Correlations between maximum standardized uptake value measured via $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography and clinical variables and biochemical indicators in adult lymphoma

ABSTRACT

Objectives: The aim of the current study was to investigate whether the maximum standardized uptake value (SUVmax) measured by $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT) could discriminate between aggressive and indolent non-Hodgkin lymphomas (NHLs) and correlations between the SUVmax and clinical variables and serum biochemical indicators in adult lymphoma.

Methods: A total of 103 patients with lymphoma confirmed by biopsy, pretreatment $^{18}$F-FDG PET/CT scans, and a complete medical record were retrospectively enrolled in the study. Clinical variables that were evaluated included stage, pathological subtype, International Prognostic Index (IPI) score, and Ki-67 index, as well as serum biochemical indicators (e.g., lactate dehydrogenase [LDH] and erythrocyte sedimentation rate [ESR]) and metabolic parameters (e.g., SUVmax of the biopsy site on PET/CT). Correlations between SUVmax and clinical variables and serum biochemical indicators were investigated.

Results: Of the 103 patients, 84 had NHL and 19 had Hodgkin lymphoma. The area under the receiver operating characteristic curve for examining the accuracy of SUVmax with regard to distinguishing between aggressive and indolent NHLs was 0.94 (95% confidence interval: 0.89–0.99), suggesting that SUVmax was a useful predictor of diagnosis. A cutoff value of 8.5 yielded a sensitivity of 76.3% and specificity of 92.0%. The SUVmax mean ± standard deviation of NHL (9.8 ± 6.0, range: 1.8–28.1) was higher than that of HL (7.5 ± 2.8, range: 3.5–13.9) ($P = 0.016$), but there was no statistically significant difference in SUVmax between NHL and HL ($P > 0.05$). SUVmax of the biopsy site was strongly positively correlated with Ki-67 index ($r = 0.813$, $P < 0.001$) and moderately positively correlated with IPI score ($r = 0.332$, $P = 0.002$), but it was not significantly correlated with clinical stage, LDH, or ESR ($P > 0.05$).

Conclusions: $^{18}$F-FDG PET/CT may yield reliable measurements of tumor proliferation, and an SUVmax >8.5 may distinguish between aggressive and indolent NHLs. In adults with newly diagnosed lymphoma, SUVmax correlates with Ki-67 index and IPI score.

KEY WORDS: $^{18}$F-fluorodeoxyglucose, Ki-67, lymphoma, positron emission tomography/computed tomography, standardized uptake value

INTRODUCTION

Malignant lymphoma originates from cells of the lymphatic system and includes multiple inducing factors, diverse clinical manifestations, and immunohistochemical features. In lymphomas vary in clinical evolution and response to treatment and are classified as Hodgkin lymphoma (HL) and non-HL (NHL). The prognostic factors of NHL have been classified into three major categories: patient...
related (age, performance status, and B symptoms), disease related (number of nodal and extranodal sites, tumor stage, and tumor size), and biologic measures including serum hemoglobin, β₂-microglobulin, and lactate dehydrogenase (LDH). The prognoses of different pathological subtypes are very different, and even the prognoses associated with different cases of the same pathological lymphoma type can vary markedly.

Thus far, ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/computed tomography (CT) and the maximum standardized uptake value (SUVmax) have been widely used for the diagnosis and initial staging of various malignant diseases, as well as for the evaluation of therapeutic responses. Fortunately, ¹⁸F-FDG PET/CT is gaining popularity for evaluating patients with lymphoma and has proven to be more sensitive and specific than contrast-enhanced CT for evaluating nodal and extranodal lymphomatous involvement (e.g., bone marrow malignant infiltration). The SUVmax, which is a semi-quantitative index of ¹⁸F-FDG concentration in tissue, has been used for the diagnosis and evaluation of treatment effectiveness in lymphoma. High ¹⁸F-FDG uptake indicates aggressive NHL, and lower ¹⁸F-FDG uptake is a sign of tumor response to therapy. In addition, SUVmax correlates with histological grade in follicular lymphoma (FL)/high-grade B-cell lymphoma, Ki-67 index, and LDH. Moreover, Ki-67 index correlates with histological grade and clinical aggressiveness.

Several studies have reported that SUVmax was significantly correlated with risk as determined by the International Prognostic Index (IPI), tumor burden, and the presence of extranodal involvement in FL and/or diffuse large B-cell lymphoma (DLBCL). In one study, SUVmax and LDH were significantly higher in the DLBCL group than in the FL group (P = 0.004 and 0.007, respectively). However, in another study investigating the diagnostic role of ¹⁸F-FDG PET/CT for FL with gastrointestinal involvement, there were no significant differences in Ann Arbor stage (P > 0.05), LDH (P > 0.05), or IPI risk (P > 0.05) between ¹⁸F-FDG-negative and ¹⁸F-FDG-positive groups, and this is in accordance with results reported by Akkas and Vural. Most of the previous studies have focused on the utilization of SUVmax and/or clinical variables or serum indicators in a single lymphoma, where some SUVs did not match the site of biopsy, and conclusions have not been consistent. The potential usefulness of SUVmax in lymphoma and the significance of correlations between SUVmax and various indicators are currently unknown. The current study investigated these aspects of SUVmax of the biopsy site in adult lymphoma patients, including cases of HL and various pathological subtypes of NHL, and analyzed direct relationships between SUVmax of the biopsy site and several important parameters.

The primary aim of the study was to investigate whether SUVmax measured via ¹⁸F-FDG PET/CT facilitated discrimination between aggressive NHL and indolent NHL. An additional aim was to investigate correlations between SUVmax of the biopsy site and clinical variables and serum biochemical indicators in adult lymphoma.

MATERIALS AND METHODS

Patients

We retrospectively analyzed the medical records of patients with malignant lymphoma treated at Gansu Provincial Hospital in Western China. One hundred and three lymphoma patients who underwent pretreatment ¹⁸F-FDG PET/CT examinations from January 2011 to December 2016 were included in the study. Patients were eligible for inclusion if they had (1) been newly diagnosed with lymphoma by biopsy but were not receiving therapy; (2) received a whole-body ¹⁸F-FDG PET/CT for pretreatment staging; (3) received complete pretreatment evaluation including history, physical examination, and the standard laboratory tests for erythrocyte sedimentation rate (ESR) and LDH; and (4) had had biopsy samples evaluated via immunohistochemical staining to determine Ki-67 expression. Patients were excluded if they (1) were aged < 18 years; (2) had incomplete clinical data; or (3) had yielded negative pathology results. Patients were staged in accordance with the Ann Arbor staging criteria. Pathology results were reviewed by expert pathologists and classified in accordance with the WHO/Revised European-American Lymphoma classification of lymphoid neoplasms. All patients provided written informed consent to undergo biopsy before the invasive examination. In addition, the committee of Gansu Provincial Hospital approved the study, and all patients gave written informed consent to be included in the study.

General information

The retrospectively collected data included sex, age at lymphoma diagnosis, Ki-67 index, LDH, ESR, clinical stage, pathological subtype, IPI score, and SUVmax of the biopsy site on initial PET/CT. Elevated LDH was defined as > 245 U/L (our institution’s upper normal threshold), and elevated ESR was defined as > 20 mm/h (our institution’s upper normal threshold). Ki-67 staining was performed to estimate the expression rate. After staining a 10% formaldehyde-fixed paraffin-embedded section of a biopsy specimen with a mouse anti-Ki-67 antibody (bsm-33070M; Bioss, Beijing, China), hematoxylin and eosin (Bioss, Beijing, China) were used for immunohistochemical staining in accordance with the manufacturer’s instructions. The percentage of Ki-67 expression was quantified by determining the number of positive cells expressing nuclear Ki-67 among the total number of tumor cells in high-power magnification fields. Specimens were reviewed by two pathologists with extensive experience who were blinded to the ¹⁸F-FDG PET/CT results and clinical presentation data. All authors had no access to information that could identify individual participants during or after data collection.
**Methods**

Statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA) software. Continuous data were expressed as mean ± standard deviation (SD), and quantitative values were expressed as numbers, ranges, and/or percentages. Receiver operating characteristic (ROC) curves of SUVmax and Ki-67 index were used for estimating the accuracy of predicting aggressive histological subtype. Student’s t-test was used to analyze differences between two groups, and one-way analysis of variance was used to analyze data derived from multiple groups. Correlations between SUVmax and clinical stage, IPI index, Ki-67, LDH, and ESR were calculated using the Spearman’s rank correlation test. Correlations were considered relevant when \( r > 0 \) and statistically significant when \( P < 0.05 \).

**Results**

**Patient characteristics**

There were 103 patients enrolled in the study: 54 men (52.4%) and 49 women (47.6%), with a mean age of 51.9 ± 15.6 years (range: 18–96 years). Among these patients, 19 (18.4%) were diagnosed with HL and the other 84 (81.6%) were diagnosed with NHL. Subtypes of HL were mixed cellularity HL (n = 14, 73.6%), nodular sclerosis HL (n = 3, 15.8%), lymphocyte-rich HL (n = 1, 5.3%), and lymphocyte-depleted HL (n = 1, 5.3%). NHL included DLBCL (n = 38, 36.9%), natural killer-T-cell lymphoma (NK-TL; n = 12, 11.8%), anaplastic large-cell lymphoma (ALCL; n = 6, 5.8%), small lymphocytic lymphoma (SLL; n = 6, 5.8%), peripheral T-cell lymphoma (PTCL; n = 8, 7.8%), T-cell lymphoblastic lymphoma (T-LBL; n = 3, 2.9%), marginal zone lymphoma (MZL; n = 3, 2.9%), and mantle cell lymphoma (MCL; n = 2, 1.9%).

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**Maximum standardized uptake value in aggressive and indolent non-Hodgkin lymphomas**

SUVmax data were available from all 103 patients, and the SUVmax mean ± SD was 9.4 ± 5.6 (range: 1.8–28.1). The SUVmax mean ± SD of NHL (9.8 ± 6.0, range: 1.8–28.1) was higher than that of HL (7.5 ± 2.8, range: 3.5–13.9) (\( P = 0.016 \)), whereas there was no correlation between NHL and HL in terms of SUVmax (\( r = 0.134, P = 0.178 \) [Table 2]. Box plotting of SUVmax by histology subtypes of NHL was performed [Figure 1]. Within the histological NHL subtypes, the collective SUVmax mean ± SD of DLBCL, NK-TL, ALCL, and T-LBL (12.0 ± 5.7) was higher than that of SLL, FL, PTCL, MZL, and MCL (4.6 ± 2.1) (\( P < 0.001 \)).

**ROC curve analysis was used to examine the accuracy of SUVmax for distinguishing between aggressive NHL and indolent NHL. The estimated area under the ROC curve was 0.94 (95% confidence interval: 0.89–0.99), suggesting that SUVmax was a useful predictor of diagnosis.** We used various cutoff values for SUVmax to obtain a reasonable balance of sensitivity and specificity; an SUVmax of 8.5 yielded a sensitivity of 76.3% and specificity of 92.0% [Figure 2].

**Table 1: Characteristics at diagnosis of all 103 patients with lymphoma**

| Characteristics | Number of patients (%) |
|-----------------|-----------------------|
| **Histology**   |                       |
| HL              | 19 (18.4)             |
| NHL             | 84 (81.6)             |
| **Ann Arbor stage** |                    |
| I–II            | 52 (50.5)             |
| III-IV          | 51 (49.5)             |
| **IPI risk (in 84 NHL patients)** |        |
| Low risk        | 37 (44.1)             |
| Intermediate risk| 30 (20.2)            |
| High risk       | 17 (35.7)             |
| **Ki-67 index** |                       |
| Low (<60%)      | 53 (51.5)             |
| High (>60%)     | 50 (48.5)             |
| **LDH (U/L)**   |                       |
| Normal          | 56 (54.4)             |
| Elevated        | 47 (45.6)             |
| **ESR (mm/h)**  |                       |
| Normal          | 37 (35.9)             |
| Elevated        | 66 (64.1)             |

**Discussion**

Elevated LDH and 66 (64.1%) had abnormal ESR. With regard to the Ki-67 index of the biopsy, 50 patients (48.5%) were ≥60% and the remaining 53 (51.5%) were <60%.

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Correlations between maximum standardized uptake value and clinical features

Correlations between SUVmax and clinical stage and IPI score are shown in Table 2. There was no significant correlation between SUVmax and stage ($r = 0.182, P = 0.066$), but there was a moderate correlation between SUVmax and the IPI score ($r = 0.332, P = 0.002$). The high-risk group differed significantly from the intermediate-risk group ($P = 0.004$) and the low-risk group ($P < 0.001$), but there was no significant difference between the intermediate-risk group and the low-risk group ($P = 0.485$).

### Table 2: Correlations between maximum standardized uptake value and clinical features and serum biochemical indicators

| Parameters                      | Number of patients | SUV$_{\text{max}}$ Mean±SD | $r$ | $P$  |
|---------------------------------|--------------------|-----------------------------|----|------|
| Histology                       |                    |                             |    |      |
| HL                              | 19                 | 7.5±2.8                     | 0.134 | 0.178|
| NHL                             | 84                 | 9.8±6.0                     | 0.182 | 0.066|
| Ann Arbor stage                 |                    |                             |    |      |
| I-II                            | 52                 | 8.3±4.5                     | 0.182 | 0.066|
| III-IV                          | 51                 | 10.5±6.4                    | 0.332 | 0.002*|
| IPI risk (in 84 NHL patients)   |                    |                             |    |      |
| Low risk                        | 37                 | 8.2±4.9                     | 0.332 | 0.002*|
| Intermediate risk               | 30                 | 9.2±6.0                     | 0.332 | 0.002*|
| High risk                       | 17                 | 14.2±5.9                    | 0.332 | 0.002*|
| Ki-67 index                     |                    |                             |    |      |
| Low (<60%)                      | 53                 | 5.5±2.2                     | 0.332 | 0.001**|
| High (≥60%)                     | 50                 | 13.5±5.2                    | 0.332 | 0.001**|
| LDH (U/L)                       |                    |                             |    |      |
| Normal                          | 56                 | 8.8±4.8                     | 0.332 | 0.001**|
| Elevated                        | 47                 | 10.1±6.3                    | 0.332 | 0.001**|
| ESR (mm/h)                      |                    |                             |    |      |
| Normal                          | 37                 | 10.6±7.1                    | 0.332 | 0.001**|
| Elevated                        | 66                 | 8.7±4.5                     | 0.332 | 0.001**|

$^aP<0.05, ^bP<0.001, ^c$Comparison between low-risk and intermediate-risk groups ($P=0.485$), $^d$Comparison between high-risk and intermediate-risk groups ($P=0.004$), $^e$Comparison between high-risk and low-risk groups ($P<0.001$). HL=Hodgkin lymphoma, NHL=Non-HL, IPI=International Prognostic Index, SD=Standard deviation, SUV$_{\text{max}}$=Maximum standardized uptake value.

DISCUSSION

$^{18}$F-FDG PET/CT is now the imaging modality of choice for staging, evaluating treatment response, and follow-up in HL and NHL. Strong evidence from a growing number of studies suggests that SUVmax is highly positively correlated with tumor aggressiveness and a worse prognosis.\[2,20,21\] In a number of previous studies, aggressive NHL has exhibited higher $^{18}$F-FDG uptake than indolent lymphoma.\[22,23\] This is
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consistent with the results of the current study, in which within the subtypes of NHL histology, the collective mean SUVmax of DLBCL, NK-TL, ALCL, and T-LBL was higher than that of SLL, FL, PTCL, MZL, and MCL (\(P < 0.001\)) [Figure 1]. In ROC curve analysis investigating the accuracy of SUVmax for distinguishing between aggressive NHL and indolent NHL, the area under the curve was 0.94 (95% confidence interval: 0.89–0.99), and an SUVmax cutoff value of 8.5 yielded a sensitivity of 76.3% and specificity of 92.0% [Figure 2]. Thus, SUVmax >8.5 may indicate aggressive NHL histology. The cutoff value of SUVmax was lower than that of previous studies such as Ngeow et al.,[22] who reported that an SUVmax cutoff value of >10 provided a sensitivity of 91% and specificity of 62%, and Schöder et al.,[23] who reported that an SUVmax cutoff value of 10 yielded a sensitivity of 71% and specificity of 81% with regard to distinguishing between indolent NHL and aggressive NHL. To the best of our knowledge, SUVmax is dependent on body composition, blood glucose level, and 18F-FDG uptake time (e.g., postinjection delay) and is influenced by partial volume effects and the recovery coefficient.[24]

Notably, however, the aforementioned previous studies were published approximately 10 years ago; medical technology

**Figure 3:** Receiver operating characteristic curve of Ki-67 index (blue solid line) in distinguishing aggressive non-Hodgkin lymphoma from indolent non-Hodgkin lymphoma in 84 patients. The green solid line is the reference line. The area under the receiver operating characteristic curve was 0.93 (\(P < 0.001\)). The sensitivity and specificity of Ki-67 index of 42.5% were 93.2% and 76.0%, respectively

**Figure 4:** (a) A fifty-year-old female patient with histologically verified diffuse large B-cell lymphoma and who was Stage IV. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (left) demonstrates hypermetabolic lymph nodes with biopsy-proven diffuse large B-cell lymphoma and right groin region with maximum standardized uptake value 28.1. Ki-67 immunohistology (right) with hematoxylin-eosin section at x400 magnification was expressed in 90% of B-cells. (b) A sixty-eight-year-old female with immunohistochemical studies confirmed the diagnosis of follicular lymphoma, showing that the lymphocytes are B-cells (CD20+). 18F-fluorodeoxyglucose positron emission tomography/computed tomography (left) images of the patient with Stage I follicular lymphoma and International Prognostic Index score showed low risk. Maximum standardized uptake value of the biopsy site on positron emission tomography/computed tomography was 1.8. Ki-67, the proliferation antigen, was expressed in 10% (right)
has improved significantly, and more research is available regarding lymphoma. In our collective opinion, the above reasons may lead to a little difference in a cutoff value of SUVmax.

18F-FDG is a glucose analog that is differentially taken up by malignant cells, due to their increased glucose metabolism.25 The sensitivity of malignant tumor detection by 18F-FDG PET/CT depends on the avidity of the tumor cells for FDG; this avidity is strongly linked to tumor aggressiveness and cellularity.26 However, FDG is not a specific tracer, and uptake may vary based on the patient, the reference background, and the PET/CT system employed.27 According to a report by Weiler-Sagie et al., DLBCL, FL, NK-TL, ALCL, and Burkitt lymphoma have high 18F-FDG avidity, while SLL and MZL do not.28 In addition, 18F-FDG avidity has a close relationship with the histopathologic subtype of NHL. For example, FL is an indolent NHL but is also an 18F-FDG-avid lymphoma. High 18F-FDG avidity in potentially curable lymphoma subtypes warrants further investigations of the utility of 18F-FDG PET/CT in these diseases at presentation.29

Reports suggest that FL has been the most common low-grade lymphoma during the past 10 years worldwide29 and that it now constitutes approximately 10%–20% of all lymphomas,29 which are characterized by a variable clinical course. FL, while an indolent NHL, is divided into three histological grades. Grade 3 FL is often treated differently from Grade 1 or Grade 2, as it is believed to be biologically more aggressive. Ngew et al. suggested that 18F-FDG PET/CT can be reliably used in aggressive B-cell NHL, T-cell NHL, and HL for staging; notably, they showed that high SUVmax (>10) may predict more aggressive B-cell NHL (sensitivity and specificity were 91% and 62%, respectively) and may be used to detect histological transformation of low-grade lymphoma.22 The observation in the current study that SUVmax >8.5 was predictive of a more aggressive histological component has potential diagnostic implications in clinical settings. In a patient with an indolent lymphoma, sites with SUVmax of >8.5 may suggest the possibility of transformation. In the present study, all six FL patients exhibited low 18F-FDG uptake (mean SUVmax: 3.7 ± 1.4, range: 1.8–5.8), and none had Grade 3 FL or aggressive transformed FL.

Ki-67, a nuclear protein expressed in all active phases of the cell cycle, is associated with cell proliferation and can be used as a cellular marker to investigate cell proliferation activity. It has been shown that Ki-67 index is correlated with clinical presentation in patients with different kinds of cancers, including breast cancer,30,31 lung cancer,33 and lymphoma.34 A number of studies have demonstrated that Ki-67 proliferation index correlates with SUVmax at the biopsy site and may help to differentiate indolent lymphoma from aggressive lymphoma.22,25 In a study of 268 patients with newly diagnosed NHL, Broyde et al.35 reported that a Ki-67 index cutoff of 70% facilitated discrimination between patients with good and bad prognoses in DLBCL (area under the curve = 0.65, P = 0.004) and a cutoff value of 45% facilitated differentiation between indolent lymphoma and aggressive lymphoma (area under the curve = 0.877, P < 0.001). Watanabe et al.36 reported a significant correlation between Ki-67 index and SUVmax at the biopsy site in NHL. Concordant with the findings in the current study, there was a significant correlation between Ki-67 index and SUVmax (r = 0.813, P < 0.001). In addition, the present study suggests that a Ki-67 index cutoff of 42.5% can differentiate indolent NHL from aggressive NHL (P < 0.001) with a sensitivity of 93.2% and specificity of 76.0%, and the area under the ROC curve was 0.93 (95% confidence interval: 0.88–0.99) [Figure 3]. Albano et al. recently demonstrated that the SUVmax of a region of interest was correlated with the Ki-67 index in gastric mucosa-associated lymphoid tissue (MALT) lymphoma,37 whereas it was not correlated with Ki-67 index in extragastric MALT lymphoma38 or splenic MZL (SMZL).39 However, Ki-67 index has been correlated with 18F-FDG avidity of gastric MALT lymphoma,37 extragastric MALT lymphoma,38 and SMZL.39 Furthermore, Eryilmaz et al. showed that Ki-67 was not correlated with SUVmax in patients diagnosed with laryngeal cancer.40 These studies have suggested that the relationship between SUVmax and Ki-67 index may be influenced by lesion location and pathological subtype. Although 18F-FDG has not been characterized as a specific tracer of cellular proliferation, it has recently been reported that 18F-fluorothyroidine accumulates in proliferating tissues and malignant tumors and that it may be a selective biomarker of tumor proliferation.41 In addition, many factors may influence the reliability of SUVmax, such as patient weight and body habits. Therefore, an in-depth study of the relationships between Ki-67 index and SUVmax values is needed.

The IPI, a strong predictor of survival in aggressive NHL, is based on five factors such as age, tumor stage, serum LDH concentration, performance status, and number of sites of extranodal involvement. The FL IPI was introduced in 2004,42 and several retrospective analyses have confirmed its accuracy as a standard prognostic index for FL.43,44 Three risk groups were defined, low, intermediate, and high. In the current study, there was a moderate correlation between the SUVmax and IPI score in NHL (r = 0.332, P = 0.002). This was consistent with the findings of Akkas and Vural, as well as those of Jung. Serum LDH, which represents a quantitative measure of tumor burden and aggressiveness in NHL, is one of the components of the IPI score. However, there was no correlation between serum LDH and SUVmax of the biopsy site in the current study, and ESR was not significantly correlated with SUVmax either.

The limitations of the present study include its retrospective design and the lack of follow-up data. Some of the subgroups were also very small: notably, there were only six FL, three T-LBL, three MZL, and two MCL patients. This may be because some potentially eligible patients were excluded in accordance with the strict inclusion criteria; it may also be
related to the relatively rare incidences of some lymphoma subtypes. In addition, our FDG uptake metrics may vary from those obtained in other institutions because of differences in technical and patient-related factors. Larger prospective studies investigating the utilization of SUVmax in combination with Ki-67 index and IPI score in lymphoma and information about progression-free survival and/or overall survival are warranted to confirm our observations.

CONCLUSION

The findings of this study highlight the potential usefulness of SUVmax of the biopsy site in pretreatment PET/CT. The results suggest that in adults with newly diagnosed NHL, high SUVmax may facilitate distinguishing between aggressive NHL and indolent NHL in clinical settings and may be used to detect histological transformation of low-grade lymphoma. SUVmax was also significantly correlated with IPI score and Ki-67 index. Further, prospective studies should be performed to ensure the efficient use of SUVmax of the biopsy site in combination with Ki-67 index and IPI score in adults with lymphoma.

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Conflicts of interest

There are no conflicts of interest.

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