

Correlation of PET/CT Maximal Standardized Uptake Values with Clinicopathologic Parameters of Aggressive Non-Hodgkin's Lymphoma

Yingci Li¹, Dongbo Wu², Mohan Tian¹

¹Department of PET/CT-MR Center, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, 150081, People's Republic of China;

²Department of Radiology, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, 150081, People's Republic of China

Correspondence: Mohan Tian, Department of PET/CT-MR Center, Harbin Medical University Cancer Hospital, No. 150, Haping Road, Nangang District, Harbin City, Heilongjiang, 150081, People's Republic of China, Email mohantianthm@21cn.com

Objective: To investigate the correlation between the maximum standardized uptake value (SUV_{max}) of positron emission tomography (PET)/computed tomography (CT) scanning imaging with the clinicopathologic parameters of aggressive non-Hodgkin's lymphoma (NHL) and its diagnostic value.

Methods: A total of 128 patients with NHL were retrospectively selected. PET/CT examination was performed to calculate SUV_{max}, and clinicopathological data were collected. Pearson correlation test was used to analyze the correlation between them, and the relevant indicators were detected according to the pathological results. ROC curve was used to analyze the diagnostic value.

Results: The level of PET/CT SUV_{max} was positively correlated with the levels of β 2-microglobulin (β 2-MG), lactate dehydrogenase (LDH), Ki-67, tumor size and bone marrow infiltration ($P < 0.05$). The PET/CT SUV_{max} and serum β 2-MG, LDH and Ki-67 levels in the aggressive group were significantly higher than those in the indolent group ($P < 0.05$). The AUC of the combined detection of PET/CT SUV_{max}, β 2-MG, LDH and Ki-67 in the diagnosis of aggressive NHL was 0.920, and the combined detection had a high diagnostic value.

Conclusion: PET/CT SUV_{max} was correlated with a variety of clinicopathological parameters. Combined detection of PET/CT SUV_{max} has high diagnostic value in aggressive NHL.

Keywords: PET/CT maximum standardized uptake values, β 2-MG, LDH, Ki-67, aggressive non-Hodgkin's lymphoma

Introduction

Non-Hodgkin's lymphoma (NHL) is the most common hematological malignancy in clinical practice, with numerous biological and clinical heterogeneity subtypes.¹ According to the World Health Organization (WHO) and International Agency for Research on Cancer (ICC) classification, it contains many biological and clinical heterogeneous subtypes, mainly divided into B-cell lymphoma and T-cell lymphoma.^{2,3} Although NHL usually manifests as aggressive spreading disease or rapidly growing mass, with the characteristics of multicentric origin and long-distance spread, not all patients have a poor prognosis.⁴ Taking diffuse large B-cell lymphoma (DLBCL) treated with CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) as an example, about 60% of patients can be cured by first-line treatment. However, there are still some patients who have resistance to radiotherapy, chemotherapy and immunotherapy, which affects their lives and health.⁵ Hematopoietic stem cell transplantation is one of the standard treatments for patients with relapsed or refractory disease after chemotherapy. However, due to potential comorbidities and chemotherapy-resistant diseases, about 40% of patients may not be suitable for hematopoietic stem cell transplantation, and about 50% of patients who receive this treatment may relapse.⁶ Therefore, early and accurate diagnosis and appropriate treatment are very important to improve the prognosis of patients with NHL.

Positron emission tomography (PET) / Computed tomography (CT) scanning imaging combines both PET and CT techniques. Imaging that combines metabolic abnormalities and tumor morphological changes plays an important role in the diagnosis, staging, efficacy monitoring, and outcome prediction of various cancers.⁷ Standardized uptake value

Maximum (SUV_{max}) is the most widely analyzed semi quantitative parameter in PET/CT. Research has found that SUV can reflect changes in glucose metabolism and proliferation activity of tumor cells.⁸ However, due to differences in individual patient situations, different variables may have an impact on the standardization of measurements.⁹

In this study, 128 patients with NHL treated in our hospital were selected as study subjects. We investigated the correlation between PET/CT SUV_{max} with the clinicopathologic parameters of NHL and the diagnostic value of PET/CT SUV_{max} , aiming to provide reference for accurately assessing the invasiveness of NHL and evaluating the prognosis.

Materials and Methods

General Materials

A total of 128 patients with NHL treated in our hospital from June 2021 to May 2024 were retrospectively selected as the research objects. In order to reduce research bias, only patients with DLBCL and follicular lymphoma (FL) were included in this study. No patients with FL transformed to DLBCL were screened. The inclusion process was shown in Figure 1. Inclusion criteria: (1) All patients met the guidelines for the diagnosis and treatment of lymphoma,¹⁰ and had been diagnosed through pathological testing. (2) All patients had complete clinical data. (3) All patients underwent PET/CT SUV_{max} examination. Exclusion criteria: (1) Patients with Hodgkin's lymphoma; (2) Patients with hepatitis B, hepatitis C, cirrhosis or liver injury; (3) Patients who had received previous relevant treatment for NHL in the past. This study was ratified by the Ethics Committee of our hospital.

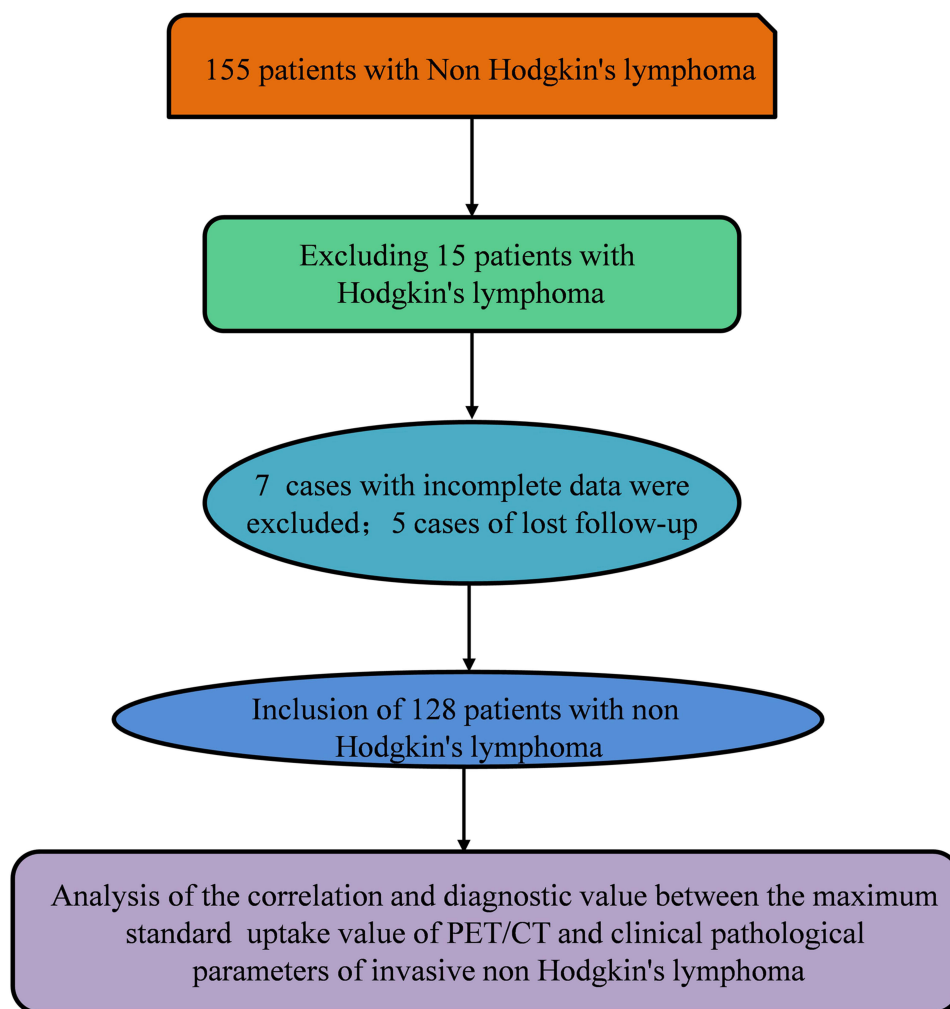


Figure 1 Process diagram for patient inclusion.

PET/CT Detection

The PET/CT examination was conducted using the Discovery 710 Clarity scanner (GE Healthcare, USA). 18F-FDG was synthesized by PETtrace cyclotron and Siemens Explora FDG4 chemical synthesis module, with a radiochemical purity of not less than 95%. The patients should fast for at least 6 hours before the examination. If blood glucose was lower than 6.1 mmol/L (non-diabetes patients) or 11.1 mmol/L (diabetes patients), the injection dose should be set to 3.7 MBq/kg. After 1 hour of intravenous injection, CT (parameter settings were listed as follows: voltage 120 kV, current intensity 40 mA, layer thickness 5 mm, interval 5 mm) and PET (parameter settings were listed as follows: 3D mode, 2 minutes/bed, layer thickness 4 mm. The brain scanning ranged from the top of the skull to the plane of the mandible, and the body scanning ranged from the base of the skull to the proximal femur) scanning were performed. Data analysis was conducted by two or more experienced diagnostic physicians who were capable of independently reading images. Visual and semi quantitative analysis methods were used to analyze and interpret images. A circular Region of interest (ROI) was drawn on PET-CT slices registered in the axial, coronal, or sagittal planes. SUV_{max} was calculated using the following standard formula and could be adjusted according to body weight: $SUV_{max} = \text{average ROI activity (MBq/mL)} / [\text{injection dose (MBq)}/\text{body weight (kg)}]$.

Collection of Clinical Pathological Parameters

Clinical and pathological parameters of patients were collected, including the age (≤ 55 years, >55 years), gender, tumor size (≤ 2 cm, >2 cm), bone marrow infiltration, clinical staging (Stage I + Stage II, Stage III + Stage IV), International Prognostic Index (IPI) (≤ 3 points, >3 points), B symptoms, globulin (≤ 19 g/L, >19 g/L), albumin (≤ 40 g/L, >40 g/L), ferritin (≤ 390 ng/mL, >390 ng/mL), $\beta 2$ -microglobulin ($\beta 2$ -MG) (≤ 2.6 mg/L, >2.6 mg/L), lactate dehydrogenase (LDH) (≤ 245 U/L, >245 U/L), cell proliferation nuclear antigen-67 (the Ki-67) ($\leq 30\%$, $>30\%$), etc.

Detection Method

The levels of $\beta 2$ -MG and LDH were detected by enzyme-linked immunosorbent assay (ELISA), and the level of Ki-67 was detected by immunohistochemistry. The specific operation was carried out according to the relevant kit instructions.

Malignant Diagnosis

Given the aggressive course of mantle-cell lymphoma, the different treatment options for T-cell NHL and the highly variable disease course, only 74 cases of DLBCL representing aggressive NHL, and 54 cases of follicular NHL, were included in this study to reduce study bias. According to the results of pathological examination, the patients were divided into aggressive group (DLBCL cases) and indolent group (follicular NHL cases).

Correlation Analysis

The correlation between PET/CT SUV_{max} and clinical pathological parameters was analyzed through Pearson correlation test. The clinical pathological parameters taken for analysis were the indicators with significant differences in Table 1.

Diagnostic Value Analysis

Establish ROC curves were established to analyze the diagnostic value of PET/CT SUV_{max} , $\beta 2$ -MG, LDH and Ki-67 alone and in combination for invasive NHL.

Statistical Analysis

Statistical analysis was conducted using SPSS 23.0. The measurement data that conformed to the normal distribution were presented as mean \pm standard deviation, and independent sample *t*-test was used for inter group comparison. The correlation between PET/CT SUV_{max} and clinical pathological parameters was analyzed using Pearson correlation test. The diagnostic value of combined detection by PET/CT SUV_{max} , $\beta 2$ -MG, LDH, and Ki-67 for invasive NHL was analyzed using ROC curve analysis. The statistical test level was set at $P < 0.05$.

Table 1 The Relationship Between PET/CT SUV_{max} and Clinical Data ($\bar{x} \pm s$)

Groups	Cases	PET/CT SUV _{max} (g/mL)	χ^2/t	P
Age (year)			1.787	0.076
≤55	53	17.66±4.36		
>55	75	19.23±5.24		
Gender (%)			0.626	0.532
Female	79	17.86±5.82		
Male	49	18.49±5.03		
Tumor size (cm)			7.479	<0.001
≤2	59	13.46±3.81		
>2	69	20.85±6.72		
Bone marrow infiltration (%)			5.625	<0.001
No	85	11.29±3.47		
Yes	43	15.18±4.11		
Clinical stage (%)			0.615	0.540
Stage I + II	76	16.70±4.84		
Stage III + IV	52	17.27±5.58		
IPI score (score)			1.905	0.059
≤3	73	18.34±5.09		
>3	55	20.11±5.35		
B symptom (%)			1.166	0.246
No	71	17.97±4.85		
Yes	57	19.02±5.32		
Globulin (g/L)			0.806	0.422
≤19	10	14.85±3.52		
>19	118	16.11±4.83		
Albumin (g/L)			1.122	0.264
≤40	60	19.25±4.39		
>40	68	20.29±5.88		
Ferritin (ng/mL)			0.877	0.382
≤390	98	19.65±5.23		
>390	30	20.59±4.81		
β2-MG (mg/L)			14.056	<0.001
≤2.6	69	12.85±3.22		
>2.6	59	24.79±6.14		
LDH (U/L)			14.113	<0.001
≤245	61	11.74±3.87		
>245	67	23.31±5.23		
Ki-67 (%)			6.659	<0.001
≤30	69	15.09±4.52		
>30	59	20.84±5.25		

Abbreviations: SUV_{max}, maximum standardized uptake value; PET, positron emission tomography; CT, computed tomography; IPI, International Prognostic Index; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase.

Results

The Relationship between PET/CT SUV_{max} and Clinical Data

PET/CT SUV_{max} levels were not associated with gender, age, clinical stage, albumin, ferritin, globulin, IPI score, and B symptoms ($P>0.05$). PET/CT SUV_{max} levels increased significantly in aggressive NHL patients with the increase of β2-MG ($t=7.479$), LDH ($t=5.625$), Ki-67 ($t=14.056$), tumor size ($t=14.113$) and bone marrow infiltration ($t=6.659$) ($P<0.05$, Table 1).

Table 2 The Correlation Between PET/CT SUV_{max} and Clinical Pathological Parameters

Indicator	PET/CT SUV _{max}	
	<i>r</i>	P
Tumor size	0.483	<0.001
Bone marrow infiltration	0.582	<0.001
β2-MG	0.451	<0.001
LDH	0.543	<0.001
Ki-67	0.480	<0.001

Abbreviations: SUV_{max}, maximum standardized uptake value; PET, positron emission tomography; CT, computed tomography; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase.

The Correlation between PET/CT SUV_{max} and Clinical Pathological Parameters

Pearson correlation analysis revealed that PET/CT SUV_{max} levels were significantly positively correlated with tumor size ($r=0.416$), bone marrow infiltration ($r=0.308$), and the levels of β2-MG ($r=0.314$), LDH ($r=0.552$), and Ki-67 ($r=0.468$) ($P<0.05$, Table 2 and Figure 2).

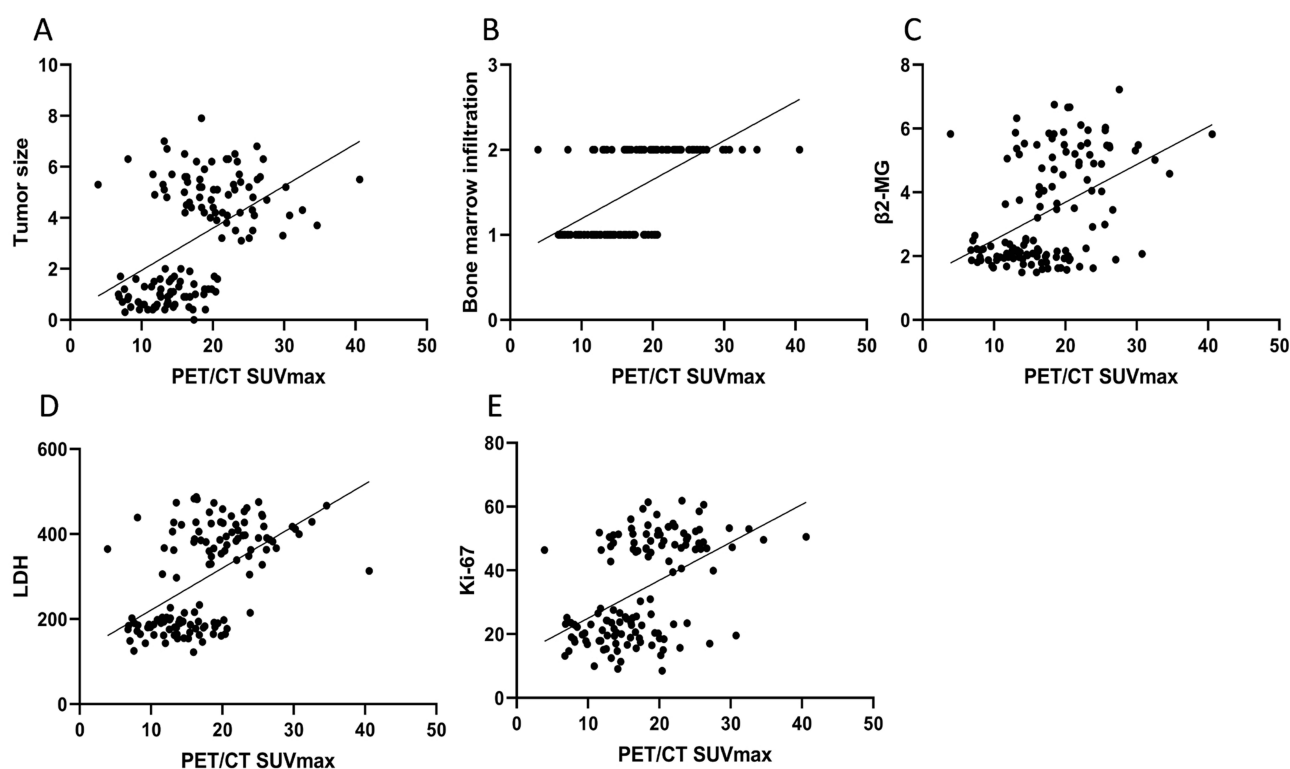


Figure 2 The correlation between PET/CT SUV_{max} and clinical pathological parameters. (A) The correlation between PET/CT SUV_{max} and tumor size; (B) The correlation between PET/CT SUV_{max} and bone marrow infiltration; (C) The correlation between PET/CT SUV_{max} and β2-MG; (D) The correlation between PET/CT SUV_{max} and LDH; (E) The correlation between PET/CT SUV_{max} and Ki-67.

The Linear-Regression Analysis

Linear regression analysis was performed with tumor size, bone marrow infiltration (yes = 1, no = 0), $\beta 2$ -MG, LDH and Ki-67 levels as independent variables and PET/CT SUV_{max} as dependent variable. The results showed that the regression equation between tumor size and PET/CT SUV_{max} was $Y=2.15X_1+5.2$ (X_1 was tumor size, Y was the predicted value of PET/CT SUV_{max}), and the regression coefficient of 2.15 was statistically significant ($P<0.05$). The regression equation between bone marrow infiltration and PET/CT SUV_{max} was $Y=3.5 X_2+10.5$ (X_2 was bone marrow infiltration), and the regression coefficient 3.5 was statistically significant ($P<0.05$). The regression equation between $\beta 2$ -MG and PET/CT SUV_{max} was $Y=1.8X_3+8.3$ (X_3 was the level of $\beta 2$ -MG), and the regression coefficient 1.8 was statistically significant ($P<0.05$). The regression equation between LDH and PET/CT SUV_{max} was $Y=2.5X_4+12.2$ (X_4 was LDH level), and the regression coefficient 2.5 was statistically significant ($P<0.05$). The regression equation between Ki-67 and PET/CT SUV_{max} was $Y=2.3X_5+9.5$ (X_5 was the level of Ki-67), and the regression coefficient 2.3 was statistically significant ($P<0.05$).

Analysis of PET/CT SUV_{max}, $\beta 2$ -MG, LDH, and Ki-67 Levels in Patients with Different Degrees of Malignancy

Compared with the inert group, the invasive group had much higher levels of PET/CT SUV_{max} ($t=15.334$) and serum $\beta 2$ -MG ($t=8.352$), LDH ($t=13.278$), and Ki-67 ($t=22.559$) ($P<0.05$) (Table 3).

ROC Curve Analysis

ROC curve analysis confirmed that the AUCs of PET/CT SUV_{max}, $\beta 2$ -MG, LDH, and Ki-67 for the diagnosis of invasive NHL were 0.786, 0.805, 0.851 and 0.830, respectively. The combined detection of the four indicators had an AUC of 0.920, specificity of 82.43%, sensitivity of 96.30%, and Jordan index of 0.787. The combined detection had higher diagnostic value for invasive NHL (Table 4 and Figure 3).

Table 3 Analysis of PET/CT SUV_{max}, $\beta 2$ -MG, LDH and Ki-67 Levels in Patients with Different Degrees of Malignancy ($\bar{x} \pm s$)

Groups	Cases	PET/CT SUV _{max} (g/mL)	$\beta 2$ -MG (mg/L)	LDH (U/L)	Ki-67 (%)
The aggressive group	74	22.85 \pm 5.79	3.81 \pm 1.03	386.09 \pm 84.28	78.60 \pm 18.34
The indolent group	54	9.95 \pm 2.52	2.41 \pm 0.79	206.78 \pm 61.25	25.29 \pm 7.49
<i>t</i>		15.334	8.352	13.278	22.559
<i>P</i>		<0.001	<0.001	<0.001	<0.001

Abbreviations: SUV_{max}, maximum standardized uptake value; PET, positron emission tomography; CT, computed tomography; $\beta 2$ -MG, $\beta 2$ -microglobulin; LDH, lactate dehydrogenase.

Table 4 Diagnostic Value of PET/CT SUV_{max}, $\beta 2$ -MG, LDH and Ki-67 for Invasive NHL

Indicators	AUC	Sensitivity	Specificity	Cutoff Value	P value	95% CI	Youden's index
PET/CT SUV _{max}	0.786	94.44	64.87	14.23 g/mL	<0.05	0.705–0.867	0.593
$\beta 2$ -MG	0.805	83.33	71.62	2.74 mg/L	<0.05	0.729–0.881	0.550
LDH	0.851	77.78	81.08	283.85 U/L	<0.05	0.756–0.817	0.589
Ki-67	0.830	98.15	62.16	47.26%	<0.05	0.758–0.903	0.603
Combined detection	0.920	96.30	82.43	—	<0.05	0.872–0.968	0.787

Abbreviations: SUV_{max}, maximum standardized uptake value; PET, positron emission tomography; CT, computed tomography; $\beta 2$ -MG, $\beta 2$ -microglobulin; LDH, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma; AUC, Area under the curve; CI, Confidence Interval.

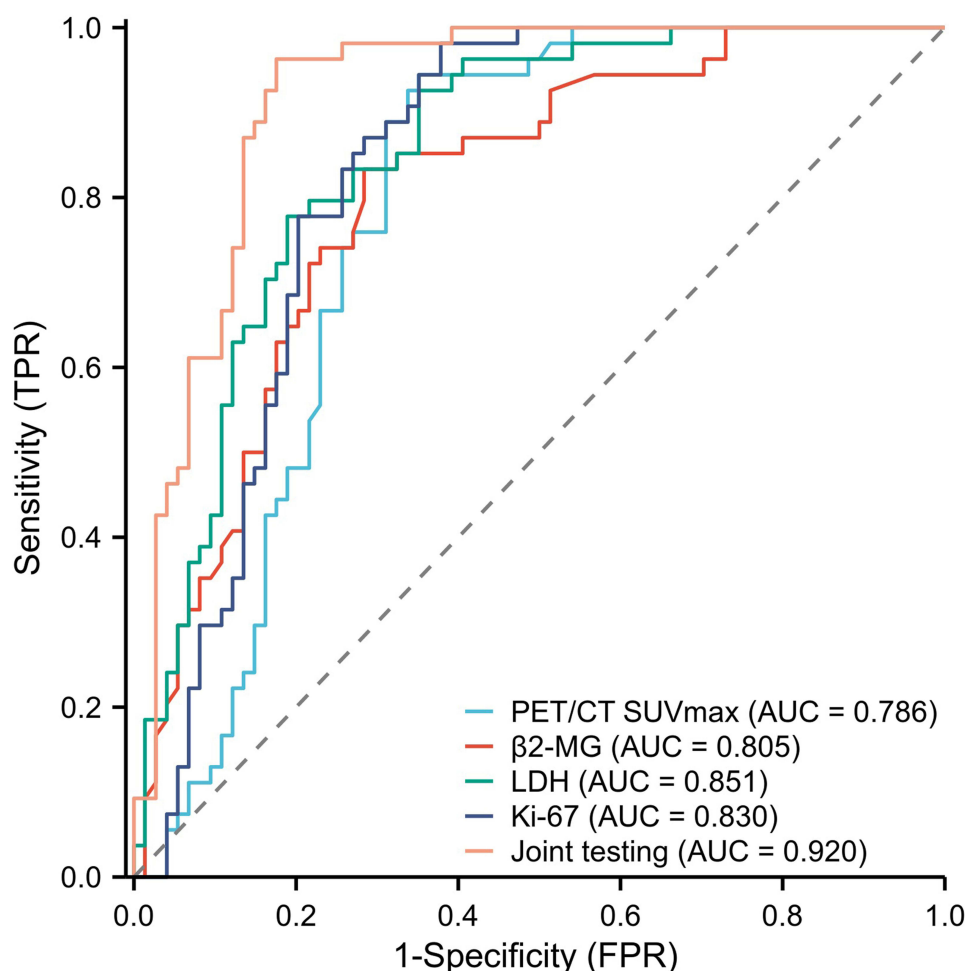


Figure 3 ROC curve analysis of PET/CT SUV_{max}, β2-MG, LDH, and Ki-67 in the diagnosis of invasive NHL.

Discussion

NHL is a malignant tumor originating from the lymphatic system. Radiochemotherapy and immunotherapy are typical treatment methods. However, approximately 20% to 30% of patients may develop resistance to the aforementioned treatments, affecting their life and health.¹ NHL typically appears in an invasive or inert form, with invasive patients having a lower 5-year survival rate and a poorer prognosis.¹¹ Therefore, early diagnosis and selection of appropriate treatment options are of great significance for improving the prognosis of NHL patients.

At present, PET/CT imaging has become the mainstream clinical imaging tool for staging, treatment evaluation, and follow-up evaluation of lymphoma patients. PET/CT imaging not only provides high-resolution anatomical information, but also information about the metabolic activity of lesions.¹² PET/CT SUV_{max} is the ratio of the radioactive activity of the imaging agent taken up by the local lesion to the total injected dose of radioactive activity. In recent years, there has been some controversy over the factors related to PET/CT SUV_{max} in lymphoma. Patients with FL in different stages had different SUV_{max}, and high SUV_{max} may be associated with more advanced diseases.¹³ There are also studies suggesting that high SUV_{max} are often associated with poorer prognosis. For example, patients with high SUV_{max} of inert lymphoma are commonly accompanied by shorter progression free survival (PFS) and overall survival (OS), leading to shorter and higher mortality rates.¹⁴ A study has found that PET/CT SUV_{max} is significantly correlated with the prognosis of NHL patients. The higher the SUV_{max} is, the greater the possibility of invasion is, and the poorer the prognosis of the patient is.¹⁵ In this study, it was found that PET/CT SUV_{max} levels were significantly positively correlated with tumor size and bone marrow infiltration. Previous studies have found that high levels of circulating tumor cells and large volume lesions

may be independent risk factors for B-cell malignancy.¹⁶ Larger tumor volume accompanied by more neovascularization and abundant blood supply can promote the development of tumor malignancy and enhanced metabolism of lesion tissue, leading to an increase in PET/CT SUV_{max} levels.¹⁷ Bone marrow is the most common site of extranodal involvement in lymphoma patients. Thus, the bone marrow status is a key step in evaluating the initial examination of lymphoma patients and can provide key information for treatment decision-making. PET/CT detection confirmed that patients with bone marrow infiltration had significantly lower survival time than those without bone marrow infiltration. Therefore, PET/CT can be used to evaluate the prognosis of patients with bone marrow infiltration.¹³ According to reports, the sensitivity and specificity of PET/CT in diagnosing bone marrow infiltration in invasive NHL are much higher than those in inert NHL.¹⁸ In the study of follicular lymphoma, it was found that PET/CT SUV_{max} levels were markedly higher in patients with bone marrow involvement than in unaffected patients,¹⁹ which was similar to the results of this study. In summary, understanding the relationship between PET/CT SUV_{max} with tumor size and bone marrow infiltration is beneficial for improving lesion detection rate.

In addition, our present study found that PET/CT SUV_{max} was closely related to levels of β 2-MG, LDH, and Ki-67. The combined detection could effectively evaluate the invasiveness of patients with invasive NHL. A study has found that higher levels of β 2-MG may indeed be related to MHC-I. MHC-I deficiency is more common in cancer cells, which may help cancer cells evade immune responses and progress to metastasis. It can be seen that β 2-MG levels may be one of the indicators reflecting tumor cell proliferation activity.²⁰ LDH has become an important prognostic biomarker for tumor diseases, and serum LDH levels are significantly negatively correlated with the survival rate of lymphoma patients. The diagnostic value of PET/CT SUV_{max} combined with LDH in NHL invasiveness is higher than that of LDH alone, with an AUC of 0.831, sensitivity and specificity of 63.10% and 80.00%, respectively.²¹ In this study, the combined detection of multiple indicators including PET/CT SUV_{max}, β 2-MG, LDH, and Ki-67 showed a diagnostic AUC of 0.920, specificity of 82.43%, and sensitivity of 96.30%, which was higher than the combined diagnosis of PET/CT SUV_{max} and LDH, further demonstrating the accuracy of the combination of various indicators in this study. Ki-67 is a nuclear protein related to the cell cycle, expressed in all the stages except the resting phase of cell division. Ki-67 reflects the rate of tumor cell proliferation, which is closely related to the ability of tumor cell infiltration, metastasis, and implantation.²² Previous studies have found that hepatocellular carcinoma patients with Ki-67 positive lesions have stronger FDG uptake ability.²³ The stronger the ability of tumor tissue to uptake FDG is, the larger the SUV is, and the stronger the diagnostic ability for NHL invasiveness is. Combined detection using PET/CT SUV_{max}, β 2-MG, LDH, and Ki-67 levels is beneficial for clarifying the patient's condition and conducting timely intervention and treatment.

Conclusion

In general, this study confirmed that PET/CT SUV_{max} was significantly correlated with tumor size, bone marrow infiltration, β 2-MG, LDH, Ki-67 and other clinicopathological parameters. The combined detection of these indicators had high value in the diagnosis of aggressive NHL, which provided a strong basis for clinical diagnosis. In this study, patients with DLBCL and FL were selected as the study subjects, which reduced the research bias caused by the diversity of histological types and made the results more reliable. However, NHL also includes other histological types. Follow-up studies can further expand the sample coverage to explore the relationship between PET/CT SUV_{max} and clinicopathological parameters in different histological types and its diagnostic value.

However, this study has some limitations due to its small sample size and single-center study. Further studies with larger sample size and multicenter studies are needed to further verify the results of this study, so as to evaluate aggressive NHL more accurately and provide more reliable guidance for the treatment and prognosis of patients.

Abbreviations

SUV_{max}, maximum standardized uptake value; PET, positron emission tomography; CT, computed tomography; NHL, non-Hodgkin's lymphoma; β 2-MG, β 2-microglobulin; LDH, lactate dehydrogenase; IPI, International Prognostic Index; ELISA, Enzyme linked immunosorbent assay; IHC, Immunohistochemistry; MALT, mucosa associated lymphoid tissue; SLL, small lymphoid lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt



lymphoma; EATL, enteropathy associated T-cell lymphoma; ALCL, anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by the Ethics Committee of The Harbin Medical University Cancer Hospital.

Patient Consent for Publication

Informed consent was obtained from participants for the participation in the study and all methods were carried out in accordance with relevant guidelines and regulations.

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Disclosure

The authors declare that they have no competing interests.

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