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Correlation of 18F-FDG PET/CT SUVmax with clinical features, D-dimer and LDH in patients with primary intestinal lymphoma

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Abstract

Objective: To investigate the characteristics of fluorine-18-deoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) maximum standardized uptake value (SUVmax) in primary intestinal lymphoma (PIL) and its correlation with D-dimer and lactate dehydrogenase (LDH).

Methods: Fifty-two patients diagnosed with PIL from June 2016 to December 2019 were analyzed. All patients underwent 18F-FDG PET/CT. The relationships between SUVmax and different pathological subtypes, clinical stages and risk grades were analyzed. The correlations between SUVmax and Ki-67, LDH and D-dimer were determined. Additionally, PET/CT imaging results were collected from 35 patients with primary intestinal cancer (PIC) and compared with the imaging features of PIL.

Results: SUVmax was significantly different between PIL and PIC groups and various PIL pathological subgroups. Patients in the high-risk PIL group had markedly higher SUVmax values than the intermediate-risk and low-risk groups. A significant positive correlation was observed between SUVmax and Ki-67 in patients with PIL. SUVmax was significantly different between the elevated and normal D-dimer groups. D-dimer showed a positive correlation with SUVmax.

Conclusion: 18F-FDG PET/CT SUVmax reflects the aggressiveness of lymphoma to a certain degree, is correlated with Ki-67 and determines the risk grades of PIL. Moreover, it facilitates differential diagnosis, clinical staging and treatment based on D-dimer levels.

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Introduction

Primary gastrointestinal lymphoma accounts for 5% to 20% of all non-Hodgkin's lymphoma (NHL) cases, more than half of which occur in the stomach (50%–60%), whereas primary NHL of the small intestine and large intestine constitutes only 14% to 38% and 10% to 20%, respectively.[1] Primary intestinal lymphoma (PIL) is clinically rare and characterized by nonspecific symptoms and a difficult diagnosis.[2,3] Traditional testing procedures, such as gastroenterography, ultrasound, endoscopy and abdominal computed tomography (CT), exhibit a certain value in the diagnosis of this disease but are limited by various factors. The role of positron emission tomography/computed tomography (PET/CT), combining imaging of metabolic abnormalities and morphological changes in tumors, has been confirmed in the diagnosis, staging and therapeutic evaluation of lymphoma.[4,5] However, PET/CT imaging analysis of newly diagnosed PIL is currently rare. At present, the most frequently used developer is the glucose analog fluorine-18-deoxyglucose (18F-FDG). Tumor cells have a substantially higher rate of glucose metabolism and thus show increased FDG uptake. As a reflection of this metabolic capacity, the standard uptake value (SUV) partly represents the proliferative activity of tumors.[6] In this study, we analyzed the association between SUV and the pathological type, clinical staging, risk grading and biological indicators of PIL to accurately determine the aggressiveness of lymphoma, better predict prognosis and guide treatment.

Materials and methods

Study participants

Clinical and imaging data were collected from patients with PIL who were examined by 18F-FDG PET/CT and confirmed by histopathology from June 2016 to December 2019.

Subjects were included according to the following diagnostic criteria of PIL (Dawson's standard):[7] (1) no superficial lymphadenopathy, (2) no mediastinal lymphadenopathy noted by chest imaging, (3) normal total number and classification of peripheral white blood cells, (4) no significant invasion, except for primary intestinal lesions and regional lymph nodes and (5) no involvement of the liver and spleen.

Patients were excluded if they met any of the following exclusion criteria: (1) diagnosed with lymphoma by pathology without confirmation of its specific cell type by immunohistochemistry, (2) a history of lymphoma prior to PET/CT or (3) intestinal lymphoma not meeting Dawson's criteria.

Patients with primary intestinal cancer (PIC group) were enrolled during the same period. The diagnosis of all patients was pathologically confirmed, and no patients were treated prior to PET/CT. Patients in the PIC group had a carcinoma other than lymphoma that occurred in the duodenum

and rectum. This study was approved by the Ethics Committee of Fujian Provincial Hospital, and written informed consent was obtained from all subjects. This study conforms to the relevant STROBE guideline.[8]

The international prognostic index (IPI)[9] was based on individual age, Eastern Collaborative Oncology Group (ECOG) score, clinical staging, number of extranodal invasion sites and the presence of elevated serum lactate dehydrogenase (LDH). One point was assigned for each of the following risk factors: age older than 60 years, stage III or IV, two or more extranodal lesions, ECOG score $\geq$2 and elevated serum LDH. Based on IPI scores, patients with NHL were classified into a low-risk group (0 or 1 point), intermediate-risk group (2–3 points) and high-risk group (4–5 points).

Instrument and developer

Patients were examined by PET/CT using a Discovery 710 scanner (GE Healthcare, Milwaukee, WI, USA). 18F-FDG was automatically synthesized by a PETtrace cyclotron and 18F-FDG chemical synthesis module (GE Healthcare), with a radiochemical purity of >95%. Patients fasted for 6 hours before 18F-FDG PET/CT examination with their blood glucose below 8.0 mmol/L. 18F-FDG at a dose of 3.7 MBq/kg was intravenously administered, and images were collected 60 minutes after intravenous injection. Data were analyzed by two or more experienced PET/CT diagnosticians capable of reading images independently. Visual and semi-quantitative analysis methods were used to analyze and interpret images. According to the intensity of intestinal FDG uptake, all subjects were classified into two groups: a bowel FDG uptake positive (+) group and a bowel FDG uptake negative (−) group. In the visual evaluation, FDG activity in the liver and urinary tract were used as reference sites.[10] If activity was present along the intestine, higher than that of the liver and nearly equal to that of the urinary tract, the subject was classified into the FDG uptake (+) group. Otherwise, the subject was classified into the FDG uptake (−) group. For semi-quantitative analysis, the region of interest (ROI) was defined, and the maximum SUV (SUVmax) was automatically calculated by a dedicated workstation (GE Xeleris Workstation, Version 4.0; GE Healthcare).[11] The volumetric ROIs (VOIs) were placed carefully over the intestinal lesion exhibiting elevated FDG activity (relative to normal tissue) to avoid overlap with adjacent FDG-avid structures and areas exhibiting physiological uptake. The volume viewer software used on a dedicated workstation provided an automatically delineated volume of interest using an isocontour threshold method based on SUV. The SUVmax was automatically calculated from the VOIs by the workstation. To define the boundaries of the lesions, a fixed SUV (SUV = 3) was used.

Immunohistochemical detection of Ki-67 expression in lymphoma tissues

Fifty-two PIL biopsy specimens were fixed with neutral formaldehyde fixatives and then embedded in paraffin wax with a section thickness of 3 μm. Later, the specimens were heated at 80°C for 60 minutes on a heating tray, deparaffinized, subject to high-temperature and high-pressure antigen retrieval with ethylenediaminetetraacetic acid antigen retrieval solution, sealed with 3% endogenous peroxidase for 10 minutes, washed with distilled water and incubated with a mouse anti-human Ki-67 antibody (1:200, Fuzhou Maixin Technology Development Co., Ltd., Fujian, China). After washing with phosphate-buffered saline (PBS), a horseradish peroxidase-labeled rabbit anti-mouse IgG antibody

(Fuzhou Maixin Technology Development Co., Ltd.) was added dropwise and incubated for 30 minutes. After washing with PBS, a 3, 3′-diaminobenzidine color development solution was added and incubated at room temperature for 10 minutes. The samples were rinsed with tap water, stained with hematoxylin for 2 minutes and rinsed with tap water for 1 minute. The slides were placed in warm water for 2 to 3 minutes, dehydrated with anhydrous ethanol, dried and sealed with neutral adhesive. Ki-67 staining that was located in the cell nucleus and brownish-yellow in color was considered positive. Ten high magnification (400×) fields were randomly selected from each section, 100 cells were counted in each field, and the percentage of positive tumor cells was calculated. The mean value was used as the positive rate of Ki-67, termed the Ki-67 index value.

Detection of D-dimer and LDH in the peripheral blood of patients with lymphoma

Early in the morning under a fasting state, 5 mL of venous blood were collected to measure D-dimer levels. The D-dimer assay was performed using a Metron coagulometer kit (Coatron-1800, TECO, Munich, Germany) in accordance with the manufacturer's guide.

For the LDH assay, venous blood was collected on an empty stomach, and the serum was separated by centrifugation without anticoagulation. An LDH assay kit (Chengdu Yuanhe Huasheng Technology Co., Ltd., Chengdu, China) and an i2000 automatic biochemical analyzer (Abbott Laboratories, Abbott Park, IL, USA) were used to detect LDH. A specially assigned person was responsible for the procedure and quality control. Specimen processing, determination and content calculation were performed in accordance with the kit manual.

Statistical analysis

Statistical analysis of the data was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Normally distributed measurement data were represented as the mean ± standard error. An independent sample t-test was used for comparisons between two groups, a one-way analysis of variance was used for comparisons between multiple groups, and Fisher's LSD test was used for pairwise comparisons among subgroups. Spearman correlation analysis was used to assess the correlation between SUVmax and biological indicators. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics

Patient clinical characteristics are summarized in Table 1. Fifty-two patients with PIL were enrolled, including 34 men and 18 women aged 21 to 89 years. There were 20 mucosa-associated lymphoid tissue cases (MALT group) and 32 aggressive NHL cases (including 22 with the diffuse large B-cell type, 3 with the T-cell type and 7 with other types) (ANHL group). Moreover, there were 25 cases with clinical stages I to II and 27 cases with stages III to IV. Twenty-six patients had lymph node invasion, 28 exhibited elevated LDH, and 24 patients showed clinical B symptoms (night sweats, pruritus or others).

Thirty-five patients with PIC were enrolled, including 23 men and 12 women aged 20 to 90 years. In this group, there were 21 adenocarcinoma, 10 sarcoma and 4 carcinoid tumor cases.

PET/CT imaging results

Fifty-two patients with PIL and 35 patients with PIC were examined by PET/CT with

Table 1. Patient characteristics.

Characteristic	n [%]
Sex	
Men	34 (65.38)
Women	18 (34.62)
Age (years)	
≥60	21 (40.38)
<60	31 (59.62)
Ki-67	
High (≥60)	35 (67.31)
Low (<60)	17 (32.69)
Risk grading	
Low	11 (21.15)
Intermediate	22 (42.31)
High	19 (36.54)
Clinical staging	
I–II	25 (48.08)
III–IV	27 (51.92)
Pathological classification	
Mucosa-associated	20 (38.46)
Invasive	32 (61.54)
Diffuse large B	22 (68.75)
T-cell	3 (9.38)
Others	7 (21.88)

FDG. High FDG accumulation (FDG uptake) suggests the presence of a malignant tumor. We observed prevalent FDG uptake in patients with PIL and PIC (Figure 1 and Table 2), suggesting the successful cancer diagnosis with PET/CT. An abnormal intestinal wall was all noted in most patients (Table 2).

SUVmax in different pathological types of PIL

The SUVmax was markedly higher in the more aggressive ANHL group than in the less aggressive MALT group, and the difference was statistically significant ($P < 0.01$). Further analysis of NHL pathology showed that the SUVmax of diffuse large B-cell lymphoma was statistically higher than that of peripheral T-cell lymphoma and other types ($P < 0.05$) (Table 3).

Comparison between SUVmax and clinical staging in patients with PIL

The clinical staging was mainly related to the extent of lymphoma involvement, and there was no statistically significant difference in SUVmax between stages I to II lymphoma and stages III to IV. In addition, there was no correlation between SUVmax and clinical staging (Table 4).

Association between SUVmax and risk grading in patients with PIL

According to the IPI scoring criteria, patients with PIL were classified into a high-risk group ($n = 19$), intermediate-risk group ($n = 22$) and low-risk group ($n = 11$). The SUVmax in the high-risk PIL group was higher than that in the intermediate-risk group and low-risk group ($P < 0.05$) (Table 4). The progression-free survival (PFS) at 3 years for the entire population was 81%. A slightly lower PFS was observed in patients with a higher SUVmax (Table 4).

Correlations between SUVmax, Ki-67 expression, LDH and D-dimer in patients with PIL

In 52 patients, a significant positive correlation was found between SUVmax (11.73 ± 4.76) and Ki-67 ($58 \pm 15\%$) by Spearman correlation analysis ($r = 0.937$, $P = 0.0001$) (Figure 2). Of these 52 patients with PIL, there were 28 patients in the elevated LDH group and 24 patients in the normal LDH group. No statistically significant difference was observed in SUVmax between the elevated LDH group and the normal group. Of these 52 patients with PIL, there were 36 patients in the elevated D-dimer group and 16 patients in the normal D-dimer group. A statistically significant difference was observed in SUVmax between the elevated D-dimer group and the normal D-dimer group

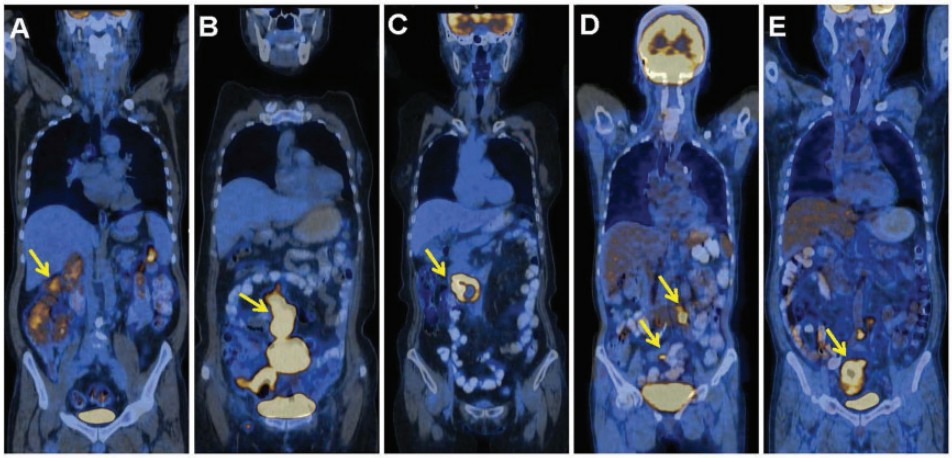

Figure 1. PET/CT imaging results of patients in this study. A) A 59-year-old male patient with MALT lymphoma. PET/CT scan showed thickening of the intestinal wall in the ascending colon with mild radioactive uptake, and the SUVmax was 4.1. B) A 56-year-old female patient with diffuse large B-cell lymphoma. PET/CT scan showed obvious thickening of the intestinal wall in the middle and lower abdomen and ileum. High radioactive uptake was observed, and the SUVmax was 28.6. C) A 72-year-old female patient with T-cell lymphoma. PET/CT showed that the intestinal wall was thickened in the horizontal part of the duodenum. High radioactive uptake was observed, and the SUVmax was approximately 13.2. D) A 69-year-old female patient with mantle cell lymphoma. PET/CT showed multiple nodular radioactive uptake in the small intestine, and the SUVmax was 4.8. There was no obvious thickening of the intestinal wall. E) A 67-year-old male patient with sigmoid colon cancer. PET/CT showed irregular thickening of the sigmoid colon wall with obvious radioactive uptake, and the SUVmax was 10.7.
PET/CT, positron emission tomography/computed tomography; MALT, mucosa-associated lymphoid tissue; SUVmax, maximum standardized uptake value.

Table 2. PET/CT imaging results

Group	n	FDG uptake (+) [case (%)]	SUVmax value	Abnormal intestinal wall [case (%)]
PIL	52	49 (94.23)	11.73 ± 4 .76	45 (86.54)
MALT	17	15 (88.24)	7.39 ± 3.25	13 (76.47)
ANHL	35	34 (97.14)	13.84 ± 3.87	32 (91.43)
PIC	35	33 (94.29)	8.37 ± 3.11	31 (88.57)

PET/CT, positron emission tomography/computed tomography; PIL, primary intestinal lymphoma; MALT, mucosa-associated lymphoid tissue; ANHL, aggressive non-Hodgkin's lymphoma; PIC, primary intestinal cancer; FDG, fluorodeoxyglucose; SUVmax, maximum standardized uptake value.

($P < 0.05$) (Table 5). The D-dimer level ($2.97 \pm 0.77\,\mu g/L$) in the elevated D-dimer group showed a significant positive correlation with SUVmax ($r = 0.869$, $P = 0.0004$) (Figure 3).

Discussion

PIL is an extranodal primary lymphoma occurring in people of all ages, but it is more common in patients over 60 years old.[12]

Table 3. Differences in SUVmax between different pathological types of primary intestinal lymphoma.

Group	n	SUVmax value	t	P	F
MALT	17	7.39 ± 3.25	−5.926	0.004	
ANHL	35	13.84 ± 3.87			
Diffuse large B-cell lymphoma	22	16.03 ± 2.55		0.02	19.506
T-cell lymphoma	3	12.27 ± 1.59			
Other types	7	9.96 ± 1.55			

SUVmax, maximum standardized uptake value; MALT, mucosa-associated lymphoid tissue; ANHL, aggressive non-Hodgkin's lymphoma.

Table 4. Comparison of SUVmax and clinical stage/risk grading in patients with primary intestinal lymphoma.

Group	n	SUVmax value	t	P	F	3-year PFS
Stage I–II	17	11.98 ± 5.06	0.361	0.720		93%
Stage III–IV	35	11.50 ± 4.54				75%
High-risk	19	16.73 ± 2.02		0.0016	81.254	74%
Intermediate-risk	22	10.32 ± 2.80				82%
Low-risk	11	5.95 ± 1.71				91%

SUVmax, maximum standardized uptake value; PFS, progression-free survival.

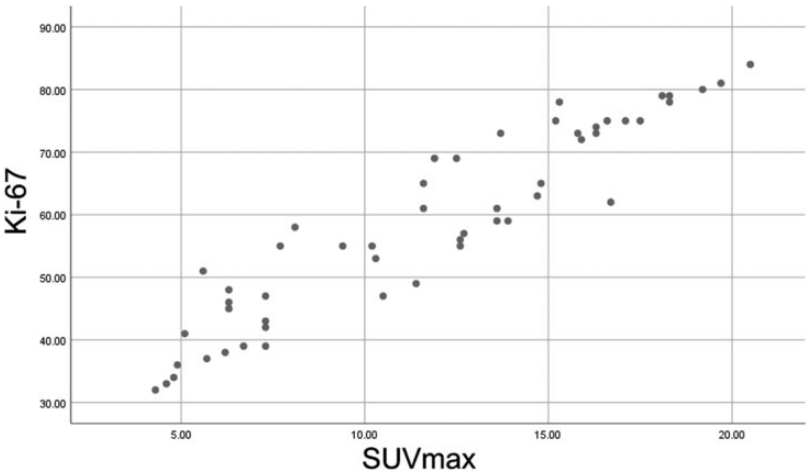

Figure 2. Positive correlation between SUVmax and Ki-67 expression in patients with primary intestinal lymphoma.
SUVmax, maximum standardized uptake value.

The clinical symptoms include abdominal discomfort, bloody stools, abdominal masses and systemic symptoms, such as fever, night sweats, fatigue and weight loss.[13]

Clinically, NHL is broadly classified as indolent and aggressive based on its clinical presentation and biological features. To more accurately determine the malignancy and prognosis of lymphoma, biological

Table 5. Correlation of SUVmax with LDH and D-dimer in patients with primary intestinal lymphoma.

Group	n	SUVmax value	t	P
Elevated LDH	28	11.67 ± 4.98	0.108	0.914
Normal LDH	24	11.81 ± 4.58		
Elevated D-dimer	36	13.31 ± 4.20	4.105	0.027
Normal D-dimer	16	8.19 ± 4.03		

SUVmax, maximum standardized uptake value; LDH, lactate dehydrogenase.

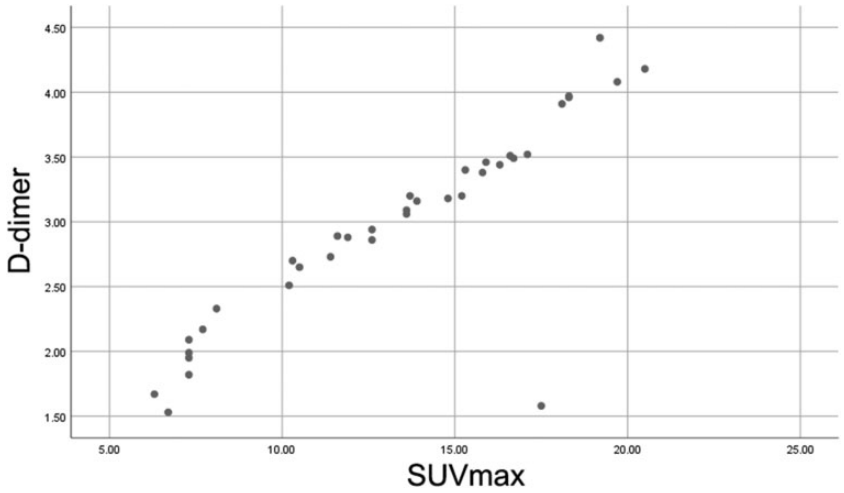

Figure 3. Correlation of SUVmax with D-dimer in patients with primary intestinal lymphoma
SUVmax, maximum standardized uptake value.

parameters are used as predictors, such as the Ki-67 index, erythrocyte sedimentation rate, LDH and β2 microglobulin.[14,15] PET/CT has been widely applied for precise staging and therapeutic evaluation. SUV is the most commonly used semi-quantitative index of PET/CT in tumor diagnosis and treatment and is affected by a variety of factors, such as the ratio of the radioactivity of the developer taken up by the local tumor tissue to the average activity of the whole body, blood glucose level, patient weight, lesion size, ROI delineation range, imaging time after injection and 18F-FDG clearance rate in the blood circulation.[16] SUVmax refers to the highest uptake value in the ROI of the tumor lesion. Compared with SUV, SUVmax is less influenced by volume effects.[17] Several studies have demonstrated that SUVmax is associated with the prognosis, staging and certain biological indicators of various tumors.[18,19] There is moderate evidence suggesting an association of SUVmax with the stage, pathological type, biological indicators and even prognosis of lymphoma, but the number of reported cases is small, the analysis is not comprehensive, and the conclusions are inconsistent.[20,21]

In this study, we further evaluated the correlation between SUVmax and the pathological types, clinical staging, risk grading and biological indicators of lymphoma by applying strict criteria and accurate measurement methods to explore the value of 18F-FDG PET/CT SUVmax in lymphoma.

In this study, there was a statistically significant difference in SUVmax between various pathological subgroups of PIL ($P < 0.05$). A statistical difference was also noted in SUVmax between patients with stages I to II and those with stages III to IV lymphoma ($P < 0.05$). Patients in the high-risk PIL group had markedly higher SUVmax values than those in the intermediate-risk group and low-risk group ($P < 0.01$). These results indicated that SUVmax reflected the aggressiveness of lymphoma and effectively determined the risk level of PIL. Therefore, SUVmax shows potential as an independent factor in the prognostic scoring system and increases the accuracy and comprehensiveness of the current prognostic score, providing a more adequate theoretical rationale for lymphoma treatment selection, efficacy evaluation and prognostic judgment.

The Ki-67 index reflects the proportion of cells entering the active phase of the cycle and, to some extent, the proliferative activity of tumor cells. Various studies have confirmed[22] that the Ki-67 index is closely associated with the tumor proliferation index and biological behaviors, especially in breast cancer and lymphoma. The results of this study showed that SUVmax and Ki-67 expression levels were positively correlated within the same PIL lesion. Therefore, SUVmax reflected the malignancy of lymphoma and predicted the prognosis.

D-dimer is a specific degradation product of cross-linked fibrin produced by the hydrolysis of fibrinolytic enzymes. It is used to monitor the diagnosis and condition of disseminated intravascular coagulation and thrombophilia.[23] Patients with malignant lymphoma have recently been found to exhibit a hypercoagulable state, dysfunction of the fibrinolytic system and a higher incidence of venous thrombosis.[24] Related reports suggest that the incidence of deep vein thrombosis in patients with NHL is 5.77%. This index has a sensitivity of >90% in the diagnosis of thrombosis and is specific for fibrinolytic activity.[25] The results of this study showed a statistically significant difference in SUVmax between the elevated D-dimer group and the normal D-dimer group ($P < 0.05$), and the D-dimer level in the elevated D-dimer group showed a significant positive correlation with SUVmax ($r = 0.869$, $P < 0.001$). These findings suggest that the SUVmax characteristics of PIL on PET/CT images, along with clinical D-dimer levels and other related indicators, offer more information for clinical staging, follow-up of treatment responses, recurrence monitoring and prognosis.

In conclusion, 18F-FDG PET/CT SUVmax reflects the aggressiveness of lymphoma to a certain degree. It is correlated with the Ki-67 index and determines the risk grades of PIL. Moreover, it facilitates differential diagnosis, clinical staging and treatment protocol selection based on the D-dimer level. Our conclusion is based on retrospective studies, which are prone to selection bias, recall bias and misclassification bias. Owing to the heterogeneity of data and small sample size, it may not represent the actual situation. A more detailed subgroup analysis based on individual diseases is required for future studies to reduce bias.

Author contributions

Shuo Zhou conceived the study, designed and supervised the study and wrote the manuscript. Wenxin Chen and Meifu Lin designed the study and wrote the manuscript. Guobao Chen and Cailong Chen collected clinical data and performed the statistical analysis. Chong Huo and Xueming Du performed the experiments. All authors have read and approved the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Nakamura S and Matsumoto T. Gastrointestinal lymphoma: recent advances in diagnosis and treatment. *Digestion* 2013; 87: 182–188. DOI: 10.1159/000350051.
2. Qiu L, Tu G, Li J, et al. The role of 18F-FDG PET and PET/CT in the evaluation of primary cutaneous lymphoma. *Nucl Med Commun* 2017; 38: 106–116. DOI: 10.1097/MNM.0000000000000614.
3. Dubreuil J, Salles G, Bozzetto J, et al. Usual and unusual pitfalls of 18F-FDG-PET/CT in lymphoma after treatment: a pictorial review. *Nucl Med Commun* 2017; 38: 563–576. DOI: 10.1097/MNM.0000000000000697.
4. Tamayo P, Martin A, Diaz L, et al. (18)F-FDG PET/CT in the clinical management of patients with lymphoma. *Rev Esp Med Nucl Imagen Mol* 2017; 36: 312–321. DOI: 10.1016/j.remn.2017.03.004.
5. Guan W, Wang QS, Wu HB, et al. [(18)F-FDG PET/CT findings of primary intestinal lymphoma: analysis of 23 cases]. *Nan Fang Yi Ke Da Xue Xue Bao* 2016; 36: 1175–1180.
6. Albano D, Giubbini R and Bertagna F. 18F-FDG PET/CT in splenic marginal zone lymphoma. *Abdom Radiol (NY)* 2018; 43: 2721–2727. DOI: 10.1007/s00261-018-1542-z.
7. Albano D, Bosio G, Bertoli M, et al. 18F-FDG PET/CT in primary brain lymphoma. *J Neurooncol* 2018; 136: 577–583. DOI: 10.1007/s11060-017-2686-3.
8. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; 12:1495–1499. DOI: 10.1016/j.ijsu.2014.07.013.
9. Elhussein A, Fawzy M, Abdel Rahman H, et al. Productivity of 18F-FDG-PET/CT Diagnostic Tool in the Management of Pediatric Lymphoblastic Lymphoma. *Nucl Med Rev Cent East Eur* 2019; 22: 23–28. DOI: 10.5603/NMR.2019.0004.
10. Yasuda S, Takahashi W, Takagi S, et al. Factors influencing physiological FDG uptake in the intestine. *Tokai J Exp Clin Med* 1998; 23: 241–244.
11. Park S, Yoon JK, Chung NS, et al. Correlations between intravoxel incoherent motion diffusion-weighted MR imaging parameters and (18)F-FDG PET/CT metabolic parameters in patients with vertebral bone metastases: initial experience. *Br J Radiol* 2018; 91: 20170889. DOI: 10.1259/bjr.20170889.
12. Qin C, Yang S, Sun X, et al. 18F-FDG PET/CT for Prognostic Stratification of Patients With Extranodal Natural Killer/T-Cell Lymphoma. *Clin Nucl Med* 2019; 44: 201–208. DOI: 10.1097/RLU.0000000000002440.
13. Lawal IO, Ankrah AO, Popoola GO, et al. 18F-FDG-PET metabolic metrics and International Prognostic Score for risk assessment in HIV-infected patients with Hodgkin lymphoma. *Nucl Med Commun* 2018; 39: 1005–1012. DOI: 10.1097/MNM.0000000000000905.
14. Albano D, Bertoli M, Battistotti M, et al. Prognostic role of pretreatment 18F-FDG PET/CT in primary brain lymphoma. *Ann Nucl Med* 2018; 32: 532–541. DOI: 10.1007/s12149-018-1274-8.
15. Albano D, Bosio G, Giubbini R, et al. 18F-FDG PET/CT and extragastric MALT lymphoma: role of Ki-67 score and plasmacytic differentiation. *Leuk Lymphoma* 2017; 58: 2328–2334. DOI: 10.1080/10428194.2017.1298754.
16. Barrington SF and Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. *Eur J Nucl Med Mol Imaging* 2017; 44: 97–110. DOI: 10.1007/s00259-017-3690-8.
17. Albano D, Bosio G, Bianchetti N, et al. Prognostic role of baseline 18F-FDG PET/CT metabolic parameters in mantle cell

lymphoma. *Ann Nucl Med* 2019; 33: 449–458. DOI: 10.1007/s12149-019-01354-9.
18. Jiang C, Teng Y, Chen J, et al. Value of (18) F-FDG PET/CT for prognostic stratification in patients with primary intestinal diffuse large B cell lymphoma treated with an R-CHOP-like regimen. *Ann Nucl Med* 2020; 34: 911–919. DOI: 10.1007/s12149-020-01536-w.
19. Albano D, Bertoli M, Ferro P, et al. 18F-FDG PET/CT in gastric MALT lymphoma: a bicentric experience. *Eur J Nucl Med Mol Imaging* 2017; 44: 589–597. DOI: 10.1007/s00259-016-3518-y.
20. Tang B, Li TN and Ding CY. [(18)F-FDG PET/CT Manifestation and Clinical Analysis of Primary Hepatic Lymphoma]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2018; 26: 1062–1066. DOI: 10.7534/j.issn.1009-2137.2018.04.020.
21. Ren Y, Huang L, Han Y, et al. 18F-FDG PET/CT for staging and response assessment of primary parotid MALT lymphoma with multiple sites involvement: A case report. *Medicine (Baltimore)* 2019; 98: e14270. DOI: 10.1097/MD.0000000000014270.
22. Sun M, Cheng J, Zhang Y, et al. Application of DWIBS in malignant lymphoma: correlation between ADC values and Ki-67 index. *J Eur Radiol* 2018; 28: 1701–1708.
23. Geng YD, Chen YR, Jin J, et al. Prognostic Value of D-Dimer in Patients with Diffuse Large B-cell Lymphoma: A Retrospective Study. *J Curr Med Sci* 2019; 39: 222–227.
24. Zhu M, Shi QQ, Sun X, et al. [Effect of Coagulation and Platelet Activation on Tumor-Associated Hypercoagulable State in Lymphoma-Bearing Mice]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2018; 26: 427–431. DOI: 10.7534/j.issn.1009-2137.2018.02.020.
25. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *J Ann Intern Med* 2004; 140: 589–602.