

Cerebellum/liver index in pretherapeutic ¹⁸F-FDG PET/CT as a predictive marker of progression-free survival in follicular lymphoma treated by immunochemotherapy and rituximab maintenance

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Abstract

The purpose of this study was to investigate the value of the “cerebellum/ liver index for prognosis” (CLIP) as a new prognostic marker in pretherapeutic ¹⁸F-Fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) in patients with follicular lymphoma treated by immunochemotherapy and rituximab maintenance, focusing on progression-free survival (PFS).

Clinicobiological and imaging data from patients with follicular lymphoma between March 2010 and September 2015 were retrospectively collected and 5-year PFS was determined. The conventional PET parameters (maximum standardized uptake value and total metabolic tumor volume) and the CLIP, corresponding to the ratio of the cerebellum maximum standardized uptake value over the liver SUVmean, were extracted from the pretherapeutic ¹⁸F-FDG PET.

Forty-six patients were included. Eighteen patients (39%) progressed within the 5 years after treatment initiation. Five-year PFS was 78.6% when CLIP was >4.0 and 42.0% when CLIP was <4.0 ($P = .04$). CLIP was a significant predictor of PFS on univariate analysis (hazard ratio 3.1, $P = .049$) and was near-significant on multivariate analysis (hazard ratio 2.8, $P = .07$) with ECOG PS as a cofactor.

The CLIP derived from pretherapeutic ¹⁸F-FDG PET seems to be an interesting predictive marker of PFS in follicular lymphoma treated by immunochemotherapy and rituximab maintenance. These results should be evaluated prospectively in a larger cohort.

Abbreviations: ¹⁸F-FDG = ¹⁸F-Fluorodeoxyglucose, ¹⁸F-FDG PET = ¹⁸F-Fluorodeoxyglucose positron emission tomography, CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone, CLIP = cerebellum/ liver index for prognosis, CT = computed tomography, CVP = cyclophosphamide, vincristine and prednisone., DICOM = Digital imaging and communications in medicine, ECOG = Eastern Cooperative Oncology Group, EOI = end of induction, FL = follicular lymphoma, FLIPI = Follicular Lymphoma International Prognostic Index, GELF = Groupe d'Etude des Lymphomes Folliculaires, HR = Hazard ratio, LDH = Lactate dehydrogenase, MTV = metabolic tumor volume, PET = positron emission tomography, PFS = progression-free survival, PS = performance status, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis, ULN = upper limit of normal.

Keywords: follicular lymphoma, positron-emission tomography, tumor burden

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Ethical approval: all procedures performed in study involving human participants were in accordance with the ethical standards with the 1964 Helsinki Declaration and its later amendments.

Informed consent and consent for publication: In accordance with French law, this retrospective study on medical records was authorized by the “Commission Nationale Informatique et Libertés” (authorization number 1118523), allowing the computerized management of the medical data at the university hospital. The participants were informed of the possibility of using the information concerning them, for biomedical research purposes, and had a right of opposition.

Availability of data and material: the data that support the findings of this study are available upon reasonable request from the corresponding author [DM]. Raw imaging data are not publicly available due to state restriction as they contain information that could compromise research participant privacy.

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma subtype behind diffuse large B-cell lymphoma and accounts for approximately 20% to 25% of all cases in Western Europe and the United States.^[1] Most of the time, FL only spreads to lymph nodes, but can also involve spleen, bone marrow, Waldeyer's ring, or peripheral blood. The diagnosis of FL is based on histological analysis and its classification depends on centroblast (germinal center proliferating B cells) and centrocyte (nondividing progeny of centroblasts) counts. The World Health Organization (WHO) classification divides FL into grades 1–2 and 3 according to the number of centroblasts, with a subdivision into grades 3A and 3B depending on the presence of centrocytes (3A) or solid sheets or entire follicles comprised of centroblasts (3B).^[2] Grades 1–2 and 3A FL are considered indolent and incurable, whereas grade 3B are considered and treated as diffuse large B-cell lymphomas.^[3]

Some criteria, including GELF criteria, are used to define FL patient populations who warrant immediate initiation of cytotoxic chemotherapy versus patients eligible to a delayed or even a “watch and wait” approach.^[4] When a treatment is indicated, approaches using chemotherapy combined with rituximab—a chimeric monoclonal antibody directed against the protein CD20 found on the surface of B cells—have led to a remarkable improvement in survival and are widely accepted as a standard of care.^[5–9] The type of chemotherapy varies but often consists in an association of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP).^[8] However, a subset of about 20% have disease progression within 2 years and a 5-year overall survival (OS) of only 50%.^[10]

The main objective of conventional computed tomography (CT) is to determine patients with a high tumor-burden FL.^[11] ¹⁸F-Fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) coupled with CT imaging is recommended when a therapy is needed^[12,13] for initial staging and response evaluation as it is considered as the most accurate modality for end-of-treatment assessment.^[13]

Studies have tried to identify good prognosis factors and scores with clinical, biological or histological data such as the Follicular Lymphoma International Prognostic Index (FLIPI)^[14] and FLIPI 2,^[15] or based on the PRIMA cohort (PRIMA PI).^[16] Functional imaging can also provide valuable information to predict the risk of recurrence. Indeed, a study suggested that baseline metabolic tumor volume (MTV) above the threshold of 510 cm³ was a risk factor for recurrence.^[17] However, MTV is not performed in routine practice yet, as it is time consuming and still needs to be validated.^[18,19]

One study has highlighted a negative linear correlation between the cerebellum physiological uptake and the total lesion glycolysis (TLG) in patients with non-Hodgkin lymphoma,^[20] thus suggesting that the cerebellum uptake could act as a reflect of the metabolic volume. Measurement of the cerebellum uptake could then act as a substitute for the cumbersome measurement of MTV.

Accordingly, we hypothesized in this study that the ratio of cerebellum uptake normalized using the liver as a reference organ and measured on the baseline PET could be a predictive marker of progression-free survival (PFS) in follicular lymphoma treated by immunochemotherapy and rituximab maintenance.

2. Material and methods

2.1. Study population

All patients with high tumor burden FL treated between March 2010 and September 2015 in our center were retrospectively screened.

Inclusions criteria were: FL grade 1–2 or 3A, high tumor burden according to GELF criteria which includes ≥ 3 lymph nodes with a diameter of ≥ 3 cm or 1 node with a diameter of ≥ 7 cm,^[21] treated by immunochemotherapy for induction followed by rituximab as maintenance therapy, baseline PET performed within 5 weeks before treatment. Exclusions criteria were: age <18 years, cerebellum not fully included in pretherapeutic PET.

Clinical, biological, and imaging data recorded from the patients files were as follows: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), B symptoms, serum level of $\beta 2$ -microglobulin and of lactate dehydrogenase, red blood cell and thrombocyte counts, presence of circulating cells, longest diameter of the largest involved node, presence of an extra-nodal involvement, FLIPI and FLIPI 2 scores, maximum standardized uptake value (SUVmax) and MTV on baseline PET.

2.2. Follow-up and endpoint

The primary endpoint, PFS, was defined as the length of time between the initiation of the immunochemotherapy and objective disease progression or any cause of death. Progression was demonstrated based on clinical examination (B symptoms or palpable adenomegaly), or imaging. CT scan follow-up was scheduled every 6 months during treatment and once a year after that.

2.3. PET protocol

Baseline PET/CT was performed in 2 different centers. All patients underwent a skull-base to proximal thigh acquisition. For center 1, PET/CT was acquired after the administration of 5 MBq/kg of ¹⁸F-FDG on a Gemini Dual GS system (180 seconds per position, reconstruction algorithm: 3D RAMLA, no time of flight). For center 2, PET/CT was acquired after the administration of 3 MBq/kg of ¹⁸F-FDG on a Gemini TF 16 system (120 seconds per position, reconstruction algorithm: Blob_OS-TF with time of flight). Capillary blood sugar and time to acquisition were also collected.

2.4. PET data collection

The following data were collected from attenuation corrected PET acquisition on a dedicated interpretation console (AW Server, General Electric, Milwaukee, WI): SUVmax, total metabolic tumor volume (MTV), cerebellum SUVmax, Liver SUVmean. Lesions were identified by a visual assessment with PET images scaled to a fixed SUV display range (0–10) and color table. MTV was obtained by summing the metabolic volumes of all nodal and extra nodal lesions according to the method detailed by Meignan et al^[17] (41% SUVmax threshold, bone marrow involvement was included only if there was focal uptake and spleen was considered as involved if there was focal uptake or diffuse uptake >150% of the liver background).

The SUVmax of the cerebellum was measured using an enclosing region of interest (ROI), excluding any voxel of the adjacent brain. Hepatic SUVmean was determined using the

default ROI available: 72cm³ cubic ROI (41% SUVmax threshold). This ROI was positioned manually in the right liver.

Cerebellum liver index for prognosis (CLIP) was calculated as the ratio of the cerebellum SUVmax by hepatic SUVmean.

2.5. Statistical analysis

Statistical analyses were performed on a dedicated software (R, version 3.4.1; R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Student *t* test was used to compare the CLIP value between center 1 and center 2. A ROC curve was drawn to determine the optimal threshold with respect to a 5-year PFS based on Youden index maximization. Patients' characteristics along CLIP threshold were compared using 2-proportion *Z* test.

Univariate analysis was performed for the following parameters: ECOG PS >1, male, FLIPI ≥3, β2-microglobulin >3 mg/L, SUVmax, T-MTV >510 cm³, the center number, the CLIP according to the threshold calculated using the ROC curve. Patients with missing values were discarded for each test.

Significant parameters with a *P* < .05 at univariate analysis were integrated in a multivariate Cox analysis to estimate hazard ratios (HR) and their 95% confidence intervals (95% CI). Survival functions and 95% CIs were calculated using Kaplan–Meier estimates for CLIP. The Logrank test was applied to compare these curves. Pearson correlation test was performed between CLIP and MTV and between cerebellum SUVmax and MTV.

Two nuclear medicine physicians, including 1 senior (9-year experience) and 1 junior calculated the CLIP for each patient. Based on the previously estimated CLIP threshold, patients were then categorized as good or poor prognosis. The reproducibility of this classification was assessed by Cohen kappa test. We retained the most unfavorable of the 2 readings for statistical analysis. *P* values < .05 were considered statistically significant.

3. Results

3.1. Population

Sixty-one patients were eligible for the study. DICOM data were missing for 8 patients and 7 patients were excluded because cerebellum was not fully included in the field of view of the baseline PET. The final population was composed of 46 patients including 30 men and 16 women (median age 61.5, range 29–85 years). Almost all patients were treated by R-CHOP (91%) followed by a maintenance treatment, 1 was treated with Rituximab-CVP and 3 were treated with Rituximab-Bendamustine. The median follow-up was 1535 days, that is >51 months. Eighteen patients (39%) progressed during the first 5 years after the initiation of the treatment.

The main clinical, biological, radiological, and nuclear medicine characteristics of patients are given in Table 1. The FLIPI, FLIPI 2, and PRIMA-PI scores were high for 25 (54%), 5 (24%), and 15 (47%) patients, respectively.

The median MTV on baseline PET was 382 cm³ (range 12–3171) and 19 patients (41%) had a MTV over the threshold of 510 cm³. Capillary blood sugar was 0.99 g/L (range 0.70–1.69) and median time to acquisition was 72 minutes (range 60–94).

3.2. CLIP

The CLIP was calculated as the ratio of the cerebellum SUVmax by hepatic SUVmean in pretherapeutic PET for all 46 patients.

Table 1

Baseline characteristics of the assessable patients.

Parameter	Total population (N = 46) (%)
Age, y	
Median (range)	61.5 (29–85)
>60 ans	26 (57)
Male sex	30 (65)
Histologic grade (n = 36)	
1–2	35 (97)
3A	1 (3)
B symptoms presence	9 (20)
ECOG PS >1	3 (7)
Ann Arbor stage III-IV	40 (87)
Hemoglobin level <12 g/dL (n = 41)	5 (12)
Thrombocyte count <150.10 ⁹ cells/L (n = 38)	6 (16)
Serum LDH greater than ULN	19 (41)
≥5 Nodal sites	27 (59)
β2-microglobulin >3 mg/L (n = 38)	15 (39)
Positive bone marrow biopsy (n = 26)	14 (54)
LodLIN >6 cm	20 (43)
Extranodal sites ≥1	24 (52)
FLIPI	
Low risk (0–1)	8 (18)
Intermediate risk (2)	13 (28)
High risk (3–5)	25 (54)
FLIPI 2 (n = 21)	
Low risk (0)	0 (0)
Intermediate risk (1–2)	16 (76)
High risk (3–5)	5 (24)
PRIMA PI (n = 32)	
Low risk (1)	9 (28)
Intermediate risk (2)	8 (25)
High risk (3)	15 (47)
SUVmax median (range)	10.3 (2.7–25.6)
MTV	
Median (range)	382 (12–3171)
>510 cm ³	19 (41)
Treatment details	
R-CHOP	42 (91)
R-CVP	1 (2)
R-Bendamustine	3 (7)
EOI PET	
Deauville's scale ≥4	8 (17)
Deauville's scale = 5	4 (9)
Progressive patient at 5 y	18 (39)
Deaths at 5 y	6 (4)

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone, EOI = end of induction, CVP = cyclophosphamide, vincristine and prednisone, FLIPI = Follicular Lymphoma International Prognostic Index, LDH = Lactate dehydrogenase, MTV = metabolic tumor volume, PET = positron emission tomography, SUVmax = maximum standardized uptake value.

Median CLIP was 3.85 (range: 2.15–6.64). No significant difference was observed between CLIP from center 1 and center 2 (*P* = .15).

An ROC curve was used to determine the optimal threshold to divide the population into 2 groups focusing on 5-year PFS (Fig. 1). The value of 4.0 was found to be the optimal threshold. The area under the curve was 0.63 (sensitivity of 0.54 and specificity of 0.78). The population was separated according to CLIP ≥4.0 or CLIP <4.0 (Table 2). In the category CLIP <4.0, 14 patients (56%) progressed whereas only 4 patients (21%) with a CLIP ≥4.0 progressed. No significant difference was found between the 2 groups regarding age, LDH levels, β2-microglobulin levels, or PET results. Sex ratio was significantly different with a predominance of male patients in the CLIP <4.0 group (Table 2).

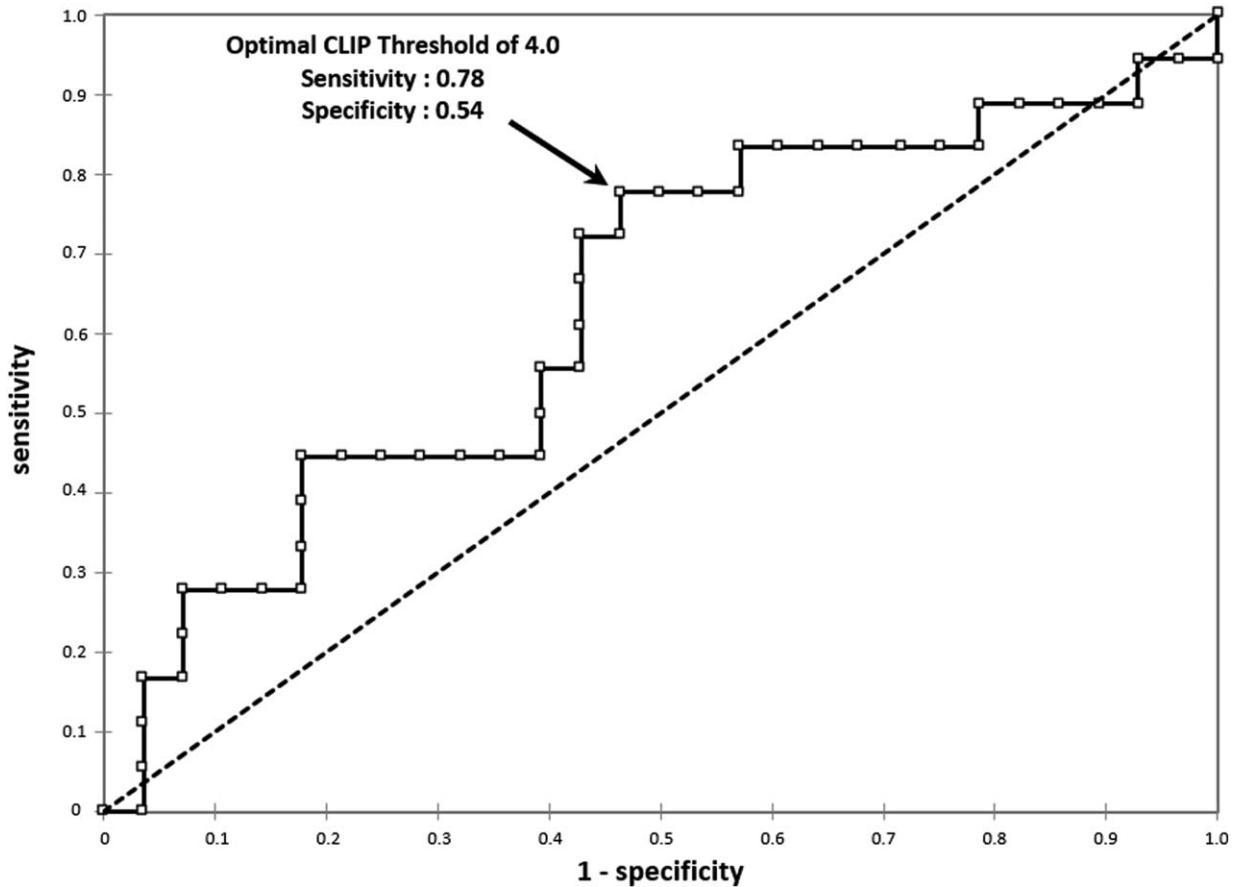


Figure 1. ROC curve for cerebellum/liver index for prognosis (CLIP) regarding 5-year progression-free survival.

Table 2

Patient characteristics according to the CLIP.

	CLIP <4.0	CLIP ≥4.0	P
Population	27	19	
Age, y			.89
Median (range)	65 (43–85)	61 (29–80)	
>60 y	16 (59)	10 (53)	
Sex			.01*
Male	22 (81)	8 (42)	
Female	5 (19)	11 (58)	
Elevated LDH	10 (37)	9 (47)	.69
β2-microglobulin >3 mg/L	11 (50)	4 (25)	.20
missing data	5	3	
FLIPI (3–5)	16 (59)	9 (47)	.62
SUVmax median (range)	9.5 [4.6–25.6]	10.7 (2.7–22.2)	
MTV			
Median (range)	371 (12–1850)	392 (25–3171)	
>510 cm ³	10 (37)	9 (47)	.69
EOI PET			
Deauville's scale ≥4	5 (19)	3 (16)	1.00
Deauville's scale =5	2 (7)	2 (11)	.32
Median PFS, mo (range)	43.4 (2.1–60.8)	60.8 (4.6–60.8)	
Progressive patients at 5 y	14 (56)	4 (21)	.05*
Deaths at 5 y	5 (19)	1 (5)	.33

CLIP = cerebellum/ liver index for prognosis, ECOG = Eastern Cooperative Oncology Group, EOI = End of induction, FLIPI = Follicular Lymphoma International Prognostic Index, LDH = Lactate dehydrogenase, MTV = metabolic tumor volume, PET = positron emission tomography, SUVmax = maximum standardized uptake value.

* Statistically significant.

Table 3
Factors associated with 5-year PFS in univariate and multivariate analysis.

	Univariate		Multivariate	
	P	HR (95% CI)	P	HR (95% CI)
Male sex	.06	3.3 (0.96–11.5)	—	—
PS ECOG >1	<.001*	13.8 (3.4–56.8)	.001*	12.0 (3.0–48.6)
FLIPI (3–5)	.41	1.5 (0.63–3.9)	—	—
β2-microglobulin >3 mg/L	.18	2.0 (0.74–5.2)	—	—
MTV >510 cm ³	.20	1.8 (0.7–4.6)	—	—
CLIP <4.0	.049*	3.1 (1.01–9.4)	.07	2.8 (0.9–8.8)
Baseline PET center	.97	0.99 (0.43–2.3)	—	—

CLIP = cerebellum/ liver index for prognosis, ECOG = Eastern Cooperative Oncology Group, FLIPI = Follicular Lymphoma International Prognostic Index, MTV = metabolic tumor volume, PET = positron emission tomography, PFS = progression-free survival.

*Statistically significant.

3.3. Univariate analysis

Scores described in the literature and in clinical routine were tested (Table 3). ECOG PS >1 was significant with $P < .001$ and HR of 13.8 (3.4–56.8). CLIP <4 turned out to be significant ($P = .05$; HR 3.1 [1.0–9.4]). The male sex was near-significant ($P = .06$). All other parameters, including MTV >510 cm³, β2-microglobulin >3 mg/L, or FLIPI “high risk,” were not significant.

Five-year PFS was 78.6% (60.0–97.2) for the subgroup CLIP ≥4 and 42.0% (21.5–62.9) for the subgroup CLIP <4 ($P = .039$), as illustrated in Figure 2.

No linear correlation between CLIP and MTV was found ($P = .31$) nor between cerebellum SUVmax and MTV ($P = .49$).

3.4. Multivariate analysis

Only ECOG PS >1 was significant (HR: 12.0, $P = .001$). CLIP <4 was near-significant (HR: 2.8; $P = .07$). Results are presented in Table 3.

3.5. Reproducibility

The classification of patients based on the CLIP showed an excellent interobserver agreement (Cohen kappa test: 0.95). The average difference between the 2 readers was 0.002 for cerebellar SUVmax and 0.02 for hepatic SUVmean.

4. Discussion

The main novelty of this study was the use of a completely new index based on the cerebellar and liver uptake as a surrogate marker of PFS in FL. Indeed, the CLIP calculated on baseline PET was a significant predictor of 5-year PFS at univariate analysis ($P = .05$; HR 3.1 [1.0–9.4]): 42.0% when CLIP <4 and 78.6% when CLIP ≥4.

CLIP was however only near-significant on multivariate analysis ($P = .07$) and did not seem suitable for the prediction of 2-year PFS as the 2 survival curves (CLIP <4.0 and CLIP ≥4.0) diverged after 2 years. These drawbacks are presumably due to a lack of power of the study.

The CLIP was based on the hypothesis that cerebellar FDG uptake could be a reflection of total tumor burden and could serve as a substitute of MTV. Indeed a previous article about aggressive lymphomas^[20] found an inverse correlation between cerebral and cerebellar uptake and TLG, product of MTV and SUVmean. The underlying explanation for this phenomenon could be a metabolic stealing process by the large tumor mass.^[20]

Contrary to our expectations, CLIP does not seem to be correlated with the MTV ($P = .31$). Explanations for the difference of results between Hanaoka's study^[20] and ours may include the use of MTV over TLG, the difference of population (FL vs aggressive lymphomas) and a possible lack of power.

CLIP interobserver reproducibility was excellent, and thus independent from the difference of experience of the 2 readers: only 1 patient, without progression within 5 years, was reclassified as good prognosis (CLIP ≥4) by observer 2.

As CLIP was based on cerebellar uptake, any factor influencing cerebellar uptake could impair its performances. A meta-analysis published in 2019^[22] highlighted a statistical association between the glycemia and the cerebral SUVmax (negative linear correlation: $P < .001$; $R^2 = 0.18$) and the hepatic SUVmean (positive linear correlation: $P < .001$; $R^2 = 0.05$). The correlation coefficients are however very low, even if the correlations are statistically significant. The median blood sugar level was 0.99 g/L (range 0.7–1.69) in our study with only 3 patients whose blood sugar was >1.5 g/L. A negative linear correlation between age and uptake of the cerebral and cerebellar parenchyma has also been reported.^[23] However, the cerebellum is one of the least affected areas.^[23] Some toxic substances, such as high doses of alcohol, can cause a reduction in the uptake of cerebellar parenchyma,^[23] but such circumstances were not encountered in our study due to the mandatory fasting period. The cerebellum uptake may be distorted by neurodegenerative pathology but cerebellum involvement is rare in such diseases.

ECOG PS >1 was a significant predictor PFS. This result is in accordance with the literature as ECOG PS is frequently integrated to risk factor models in LF.^[24] However, the “high risk” FLIPI score was not found as significant in our study. This score, reported in 2004,^[14] was however originally designed based on overall survival. The FLIPI 2 and PRIMA-PI scores, despite their validity in the literature could not be systematically obtained due to the fact that bone marrow biopsy was no longer systematically recommended^[25]: these scores could not be calculated for 25 (54%) and 14 patients (30%), respectively. Conversely, β2-microglobulin, one of the parameters of the PRIMA PI score could be studied but was not significant at univariate analysis.

By contrast to previous publications,^[17,26] MTV using the 41% thresholding method is not significant. The median MTV in our study (382 cm³–41% patients above 510 cm³) are within the upper limits compared to other studies: 116 cm³ (8%)^[27]; 354 cm³ (38%)^[28]; and 297 cm³ (29%).^[17] This variability despite an

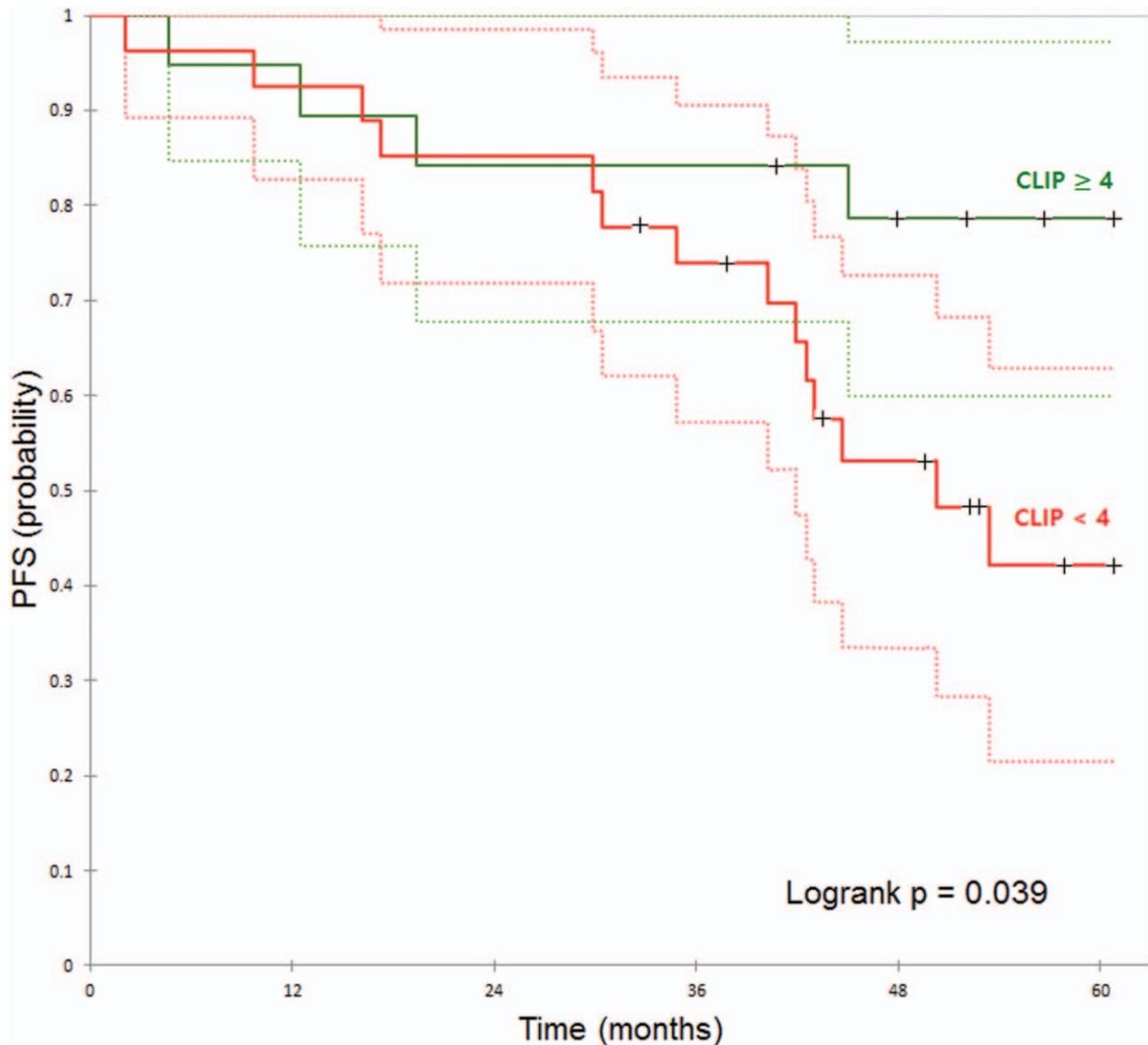


Figure 2. Progression-free survival (PFS) according to cerebellum/liver index for prognosis (CLIP) score in 2 classes (<4, ≥4). Red: CLIP <4; green: CLIP ≥4.

identical methodology might highlight reproducibility difficulties in MTV measurement.

Some limitations to this study must be acknowledged. Our results are limited by the small sample size and will require larger studies to be confirmed. SUV might vary from one PET system to another^[29] and the CLIP was calculated on 2 distinct machines in this study. There was no difference between the 2 centers in terms of CLIP measurement: the normalization of the cerebellar uptake by the hepatic SUVmean probably limited the variability of the CLIP measurements. However, the extrapolation of these results to new generations of PET, which are more sensitive and likely to provide higher SUV, is questionable.

5. Conclusion

CLIP in baseline ¹⁸F-FDG PET seems to be a promising tool to identify patients with a good prognosis in follicular lymphomas treated by immunochemotherapy and rituximab maintenance. It is a simple score to calculate and it is reproducible. Larger studies will be needed to confirm these results.

Author contributions

FG: data curation, formal analysis, original draft

ED: data curation, formal analysis, supervision, review and editing

CD: data curation, review and editing

CH: supervision, review and editing

AD: supervision, review and editing

DM: conceptualization, project administration, data curation, formal analysis, review and editing

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