkin lymphoma; CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; Mono, monocyte counts; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SUV, standardized uptake value; SLR, spleen-to-liver SUV ratios; BLR, bone marrow-to-liver SUV ratios.

correlation between diffuse increased splenic uptake in ^{18}F-FDG PET/CT and serum inflammatory markers such as WBC, neutrophils, platelet counts and CRP (9,15,20,21). Nam *et al.* have demonstrated a positive correlation between CRP and diffuse splenic ^{18}F-FDG uptake, while Kim *et al.* have reported a significant correlation between SLR and NLR and PLR (9,17). In our study, we found that SLR was significantly correlated with CRP and PLR, consistent with previous findings. This correlation between SLR and PLR suggested an immune response by the spleen to systemic inflammation in lymphoma patients. However, Salaun *et al.* have found no statistical correlation between diffuse increased splenic uptake and inflammatory markers, suggesting that inflammatory changes may not affect splenic uptake (22). The spleen is the most frequently involved abdominal organ, with diffuse spleen infiltration present in up to 40% of HL patients and up to 80% of NHL patients (23). However, since diagnostic laparotomy is no longer routinely performed, there is a lack of histopathological analysis to confirm whether diffuse spleen involvement is associated with lymphoma or inflammatory changes.

In the present study, we found that for aggressive NHL patients, the prognostic value of SLR was significantly associated with OS and PFS in both univariate and multivariate analyses. This finding indicated that SLR could be a helpful PET parameter in predicting clinical outcomes compared with other systemic inflammatory markers. Regarding this issue, the ^{18}F-FDG uptake of the spleen has been found to be an independent prognostic factor for predicting the recurrence and death of patients with various tumors (16,17,20,22,24). It has been suggested that a decrease or resolution of splenic uptake post-chemotherapy is one of the signs of remission in aggressive NHL (25).

Diffuse increased ^{18}F-FDG uptake of BM can be observed in patients with various types of malignant tumors, including lymphoma, and BM SUV_{mean} is significantly positively correlated with WBC, NLR, PLR, and CRP levels, indicating that ^{18}F-FDG uptake of BM is related to the systemic inflammatory response (26-28). Previous studies have shown that increased BM ^{18}F-FDG uptake is an important indicator for predicting PFS and OS in patients with lymphoma, such as DLBCL and FL (29,30). Lee *et al.* have found that increased BM uptake is an independent predictor of disease progression in patients with small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), gastric cancer, and colorectal cancer (27,31-33). We also demonstrated that BLR was an independent prognostic factor for OS in lymphoma patients. However, in our study, there was no statistical correlation between BM uptake and inflammatory markers. Both malignant infiltration of BM and benign diseases may lead to a diffuse increase in BM ^{18}F-FDG uptake. Our result might indicate that diffuse BM ^{18}F-FDG uptake in lymphoma was more likely attributed to BM infiltration rather than inflammatory changes in BM.

Many systemic inflammation markers have been suggested to be prognostic predictors in both solid and hematological malignancies (34-37). There is a debate concerning the prognostic significance of NLR and PLR. Previous studies in lymphomas have shown that high NLR and PLR are prognostic indicators of poorer outcomes (37,38). However, our results differed, as NLR and PLR were not associated with both OS and PFS, which is consistent with the findings of Azuma *et al.* (39). This discrepancy might be attributed to lymphoma being a cancer of lymphocytes, in which the host innate immunity is compromised, leading to a decrease in the number of tumor-infiltrating lymphocytes. Therefore, we hypothesized that it was difficult to predict the outcome of lymphoma using NLR.

In our present study, LDH and B symptoms remained significant factors affecting survival, consistent with previous studies (40-42). Additionally, we found that Mono was significantly associated with OS in the univariate analysis for aggressive NHL. Accumulating evidence has shown that an elevated absolute Mono is independently associated with inferior PFS and OS in DLBCL patients, which is consistent with our results (43-45). Monocytes possess host anti-tumor immunity suppression activity and can promote the growth and survival of malignant lymphocytes by providing nutrient stimulation. Therefore, as a biomarker of host immunity and TME, the Mono can affect the prognosis of lymphoma.

Our study creatively identified the prognostic value of diffuse increased ^{18}F-FDG uptake within the RES in lymphoma patients. However, several limitations should be considered. First, this was a retrospective study with a small sample size, which weakens the strength of our results. Further prospective studies with a larger sample size are necessary to confirm our findings. Second, lymphoma patients should be categorized into more detailed PET time points, and more biomarkers and PET parameters should be included for a more comprehensive analysis. Furthermore, there are many potential confounding factors that can affect the relevance and accuracy of the results, and

histopathological analysis of tissue samples from the RES organs was not performed. Therefore, further research is warranted.

Conclusions

In conclusion, our study demonstrated that diffuse increased splenic ^{18}F-FDG uptake in lymphoma patients might be more associated with inflammation, while diffuse BM uptake was likely attributed to BM infiltration rather than inflammatory changes. Moreover, SLR and BLR could potentially be used as independent predictors of OS. Additionally, SLR was identified as an independent prognostic factor for PFS in aggressive lymphoma patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-180/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-180/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (No. 2021-157), with a waiver of informed consent.

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