

The Prognostic Value of Therapeutic Evaluation Criteria in F18 FDG PET CT In Patients with Lymphoma: Comparison Between Lesion to Liver Ratio and Visual Deauville Score

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ABSTRACT

Background: Malignant lymphoma is regarded as the most prevalent hematological malignancy in adults and is ranked as the fourth most frequent adult malignancy, accounting for around 8.4% of all adult malignancies diagnosed yearly.

Objective: To evaluate the prognostic value of TLR in 18F-FDG PET/CT in lymphoma patients and assess its role in the treatment response assessment and follow-up.

Methods: This cohort analytical study involved 80 patients with 139 PET/CT study diagnosed with lymphoma (including Hodgkin and non-Hodgkin lymphoma), all referred to the Center of Clinical Oncology and Nuclear Medicine (NEMROCK) between April 2022 and May 2024.

Results: TLR demonstrated excellent performance in distinguishing CMR from other outcomes, with high AUC values at interim (0.980), EOT (0.967), and follow-up (1.000) time points. Optimal TLR cut-off values were 1.111 for interim and 0.959 for EOT and follow-up assessments. TLR showed high sensitivity (75-87.50%), specificity (90.48-100%), and accuracy (85-91.94%) in predicting CMR. Significant variances in PFS have been found between patients achieving CMR and those who did not, particularly at interim (PFS: 100% vs 18.3%) and EOT (PFS: 92.4% vs 42.8%) assessments. Strong correlations were found between TLR and DS at all-time points (correlation coefficient > 0.9, p-value under 0.001).

Conclusion: TLR is a valuable specific semi-quantitative measure for assessing treatment response and predicting outcomes in lymphoma patients.

Keywords: Lymphoma- 18F-FDG PET/CT -Tumor/Liver Ratio -Deauville Score

1. INTRODUCTION

Malignant lymphoma is regarded as the most prevalent hematological malignancy in adults and is ranked as the fourth most frequent adult malignancy, accounting for around 8.4% of all adult malignancies diagnosed yearly (1).

Despite advances in treatment modalities, accurate staging and response evaluation are crucial for optimum management of patient. Currently, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) is considered the gold standard in lymphoma management, playing a vital role in staging, response evaluation, and risk stratification (2,3).

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines classify DS 5 as an uptake above that of the liver in the presence of new disease locations percent (4). The interobserver agreement for positive readings with 5PS was only seventy-four to seventy-six (5). Research has evaluated the ideal ratio of lesion uptake to liver uptake as the criterion for determining PET positivity in order to enhance the 5PS scale.

The Tumor-to-Liver Ratio (TLR) is currently being suggested for assessing interim and final therapy FDG-PET/CT in lymphoma cases. The ratio offers significant advantages: it is unaffected by the administered activity and body weight, facilitates the conversion of a visual qualitative scale (e.g., 5p-DS) to a continuous semi-quantitative scale, and enables the assessment of FDG-PET/CT using a clearly defined semi-quantitative cut-off point (6-8).

This research aimed to evaluate the prognostic value of TLR in 18F-FDG PET/CT in lymphoma patients and assessing its role in the treatment response assessment and monitoring

1. Patients and methods

This cohort analytical research included 80 patients with 139 PET/CT study diagnosed with lymphoma (including non-Hodgkin and Hodgkin lymphoma), all referred to the Center of Clinical Oncology and Nuclear Medicine (NEMROCK) between April 2022 and May 2024.

Inclusion criteria: Adult patients (18-85 years), patients with histopathological and immunohistochemistry proven lymphoma, referred for assessment study, interim.... following 2 cycles of chemotherapy, end of treatment.....following six cycles of chemotherapy, available Follow ups after end of therapy (6 months), written informed consent will be acquired from all patients, ECOG ≤ 2 , all stages of lymphoma and nodal and extra-nodal.

Exclusion criteria: Cases less than eighteen years old, Liver infiltration by the disease, Pregnancy, follow up < 6 months, ECOG > 2 , T cell lymphoma, Patients who received chemotherapy in the last 2 weeks prior to the reserch, Cases who received radiotherapy in the last three months prior to the research, Cases who received GM-CSF in the last 15 days, Patients with large FDG extravasation at the injection site, double malignancy, Patients with resistant uncontrolled diabetes and incomplete data and images.

2. Methods

All patients were subjected to the following:

Each patient underwent a comprehensive clinical evaluation by a lymphoma-specialized oncologist, with detailed documentation of clinical history, including the onset and presence of B symptoms. Pre-therapy investigations included complete blood count, blood sugar levels, lactate dehydrogenase (LDH), liver function tests (AST, serum albumin and ALT), kidney function tests (creatinine and urea), and lymph node biopsy.

18F-FDG PET/CT scan

Patient preparation and technical consideration

Cases were prepared with regard to EANM guidelines for FDG PET/CT tumor imaging (version 2.0), involving fasting for at least four hours prior to receiving an intravenous dose of 18F-FDG (5 MBq/kg). To minimize muscle uptake, patients limited physical activity for 24 hours before the scan and were kept in a relaxed, warm state, avoiding talking, chewing, or swallowing. Blood glucose concentration was confirmed to be below 200 milligrams per deciliters. Patients also received 500 milliliters of water and were instructed to void frequently before positioning on the PET/CT table.

Image acquisition and reconstruction

Imaging was performed using the Ingenuity TF 64 PET/CT scanner (Philips Healthcare), which combines a LYSO-based PET system with a 64-slice CT component. The PET system features a 90 cm ring diameter, 18 cm axial field of view, and 28 detector modules, utilizing TOF-OSEM reconstruction algorithms with list-mode data acquisition. Imaging began 45–65 minutes post-intravenous 18F-FDG injection (mean 55 minutes), with patients positioned arms-up when possible, scanned from skull to upper thighs. PET was acquired caudocranially over approximately 9 bed positions (1.5–2 minutes each), followed by high-dose CT for anatomical correlation. Patients fasted, remained still, breathed shallowly, and were scanned in a relaxed state. The system supports multiple FOVs and reconstruction types, and scanner calibration is conducted quarterly with bimonthly SUV validation, ensuring quantitative accuracy.

Image analysis

Qualitative Imaging: FDG PET/CT scans were visually interpreted by two nuclear medicine doctors with 8 years of experience. A positive outcome has been defined as focal FDG uptake above surrounding tissue intensity, not attributable to benign or physiological processes, and correlating anatomically with abnormal findings.

Semi-Quantitative Measurement with PET: PET imaging provided quantitative assessment of radiotracer uptake, primarily using the maximum standardized uptake value (SUVmax), normalized to body weight. Regions of interest (ROIs) were drawn semi-automatically on axial images around the main pathological lesion, with manual adjustments to avoid adjacent FDG-avid structures. In multifocal disease, measurements focused on the largest lesion. SUV was calculated as $(\mu\text{Ci/gram in tissue}) / (\text{total mCi injected} \times \text{body weight})$, with SUVmax defined as the highest voxel value. Tumor-to-liver ratio was derived by dividing the tumor SUVmax by the liver SUVmax. Liver ROIs were 3 cm spheres placed within the right lobe, avoiding vessels and edges, and mediastinal blood pool ROIs were drawn just above the aortic root, excluding vessel walls and calcifications. ROI sizes were guided by PERCIST criteria. In cases with no detectable lesions, SUVmax

was taken as the average homogeneous FDG uptake of the organ. Only SUVmax was used to prevent errors associated with other SUV parameters like SUVmean or SUVpeak.

18F-FDG PET/CT Response Criteria

Evaluation of response depending on 18F-FDG PET/CT relies on metabolic activity, characterized by 18F-FDG uptake, with the Standardized Uptake Value (SUV) serving as a key metric. Response assessment is guided by visual analysis using a five-point scale, incorporating the Deauville criteria for interim, post-treatment, and monitoring 18F-FDG PET/CT scans (5):
DS1: uptake
DS2: Uptake ≤ Mediastinu, DS3: Uptake > Mediastinum but ≤ Liver, DS4: Slightly to moderately increased uptake compared to the liver, DS5: Markedly elevated uptake compared to the liver ($\geq 2 \times$ liver uptake) and/or presence of new lesions, Dx: Novel areas of uptake unlikely related to lymphoma. Depending on this scale, four response groups are defined: (a) Complete metabolic response—score of 1, 2, or 3, (b) Partial metabolic response—score of 4 or 5 with diminished 18F-FDG uptake, (c) Stable Disease—score of 4 or 5 without significant alteration in 18F-FDG uptake and (d) Progressive metabolic disease—score of 4 or 5 with elevated 18F-FDG uptake or newly developed lesions. In interpreting the five-point scale, scores of 1 or 2 are regarded as negative for lymphoma, whereas scores of 4 or 5 are deemed positive. A score of 3 may additionally represent a complete metabolic response during interim PET/CT, indicating a favorable prognosis and is therefore commonly interpreted as negative (9).

Follow-up Protocol

Clinical and monitoring information have been obtained from patient records at NEMROCK to evaluate therapeutic response, with a monitoring duration of 6 months' post-therapy. Progression-free survival was defined as the time from the 1st chemotherapy cycle to the 1st sign of disease progression (8), while overall survival referred to the time from diagnosis to death (132); however, overall survival could not be assessed in this study due to the absence of mortality events during the follow-up period.

Statistical methods

Data were statistically characterized using mean \pm standard deviation (\pm SD), median and range, or percentages and frequencies (number of cases) as suitable. Numerical information was evaluated for normality utilizing the Kolmogorov-Smirnov test. The Mann Whitney U test has been utilized to compare the research groups as independent samples. The correlation among numerous variables has been conducted utilizing the Spearman rank correlation equation. Accuracy has been represented by the terms specificity and sensitivity. Receiver operator characteristic (ROC) analysis has been utilized to ascertain the optimal cutoff value for the Tumor to Liver Ratio. Survival analysis has been conducted for several results measures utilizing Kaplan-Meier statistics to calculate the mean and median survival times for each group, along with their ninety-five percent confidence intervals and related survival graphs. The Log rank approach, utilizing the Cox-Mantel equation, has been utilized to compare multiple factors. Two-sided p-values below 0.05 have been deemed statistically significant. Statistical analyses were conducted utilizing IBM SPSS (Statistical Package for the Social Sciences; IBM Corp, Armonk, NY, United States of America) version 22 for Microsoft Windows.

3. Results

Table (1): Clinical characteristics of 80 patients with lymphoma

Age	Range (19-70)	Mean \pm SD(40.22 \pm 14.69)
		%
Gender	Female	61.2
	Male	38.8
pathology	HL	43.8
	NHL	56.2
Subtypes	Nodular sclerosis	22.1
	Mixed cellular	14.7
	Lymphocytic rich	1.5
	DLBCL	58.8
	Marginal zone	2.9
Immunohistochemistry	CD20	95.7
	CD15	78.3
	CD30	62.1
	CD3	40.6

Ann Arbour Stage	I	2.5
	II	22.5
	III	38.8
	IV	36.2
LDH	Normal <250	27.1
	High >250	72.9
B symptoms	Negative	47.9
	Positive	52.1
Bulky disease	Negative	84.7
	Positive	15.3
IPI	Low	16.7
	Intermediate- high	83.3
IPS	Low	15.4
	Intermediate- high	84.6
1st line chemotherapy	ABVD	43.8
	RCHOP	56.2
2nd line chemotherapy	DHAP	4.1
	ESHAP	15.0

The research involved 80 cases with a mean age of 40.22 years and a female predominance (61.2%). The average weight was 77.39 kg. Hodgkin's Lymphoma (HL) was diagnosed in 43.8% of patients, with nodular sclerosis as the most common subtype. Non-Hodgkin's Lymphoma (NHL) was found in 56.2%, predominantly Diffuse Large B-Cell Lymphoma (DLBCL). Immunohistochemistry illustrated high positivity for CD20 (95.7%), followed by CD15, CD30, and CD3. Prognostic scoring showed over half of both HL and NHL patients were in intermediate to high-risk categories. B symptoms were present in 52.1% of patients, while 84.7% did not have bulky disease. Elevated LDH levels were observed in 72.9% of cases. According to Ann Arbor staging, most cases were in stage III or IV. First-line treatment included ABVD in 43.4% and R-CHOP in 56.6% of patients. Fourteen patients required second-line chemotherapy, mainly ESHAP. (Table 1)

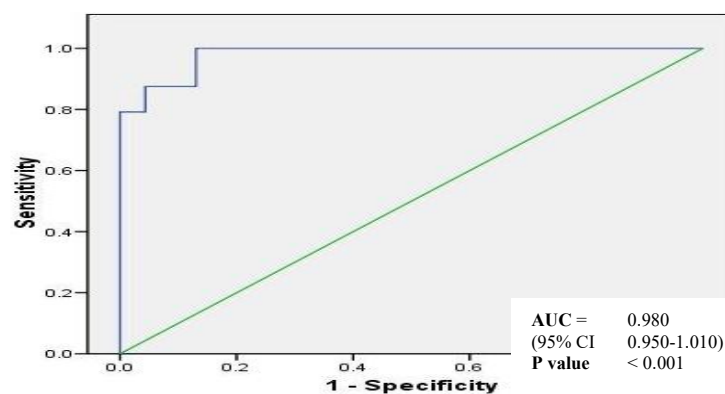


Fig (1): ROC Curve for interim TLR in expecting CMR

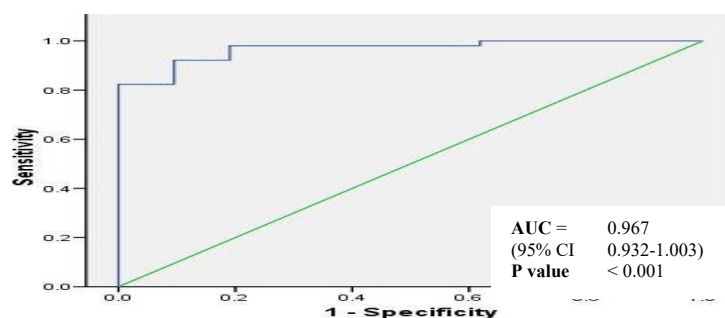


Fig 2: ROC Curve for EOT TLR in expecting CMR

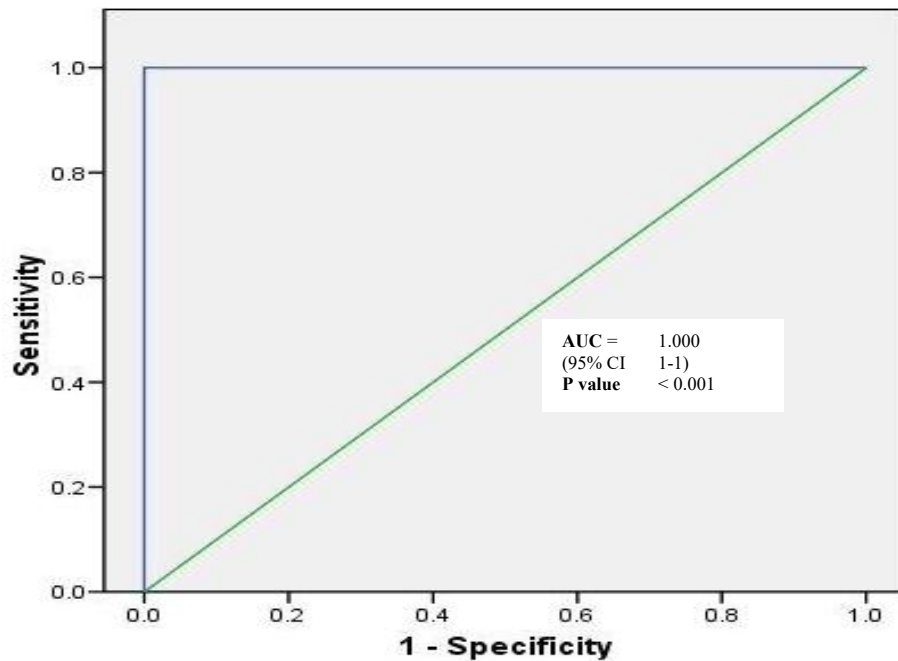


Fig (3): ROC Curve for follow up TLR in expecting CMR

Table (2): Prognosis accuracy of TLR in different time point

TLR	Outcome	Cut off	TP	FN	TN	FP	Sensitivity	Specificity	(+)ve PV	(-)ve PV	Accuracy
Interim	CMR from others	1.111	21	3	22	1	87.50	95.65	95.45	88.00	91.49
EOT		0.959	44	7	19	2	86.27	90.48	95.65	73.08	87.50
Follow up		0.959	9	3	8	0	75.00	100.00	100.00	72.73	85.00

TP: true positive, FN: false negative, TN: true negative, FP: false positive, (+) ve PV: positive predictive value, (-) ve PV: negative predictive value

ROC curves analysis for TLR

This comprehensive analysis evaluates the effectiveness of TLR in predicting CMR and differentiating between various metabolic responses in lymphoma patients at different treatment stages. The results derived from both ROC (Receiver Operating Characteristic) curve analysis and specific cut-off point performance data.

Distinguishing CMR from other outcomes:

The Interim TLR (cut-off 1.111, AUC = 0.980) demonstrated excellent performance with high sensitivity (87.50%), specificity (95.65%), and accuracy (91.49%), along with very good positive and negative predictive values (95.45% and 88.00% respectively) (Fig. 8). The EOT TLR (cut-off 0.959, AUC = 0.967) showed strong performance, slightly lower than interim, with sensitivity 86.27%, specificity 90.48%, accuracy 87.50%, high positive predictive value (95.65%), but lower negative predictive value (73.08%) (Fig. 9). Lastly, the Follow-up TLR (cut-off 0.959, AUC = 1.000) achieved perfect discrimination with 100% specificity and positive predictive value, but had lower sensitivity (75%), accuracy (85%), and negative predictive value (72.73%) (Table 2)

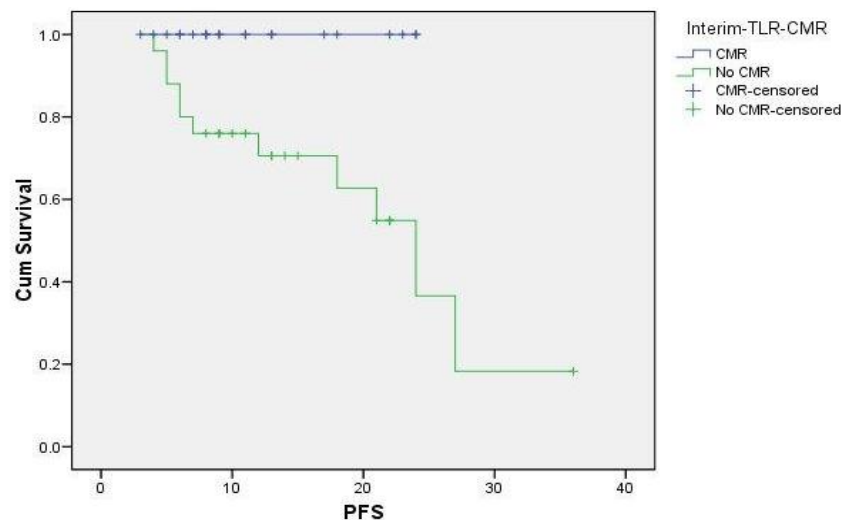


Figure (4): Kaplan-Meier analysis of PFS on interim TLR with regard to CMR vs no CMR/ PMR group

Patients achieving CMR (<1.11 cutoff point) showed significantly better PFS compared to those who did not (>1.11 cutoff point) (Log-rank $p=0.007$). The CMR group maintained a 100% PFS rate throughout the study period, with all cases censored, indicating no events occurred in this group, while the non-CMR group's cumulative survival decreased from 96.0% at 4 months to 18.3% at 27 months. The median survival time for the CMR group wasn't reached, as all patients remained event-free at the end of the study. For the No CMR group, the median survival time can be estimated to be around 21 months. The Log-rank test produced a p-value of 0.007, illustrating a statistically significant variance in the survival distributions among the CMR and No CMR groups. This suggests that patients achieving CMR had a significantly longer progression-free period compared to those who did not achieve CMR. (Figure 4)

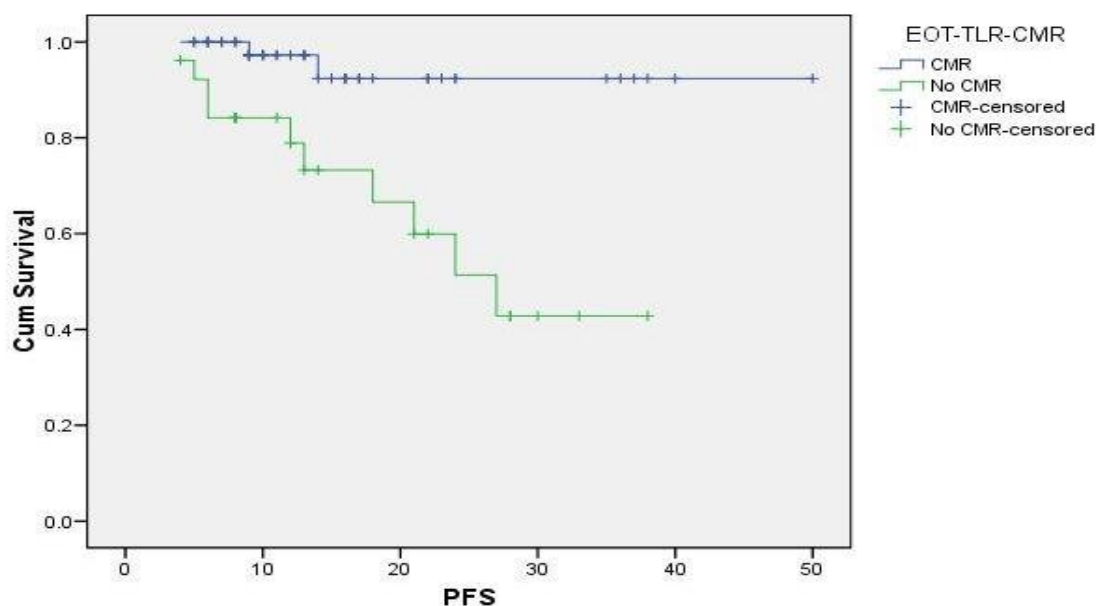


Figure (5): Kaplan-Meier analysis of PFS on EOT TLR according to CMR vs no CMR/ PMR group

CMR vs No CMR, the survival analysis illustrated that the CMR group (<0.959 cutoff point) had a higher PFS probability throughout the study period, starting at 97.2% at 9 months and declining to 92.4% at 14 months, with no further events recorded. The No CMR group (>0.959 cutoff point) showed a more rapid decline, from 96.2% at 4 months to 42.8% at 27 months. The median survival time for the CMR group wasn't reached, meaning over 50% of patients were still event-free at the end of the research, while for the No CMR group it was 27 months. This suggests that patients achieving CMR had a longer progression-free period compared to those who did not achieve CMR. The p-value was 0.002, which illustrated that there was a highly significant variance in the survival distributions between the CMR and No CMR groups. (Figure 5)

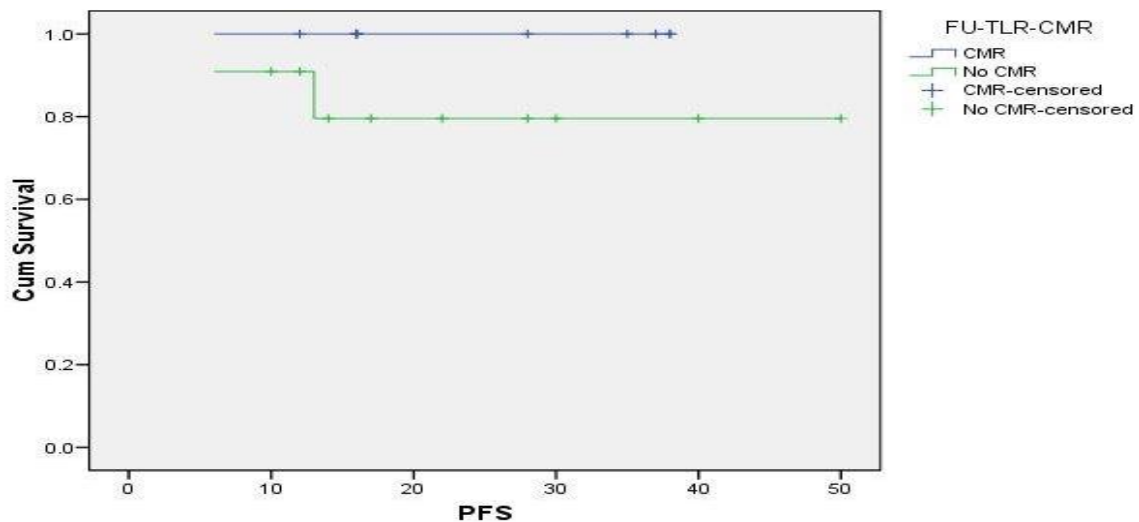


Figure (6): Kaplan-Meier analysis of PFS on follow up TLR according to CMR vs no CMR groups

CMR vs No CMR: The survival analysis illustrated that the CMR group (<0.959 cutoff point) maintained a 100% PFS probability throughout the study period, with no events recorded. The No CMR group (>0.959 cutoff point) showed a decline in PFS, starting at 90.9% at 6 months and dropping to 79.5% at 13 months, with no further events recorded after that point. The median survival time for the CMR group wasn't reached, meaning over 50% of patients were still event-free at the end of the research. For the No CMR group, the median survival time was also not reached, as only 2 out of 11 patients experienced events. This suggests that patients achieving CMR might have had a longer progression-free period compared to those who did not achieve CMR. However, the p-value was 0.178, which indicates that the difference in survival distributions between the CMR and No CMR groups didn't reach statistical significance. The high censoring rate (90% overall) suggests that longer follow-up or a larger sample size might be needed to detect significant differences between the groups. (Figure 6)

Correlation Analysis between TLR and Deauville Score at Different Time Points

The analysis used Spearman's rho correlation coefficient. All three time points showed very strong, positive correlations between TLR and DS (high correlation coefficient), with all correlations being highly statistically significant. This suggested a consistent and strong relationship between these two indices throughout the course of treatment and follow-up (table 3).

Table 3: Correlation Analysis between TLR and DS at Different Time Points

			Interim-TLR	EOT-TLR	FU-TLR
<i>Spearman's rho</i>	Interim-DS	Correlation Coefficient	0.910		
		p value	<0.001		
		N	47		
	EOT-DS	Correlation Coefficient		0.910	
		p value		<0.001	
		N		72	
	FU-DS	Correlation Coefficient			0.934
		p value			<0.001
		N			20

4. Discussion

This research aimed to assess the prognostic value of TLR in F18 FDG PET/CT in lymphoma cases and its important roles in the follow up and evaluation response to therapy.

TLR ratio is a semi-quantitative method which is numerical and more objective. TLR could have certain technical and methodological advantages over visual analysis. It is independent from the subjective image contrast and intensity, converts

a visual scale into a semi-quantitative scale, and it illustrates a well-defined semi-quantitative cut-off point (10–12).

Our ROC curve analysis demonstrated excellent performance of TLR in distinguishing CMR from other outcomes, particularly at interim (AUC = 0.980, cut-off 1.111), EOT (AUC = 0.967, cut-off 0.959) and follow up (AUC = 1, cut-off 0.959) time points. The TLR demonstrated high sensitivity (87.50% for interim, 86.27% for EOT and FU 75%), specificity (95.65% for interim, 90.48% for EOT and FU 100%) and accuracy (91.94% for interim, 87.5% for EOT and FU 85%) in predicting CMR. These results highlight its potential as a robust prognostic tool.

Only Toledano et al. (10) and Zhang et al. (12) have analyzed the added value of TLR at both interim and EOT PET/CT in DLBCL. Our findings are comparable to and in some instances superior to those reported in these studies.

Toledano et al. (10) illustrated the following results in interim (AUC = 0.769, cut-off 1.38-fold of SUVmax-liver) and EOT (AUC = 0.746, cut-off 1.36-fold of SUVmax liver) time points with sensitivity (51.6% for interim, 57.4% for EOT), specificity (98.1% for interim, 91.5% for EOT) and accuracy (74.85% for interim, 80.6% for EOT). These results were comparable to their Deauville Score (DS) findings with sensitivity (57.14% for interim, 58.06% for EOT), specificity (82.88% for interim, 88.35% for EOT) and accuracy (72.93% for interim, 76.96% for EOT).

Zhang et al. (12) reported at Interim, cut-off 1.6-fold of SUVmax-liver with sensitivity 44.00%, specificity 100% and accuracy 82.28%. EOT, cut-off 1.4-fold of SUVmax-liver with sensitivity 33.33%, specificity 100% and accuracy: 85.71%. Their DS results were similar at interim: sensitivity 52.00%, specificity 94.44%, accuracy 81.01%. EOT: sensitivity 33.33%, specificity 98.48%, accuracy 84.52% (12).

Our results demonstrate superior performance of the TLR compared to the previous studies, particularly in terms of overall discriminatory power (AUC) and sensitivity. Our study also maintains high specificity and accuracy.

Based on the results reported by Toledano et al. (10) and Zhang et al., (12) we can observe that the TLR and DS indeed show comparable performance in evaluating response to treatment in lymphoma cases. This suggests that TLR is a valuable tool in evaluating response to therapy in lymphoma cases.

Annuziata et al. (11) conducted two separate studies evaluating TLR in different lymphoma subtypes. The first study in 2016 focused on interim FDG-PET/CT in Hodgkin lymphoma and established a TLR cut-off point of 1.14 (AUC = 0.81, sensitivity 53%, specificity 95%) (140). The second study in 2018 examined FDG-PET/CT at the end of immuno-chemotherapy in follicular lymphoma and determined an optimum TLR cut-off point of 0.98 (AUC = 0.75, sensitivity fifty-three percent, specificity ninety-six percent). These cut-off points align closely with our findings, and while their specificity results were comparable to ours, we achieved notably higher sensitivity values in our study.

Adding to this body of research, Ferrari et al. (13) performed a ROC analysis in diffuse large B-cell lymphoma cases at the end of treatment, which identified an optimum TLR cutoff value of 1.80. This cutoff demonstrated a sensitivity of 58%, specificity of 95%, and accuracy of 80%, with an area under the curve (AUC) of 0.791. The cut-off point reported in this study is higher than the cutoff point used in our research. While their specificity is nearly comparable to our findings, their sensitivity is lower than what we observed in our study.

Various studies have investigated the use of various reference values extracted from the PET scans in a pattern similar to tumor-to-liver ratio on interim PET scans.

Kaplan-Meier survival analyses used in our study suggest greater accuracy of outcome prediction with TLR. The results revealed significant variances in progression-free survival (PFS) among patients achieving CMR compared to those who did not particularly at interim (where the PFS were 100% and 18.3% respectively) EOT (where the PFS were 92.4% and 42.8% respectively) assessments. This aligns with the findings from several studies (10–12,14).

The strong correlation we found between TLR and DS at all-time points (correlation coefficient > 0.9, $p < 0.001$) supports the potential of TLR as an objective numerical alternative to the visual Deauville score. This addresses concerns about inter-observer variability in visual assessments, as highlighted by many authors, and suggests that TLR could provide a more standardized approach to response assessment (10–12,14, 13, 15).

Collectively, these studies, along with our novel contributions, highlight the potential utility of tumor-to-liver ratio as a semiquantitative assessment tool across various lymphoma subtypes, treatment stages, and clinical outcomes. In addition, by offering valuable insights into treatment response and outcome prediction, the TLR approach may significantly improve patient stratification and lead to informed personalized treatment decisions in lymphoma care.

5. Conclusion

Our study demonstrates the potential of TLR as a valuable semi-quantitative measure for assessing treatment response and predicting outcomes in lymphoma patients. Its strong correlation with the visual Deauville score, combined with its objective numerical nature, suggests that TLR could serve as a robust tool for guiding treatment decisions in lymphoma management. While further research is needed to fully establish its clinical utility, TLR represents a promising step towards more personalized and effective lymphoma treatment strategies.

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