Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH

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Deauville score versus ratio Deauville score in the interpretation of interim 18F-FDG PET-CT and in prediction of outcome in children with FDG-avid extra-nodal lymphomas

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Abstract

Background: Pediatric lymphoma is a common hematological neoplasm, representing the third most frequent childhood malignancy. 18F-fluoro-2-deoxyglucose–positron emission tomography has been found to be useful in lymphoma staging, prediction of prognosis and risk stratification of lymphoma patients. Although the interpretation of interim PET (after two cycles of chemotherapy) using the qualitative visual method of 5-point Deauville score has been widely accepted, semiquantitative methods of interpretation were evaluated by many studies and showed a better prediction of prognosis. The purpose of this study was to evaluate the prognostic role of the semiquantitative ratio Deauville score (rDS), defined as the ratio between target lesion and liver maximum standardized uptake values in children with FDG-avid extra-nodal lymphomas, undergoing interim FDG-PET/CT, and to compare it with the 5-point Deauville score (5p-DS).

Methods: This prospective study included 89 children with FDG-avid extra-nodal lymphoma. Interim PET was interpreted using both visual (5p-DS) and the semiquantitative method (rDS). The visual method depends on visual comparison of FDG uptake between lesions and liver as a reference organ for activity and considered lesions with activity higher than liver to be positive, while the semiquantitative method depends on making a ratio between the most active lesion and liver SUVmax. Receiver operating characteristic approach was applied to identify the optimal cut-point of rDS with respect to response to therapy and prognosis, and the prognostic significance of rDS was compared with 5p-DS.

Results: The ROC analysis for rDS as a predictor of progression showed an optimal cut-point of 1.25. Both 5p-DS and rDS were strong outcome predictors. Patients with negative 5p-DS and patients with rDS < 1.25 had a similar 3-year PFS (87%). Patients with a positive 5p-DS had a 3-year PFS of 67.4%, while patients with rDS > 1.25 had a 3-year PFS of 60%.

Conclusions: rDS could be suggested as an accurate prognostic factor in children with lymphoma undergoing interim FDG-PET/CT. However, larger studies with more homogenous sample regarding histopathological subtypes and chemotherapy lines are needed to confirm these data.

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Keywords: Deauville score, Ratio Deauville score, Interim 18F-FDG PET-CT, Outcome, Children, Extra-nodal lymphomas

Background

Pediatric lymphoma is a common hematological neoplasm, representing the third most frequent childhood malignancy [1]. During the past 2 decades, 18F-fluoro-2-deoxyglucose–positron emission tomography (FDG-PET) has been found to be useful in providing information about the metabolic activity in patients with lymphoma and has been utilized in lymphoma staging [2, 3].

Early evaluation of disease response to chemotherapy (CTH), using 18F- FDG PET, was found to be a surrogate marker of therapeutic outcome, and it has been found to be a useful tool for predicting prognosis and risk stratification of lymphoma patients that consequently has a crucial role in management of such cases. Also, it helped to minimize the side effects of therapy without losing treatment efficacy and reduce the number of chemotherapy cycles to the optimum for each individual patient [2, 4].

The interpretation of early response evaluation PET (interim PET done after two cycles of CTH) is a subject of ongoing debate. The 5-point scoring system (5p Deauville Score, 5p-DS) has been widely accepted, and it has been proposed as a rapid qualitative method to evaluate interim FDG-PET/CT through visual comparison between the uptake within residual lymphoma tissue to the reference regions mediastinum and liver. Many studies illustrated some disadvantages for that qualitative assessment, including its dependence on the amount of administered activity and body weight and high liability to inter-observer disagreement. Recently, a ratio between semiquantitative parameters (e.g., target lesion and liver SUV) has been proposed for interim FDG-PET/CT interpretation as it allows conversion of the visual qualitative scale to a continuous semiquantitative scale and permits evaluation of interim FDG-PET/CT through a well-determined semiquantitative-based cut-point [5].

The aim of this study is to evaluate the prognostic value of the ratio between target lesion and liver SUVmax (rPET/rDS) in children with lymphoma affecting extra-nodal sites who undergo interim FDG-PET/CT during the first-line chemotherapy and to compare rDS with 5p-DS.

Methods

This prospective study was performed during the period between January 2017 and November 2019. It included 92 children with pathologically proved lymphoma. Three patients were excluded from this study because one of them had tonsillar lymphoma (considered a nodal site), the second one had severe nasopharyngeal lymphoma with intracranial extension that needed urgent treatment without waiting for a baseline PET study, while the last child died after two cycles of CTH. All patients proved to have either extra-nodal lymphomatous lesion(s) without nodal involvement, called primary extra-nodal lymphoma, or with mixed nodal and extra-nodal lesions (secondary extra-nodal lymphoma). *Our study was approved by the ethical committee of Faculty of medicine, Cairo University, and the radiation safety committee of national cancer institute had given approval for study design.* The selection process included patients who fulfilled the criteria given below:

Inclusion criteria

Children less than 18 years, with pathologically proved FDG avid either Hodgkin or non-Hodgkin lymphoma; patients with lymphomatous extra-nodal involvement either primary or secondary; and whole-body FDG PET/CT study done at initial staging and after two cycles of CTH.

It is worth mentioning that stage 1 and 2 extra-nodal lymphoma were our main target group; however, during collection of data, we found only very small numbers of both stages, so we added stage 3 and 4 to have a representative sample size.

Exclusion criteria

Adults more than 18 years; lymphoma affecting only lymph nodes or lymphatic organs as spleen and Waldeyer's ring; lymphoma subtypes that are not FDG avid at the initial staging; relapsing lymphoma even if associated with extra-nodal involvement; patients with no baseline or interim PET/CT studies; life-threatening impairment of organ function; diabetes mellitus; and those who have double primaries.

All patients underwent conventional tumor staging procedures at baseline including careful history taking (including onset and presence of B symptoms), meticulous clinical examination (examination of all groups of lymph nodes, liver and spleen) and pre-treatment investigations (including complete blood picture, erythrocyte sedimentation rate, lactate dehydrogenase, liver, kidney function tests, lymph node biopsy as well as bone marrow biopsy if indicated. Patients were treated according to the hospital protocol in respect of their risk groups as follows: For Hodgkin's lymphoma, low-risk group

patients were treated with four cycles of ABVD + IFRTH, intermediate-risk group patients were treated with six cycles of ± IFRTH, and high-risk group patients were treated with eight cycles of ABVD. For non-Hodgkin's lymphoma, treatment depends on histological subtype as well as risk stratification. All patients were treated according to the modified (LMB 96) protocol.

Methods

Patient preparation

Patients were instructed to fast for 4–6 h before PET scanning. The blood glucose level should be less than 160 mg/dl. Patients received an intravenous injection of 5.55 megabecquerel (MBq)/kg (0.15 milli-Curie/kg) body weight dose of 18F-FDG (minimum dose, 74 MBq (2 mCi). Patients must sit still in a quite warm room. Sedation was used in most of the patients.

PET/CT imaging protocol

Image acquisition was started after 45- to 60-min period of uptake. CT was done from the base of the skull to the mid-thighs with the arm extended above the head. Intravenous contrast media was given in some studies. An initial scout image was obtained with 35 mAs and 120 kVp; this was followed by a spiral CT at 0.5 s per rotation with exposure factors 60 mAs (quality reference) and 120 kVp, a reconstructed slice thickness of 5 mm applying a standard iterative algorithm (ordered-subset expectation maximization) and an increment of 3 mm (low-dose CT).

Immediately after acquisition of the CT images, PET was performed (5–7 bed positions; acquisition time, 1–2 min/bed position), using a dedicated PET/CT scanner (GE, PET/CT Discovery). This camera integrates a PET scanner with a dual-section helical CT scanner and allows the acquisition of co-registered CT and PET images in one session.

Imaging Interpretation Images were interpreted at a workstation equipped with fusion software (advantage Window AW version 5, GE) that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images. Initial pre-treatment and interim FDG PET/CT were interpreted and compared with each other by two experienced nuclear medicine physicians blinded to patients' outcome with at least 8-year experience in the field of PET/CT interpretation. All images were qualitatively and quantitatively interpreted.

Initial PET/CT image

Qualitative parameters Any focal uptake, higher than mediastinal or hepatic reference, was interpreted as abnormal FDG uptake.

Quantitative parameters All parameters including standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated automatically by the boundaries of voxels presenting SUV more than 3.0 [6] on software (Planet Onco, version 2.0; DOSI Soft).

Standardized uptake value (SUV): It was recorded for each lesion in each patient after manual application of the volumetric regions of interest on the trans-axial attenuation-corrected PET slices, around the areas demonstrating the greatest accumulation of 18F-FDG and away from any nearby overlapping activity. Another sizable ROI was drawn over the normal liver where its max SUV was considered reference activity for further quantitative analysis to calculate max SUV lesion/max SUV liver ratio.

SUVmax is the count in the most active pixel in the VOI, and it was calculated from the counts per pixel and normalized to body weight (BW), using the following formulas: SUV(BW) = Tissue activity (KBq/ml) ÷ Injected activity (MBq)/weight (Kg), while SUVmean is the average of the counts in all pixels in the VOI.

Metabolic tumor volume (MTV): It was measured using a semiautomatic contouring software (GE TrueD) after applying a predefined threshold of the SUVmax value within the volume of interest (VOI). VOI is identified and drawn, for each lesion either nodal or extranodal lesion automatically for generating 3D iso-count contours using a fixed threshold of 40% of the SUVmax (V40%).

Total lesion glycolysis (TLG): It was automatically calculated by multiplying the selected PET volume (MTV) on the investigated lesions as mentioned above by the SUVmean within that volume [TLG = MTV X SUV mean].

Bone marrow was considered to be positive for active lymphoma if single or multiple foci of clearly elevated FDG uptake within the bone marrow were present, while diffuse bone marrow activity/uptake was considered negative. Clinical information regarding recent treatments was investigated to help in differentiation between treatment-induced increased hematopoiesis and true disease.

Also, GIT was considered to be positive for active lymphoma if single or multiple foci of clearly elevated FDG uptake were present in association with CT-detected thickening/mass. In patients whose GIT showed diffuse activity, meticulous interpretation of other findings such as the presence or absence of bowel masses, accompanied nodal or extra-nodal lesions as well as history of inflammatory bowel disease is included for final suggestion.

Interim PET/CT (early response evaluation)

Interim PET results have been interpreted using two different methods:

A. 5-Point scoring system (Deauville score)

Using Deauville score, which depends on the visual comparison of activity between residual lesion/s and reference activities (liver and mediastinum) (Table 1), we divided our studied patients into two groups (positive and negative early response PET). The positive group involved all cases with residual, stationary or progressive disease (DS4 and DS5), while the negative group involved all patients with complete metabolic regression and no residual active lesions (DS1 and DS2) [7].

B. Ratio between target lesion and liver SUVmax (rDS/rPET)

The rDS approach uses the strictly quantitative target-to-liver SUVmax ratio, without any connection to a visual analysis. The efficiency of the rDS approach in identifying patients with aggressive disease for improving their treatment management was determined by applying the receiver operating characteristic (ROC) analysis with respect to PFS.

For an rPET/rDS outcome of 1, that is, when the borderline equality target "SUVmax = liver SUVmax" is found in clinical practice, the corresponding metabolic uncertainty (MU) provides the upper and lower limits of the confidence interval around the outcome of 1 (CI; usually given with 95% reliability) where the "true rPET" value may range. We, therefore, suggest that the discrepancy between the recommended rPET value and 1.00 may be related to the rPET MU that should be taken into account [8, 9].

The follow-up period for all patients ranged between 6 and 40 months with a mean of 24 months. Meticulous clinical examination, follow-up CTs neck/chest/abdomen, and PET/CT were performed to all patients during the follow-up period with at least one follow-up PET study, while subsequent follow-up PET studies were done if clinically indicated. Progression-free survival (PFS) was the end point of our study.

Table 1 The 5-point scoring system (Deauville score)

Criterion 1	No uptake
Criterion 2	Uptake ≤ mediastinum
Criterion 3	Uptake > mediastinum but ≤ liver
Criterion 4	Uptake moderately more than liver uptake, at any site
Criterion 5	Markedly increased uptake at any site and new sites of disease

Statistical analysis

- Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of patients) and percentages when appropriate.
- Numerical data were tested for the normal assumption using Kolmogorov–Smirnov test.
- For comparing categorical data, chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5.
- Correlation between various variables was done using Spearman rank correlation equation. Two-sided p values less than 0.05 was considered statistically significant.
- Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables.
- All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.
- Kaplan–Meier survival curve was used to estimate PFS.
- Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables.
- The receiver operating characteristic (ROC) approach was applied to identify the optimal cut-point of rPET with respect to events, to calculate accuracy values and to define the area under the curve (AUC).
- A log-rank test was used to compare the survival probabilities between the two groups. All borderline significant variables were entered into a Cox regression model and Hazard ratios [HRs] were stated. P value was set significant at 0.05 level.

Results

Characteristics of the patients

From the 89 children with proved extra-nodal lymphoma, 66 (74.2%) were males and 23 (25.8%) were females. Their age ranged from 2 to 17 years with a mean of 9.66 ± 3.874 years. Non-Hodgkin lymphoma (NHD) was found in 55 patients (61.8%), while Hodgkin lymphoma was found in the remaining 34 patients (38.2%). Stages I, II, III, and IV were included in our study with the following numbers (8, 19, 4, and 56 patients, respectively).

Clinicopathological features based on interim negative* and *positive 5-point Deauville scoring system

The DS interim negative group included 65 patients, while the positive group included 24 patients. In the DS interim negative group, male children were 50/65 patients (representing 77% of interim negative group), while in the interim positive group, male children were 17/24 (representing 71% of interim positive group). The mean age of children in interim negative group was 11.2 ± 3.43, while the mean age of children with interim positive group was 9.33 ± 2.874. In interim negative group, 41 patients had NHD, while the remaining 24 patients had HD. Positive bone marrow biopsy was found in 25 patients, 10 of them were negative in interim PET, while the rest of them were interim positive. Clinicopathological criteria are summarized in Table 2.

GIT and BM were the most frequently involved extra-nodal sites. Involved extra-nodal sites are illustrated in Table 3. (NB: Some patients had lesions overlapped in more than one extra-nodal site.)

Baseline PET study detected marrow lesions in additional 17 patients who showed negative bone marrow biopsy (BMB). All of them were considered to be falsely negative at BMB because evidence of true disease was confirmed during subsequent follow-up and using complementary targeted magnetic resonance imaging, and/or

Table 2 Clinicopathological features of DS interim negative and positive groups

	Interim –ve (*N* = 65)	**Interim + ve (*N* = 24)**
Age	Range (3–17), mean 11.2 ± 3.43	Range (2–17), mean 9.33 ± 2.874
Sex	M: 50 F: 15	Male: 17 Female: 7
Pathological types	HD: 24 NHD: 41	HD: 9 NHD: 15
Most common subtypes	Burkitt's: 35 Nodular sclerosis: 13	Burkitt's: 12 Nodular sclerosis:7
B symptoms	Positive: 13	Positive: 8
BM biopsy	Positive: 10 (15.3%)	Positive: 15 (62.5%)
LDH	Range: (304–3859) Mean: 1683 ± 343	Range: (329–6382) Mean: 2867 ± 786

Table 3 Extra-nodal involved lymphoma sites in our study group

Extra-nodal site involved	**Total no.**	
	Only one extra-nodal system	**> One extra-nodal system**
GIT	42	
	25	17 (11BM, 2 kidney, 2 lung, 1 pancreas, and 1 testis)
BM	42	
	7	35 (11 GIT, 10 musculoskeletal, 7 kidney, 5 lung, and 2 testis)
Lung	13	
	0	13 (6 musculoskeletal, 5 BM, and 2 GIT)
Musculoskeletal	28	
	10	18 (10 BM, 6 lung, and 2 kidney)
Kidney	13	
	1	12 (7 BM, 2 GIT, 2 musculoskeletal, and 1 testis)
Testis	4	
	0	(2 BM, 1 kidney, and 1 GIT)
Pancreas	1	
	0	1(GIT)

local biopsy. (Local biopsy was done for 7 cases, targeted MRI was done for 6 cases, while in the last 3 cases, two of them showed regression of the disease in the form of partial response, while the last patient had progression of the disease.)

Semiquantitative parameters of studied cases

Metabolic parameters of the highest FDG-avid lesion were recorded for all studied cases as given in Table 4.

Follow-up after the end of therapy

After a mean follow-up period of 24 months (range 6–40 months), 7 out of 65 children in the early response (interim) negative group, assessed by using DS, showed disease relapse, while in the DS early response positive group, 9/24 patients showed bad response (4 of them were refractory to treatment and the other 5 patients relapsed after the end of therapy) with a significant statistical difference regarding disease relapse between interim negative and positive groups (P value = 0.002) as illustrated in Fig. 1 and Table 5.

More detailed criteria about patients who showed bad prognosis during follow-up in spite of negative interim PET are summarized in Table 6.

Survival outcome in DS negative and positive patients

To study the survival outcome in our study, we used the progression-free survival (PFS) as our study end point, while overall survival was not representative and cannot be calculated because of very low number of events (deaths) in our sample. For PFS calculation, we excluded 4 out of 24 patients of interim positive group because they were refractory to treatment (that opposed PFS definition). The survival outcome in the interim negative group was significantly better than that of the interim positive group with a 3-year PFS of the former group 87.2%, while the 3-year PFS in the latter group has 67.4% (P value = 0.002) as illustrated in Table 7 and Fig. 2.

Univariate analysis

We studied the effects of all studied clinical factors, such as the age, gender, pathological type/subtype, LDH, BM infiltration, B symptoms, different extra-nodal sites, number of involved extra-nodal sites in the initial PET study (single extra-nodal site, 2 extra-nodal sites, and >2 sites) as well as semiquantitative parameters in both initial and interim PET, on progression-free survival. We also divided interim positive patients according to the number of residual diseased sites in interim PET study into three groups (single residual, two sites, or multiple sites ≥ 3) and studied the effect of number of these residual sites on prognosis.

Table 4 Metabolic parameters of all studied cases

Case No.	SUVmax	MTV	TLG
1	30	64.7	1269.9
2	9.7	21.6	133.48
3	16	37.3	378.8
4	9.8	426.8	2607.2
5	15	92.3	868.7
6	1.6	12.1	16.7
7	28.2	60.8	774
8	11.6	49.9	268.3
9	7.6	26.5	111.2
10	31.1	59.7	1145.9
11	8.8	25	138.7
12	3.4	56.2	108.7
13	11.9	203.7	1374.9
14	12.5	23.3	211
15	11.6	663.4	4784
16	6.8	340	1502
17	17.6	6.5	73.3
18	13.6	39.3	287
19	10.3	12.8	89.3
20	8.2	195.6	1069
21	11.8	61.3	464.9
22	6.1	76.2	286
23	17	49.4	535.5
24	9.7	12.7	59.1
25	10	158.2	1198.2
26	7.2	2	9.4
27	5.2	35	255
28	6.3	39.6	132.3
29	5.8	5	10.7
30	6.5	3.6	13
31	18.2	4.4	53.9
32	11.1	26.4	189.7
33	13.3	2.4	18.7
34	3.2	1.9	1.7
35	5.6	2.6	12.2
36	6.8	8.5	32
37	15	8	77.7
38	18.2	8.8	104.5
39	18.5	9.8	11.2
40	10.1	4.2	24.9
41	9	20.4	102
42	10	124.6	826.3
43	9.8	3.8	22.6
44	22.9	555.8	8213
45	14.8	242	1921
46	7.2	13.4	52.9
47	4.8	2.8	43.5
48	8	60	280.9
49	20.4	26.5	333.3

Table 4 (continued)

Case No.	SUVmax	MTV	TLG
50	9.1	10	51.2
51	7.4	2.5	11
52	11	53.3	322
53	11.6	126	934.6
54	13.6	33.2	232.7
55	3.9	3.3	7.3
56	13.1	10.5	31
57	13.8	30	500
58	8	128.3	1176
59	14	8	33.4
60	25	145.3	1233
61	13	115	1640
62	12.7	78	1020
63	13.7	140	970
64	16.5	11	560
65	4.3	15.6	54
66	2.9	6.5	26.1
67	21	32.3	398
68	8.4	1.4	6.9
69	12.1	11.6	89.6
70	4.7	15.5	34
71	3.1	2.8	5.5
72	20.7	14.8	190
73	10.9	384	2349.7
74	15.7	3.5	31.3
75	8	3	25
76	15	8.7	88
77	16	8	66.2
78	15.7	222.3	2235.6
79	25.4	54.6	902
80	4.5	122.6	358.2
81	13.5	60.7	445.1
82	5	182.8	555.5
83	11.9	6.7	47.5
84	4.8	5	14.2
85	29.4	39.6	756.6
86	5.6	41	136
87	4.3	267	899
88	11.7	20.2	149.5
89	11.4	200	1100

Positive initial bone marrow biopsy, presence of B symptoms and the number of involved extra-nodal sites in initial PET, visual assessment of interim PET, and the number of residual diseased sites were significantly correlated with prognosis, while none of the semiquantitative parameters correlated significantly as illustrated in Table 8. Multivariate analysis was difficult to be done because of the limited number of significantly correlated factors in the univariate analysis.

Ratio Deauville score (rDS)

In a trial to compare the prognostic significance of visual and ratio Deauville score, we calculated rDS ratios in all patients and calculated the best cutoff value that may predict prognosis. The rDS values for patients with no residual lesions in interim PET were ≤ 1.13, while they ranged between 1.25 and 8.20 in interim positive group. The ROC curve showed two cutoff values (1.25 and 1.40): the first value (Fig. 3) showed a sensitivity of 91.7%, while and the second value showed a sensitivity of 83.3%. Both values had 100% specificity. The first cutoff was chosen, and it showed a significant statistical difference with the response at the end of therapy with a P value $= 0.009$ (the mentioned sensitivity and specificity are according to the ROC curve to specify the cutoff value) (Table 9).

Survival outcome in ratio Deauville score

Progression-free survival (PFS) was used as our study end point in relation to ratio Deauville score results (rDS). The survival outcome in the rDS group ≤ 1.25 (our selected cutoff value) was significantly better than that of rDS > 1.25 with a 3-year PFS of the former group 87.6%, while the 3-year PFS in the latter group was 60% as illustrated in Table 10 and Fig. 4.

Deauville and ratio Deauville score

In a comparison between Deauville and ratio Deauville score in interpretation of interim PET, the results were matched in all cases except in 2 patients who were positive in DS and negative in ratio Deauville score as showed in Figs. 5, 6, and 7. There was an agreement in almost all cases between the observers with no significant inter-observer differences, as the number was not enough for statistical calculations.

Univariate analysis in ratio Deauville score

We studied the effects of all studied clinical factors, as well as semiquantitative parameters in initial PET, in relation to the rDS. Bone marrow infiltration and the number of involved extra-nodal sites in initial presentation were significantly correlated with the ratio Deauville score (0.036 and 0.002, respectively). However, none of the semiquantitative parameters were correlated with rDS.

Discussion

Interim PET was proved to be a surrogate marker of therapeutic outcome, and it has been found to be a useful tool for predicting prognosis and risk stratification of lymphoma patients that consequently has a crucial role in management of such cases [2, 4]. For the interpretation

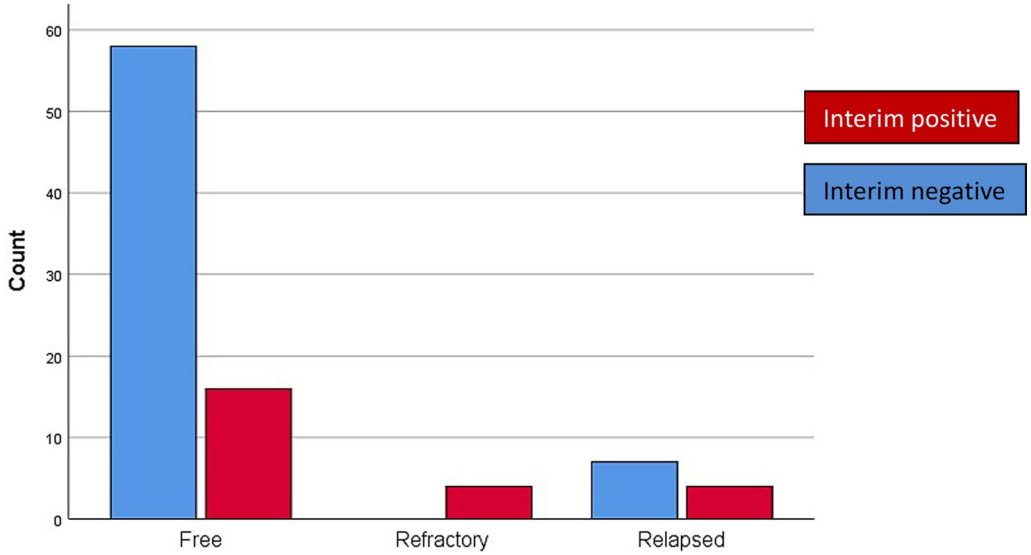

Fig. 1 Response to therapy in interim negative and positive group

Table 5 DS early response assessment and prognosis in extra-nodal lymphoma

	DS interim -ve (*N* = 65 patients)	DS interim + ve (*N* = 24 patients)	Total number (*N* = 89 patients)
Good response no.	58 (89.2%)	16 (66.6%)	74
Poor response			
Total no.	7	8	15
Relapsed	7 (10.8%)	4 (16.7%)	11
Refractory	0	4 (16.7%)	4

Table 6 Summary of DS-based interim -ve patients with disease relapse during follow-up

Total no.	7/65 (10.8%)
Sex	100% Males
No. of involved extra-nodal sites	5 Patients: > 1 involved extra-nodal sites 2 Patients: single involved site
Involved extra-nodal sites	1 Patient: Musculoskeletal (intra-muscular lesions 1 Patient: Extensive BM infiltration 1 Patient: Combined musculoskeletal (intra-muscular) and soft tissue lesions 1 Patient: Lung, BM, and IM lesions 3 Patients: Combined lung and BM lesions
Pathological types	HD: 5 patients NHD: 2 patients
Most common pathological subtype	3 Patients: Mixed cellularity

Table 7 PFS in DS interim negative and positive lymphoma groups

	Early *R* negative (%)	Early *R* positive (%)
2-year PFS	93.4	86.5
3-year PFS	87.2	67.4

of interim PET, the 5-point scoring system (5p Deauville Score, 5p-DS) has been widely accepted and it has been proposed as a rapid qualitative visual method to evaluate interim FDG-PET/CT [3].

Later, some studies started to discuss the benefit of using a ratio between semiquantitative parameters (e.g., target lesion and liver SUV) for interim FDG-PET/CT interpretation as an alternative to 5p-DS. This ratio has some important technical and practical advantages over visual analysis as it is independent of the amount of administered activity and body weight; it also allows conversion of a visual qualitative scale (as 5p-DS) in a continuous semiquantitative scale through a well-determined semiquantitative-based cut-point [8, 9].

The aim of our study was to evaluate the prognostic role of the ratio between the SUVmax of the hottest target residual lesion and liver SUVmax (rPET/rDS) in children with FDG-avid lymphomas undergoing interim FDG-PET/CT during the first-line chemotherapy and to compare rPET with 5p-DS.

In this study, 5p-DS and rDS were obtained considering the same reference organ (liver parenchyma). Using the ROC curve, we identify the optimal cut-points of rPET

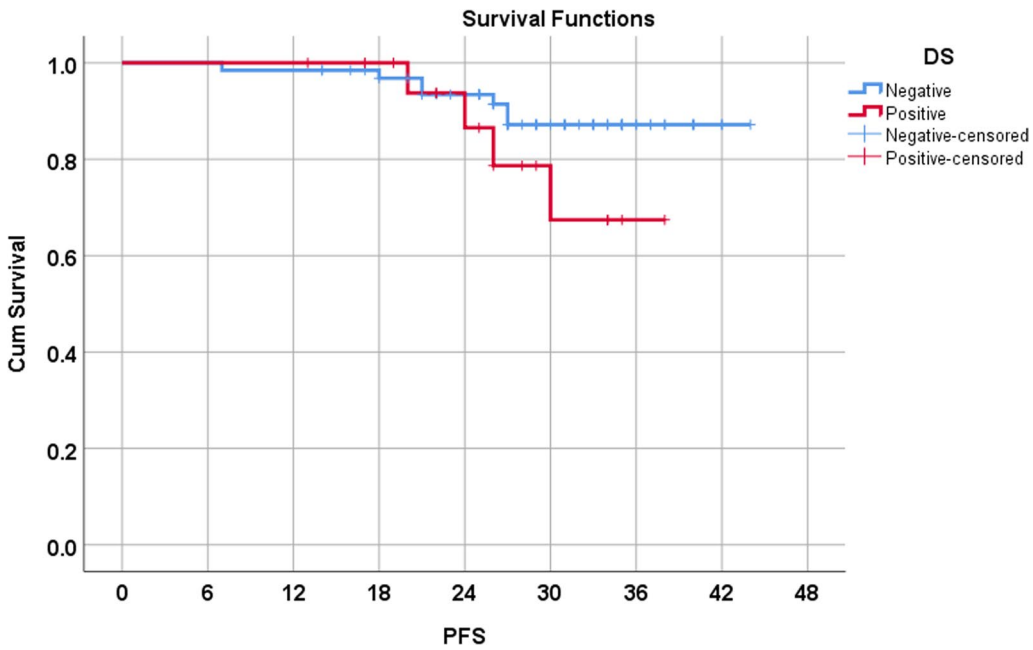

Fig. 2 Progression-free survival curves for DS interim negative and positive groups

Table 8 P values of significantly correlated clinical factors

Parameter	*P* value
Positive BM	$P \leq 0.001$
B symptoms	$P \leq 0.037$
No. of involved extra-nodal sites	$P < 0.001$
Interim PET	$P \leq 0.002$
No. of residual sites in interim PET	$P < 0.001$

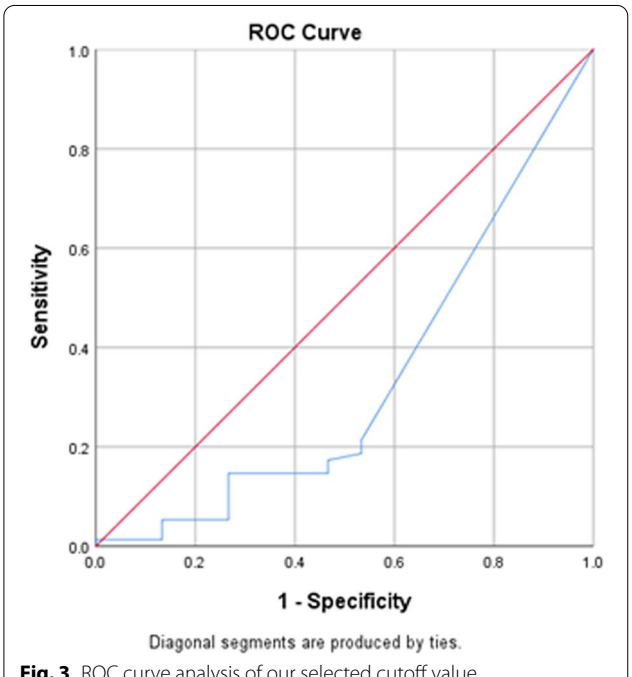

Fig. 3 ROC curve analysis of our selected cutoff value

with respect to events and chose the rPET cutoff of 1.25, because it had the best specificity (100%) and sensitivity (91.7%) among rPET values. These results are very close to the results of Annunziata et al. [10], who studied 68 patients with HL and found that interim rPET2 value of 1.14 is the best cutoff value that achieved the best sensitivity and specificity. On a retrospective study conducted by Toladeno et al. [9], on 181 patients with DLBCL, ROC analysis revealed the optimal cutoff value to be 1.4-fold of SUVmax-liver on iPET4 which is higher than our cutoff point that can be explained by different timing of interim PET (iPET4 not iPET2) that may be affected by post-therapy inflammatory changes, while Fan et al. [11] studied 119 adult patients with newly diagnosed DLBCL and found that a higher interim2 cutoff value of 1.6 achieves the highest specificity and makes more accurate reproducibility and outcome prediction.

Regarding our results, patients with rPET more than 1.25 had a worse prognosis than patients with rPET less than or equal to 1.25 with a significant statistical difference between both groups with a *P* value = 0.009. Moreover, regarding our results, patients with rPET more than 1.25 had a worse prognosis than patients with positive 5p-DS (PFS at 3 years of 60% and 67.4%, respectively). Annunziata

Table 9 rDS above and below the cutoff value and prognosis in extra-nodal lymphoma

	rDS ≤ 1.25 (*N* = 67 patients)	rDS > 1.25 (*N* = 22 patients)	Total number (*N* = 89 patients)
Good response no.	60	14	74
Poor response			
Total no.	7	8	15
Relapses	7 (10.8%)	4 (16.7%)	11
Refractory	0	4 (16.7%)	4

Table 10 Progression-free survival in children with rDS above and below the cutoff value

	< = 1.25 (%)	> 1.25 (%)
2-year PFS	93.6	84.4
3-year PFS	87.6	60

et al. [10] showed that patients with rPET > 1.14 have a worse prognosis than patients with positive 5p-DS (2-year PFS of 15 and 27%, respectively), yet with a marked difference in the number of survival years between the two studies that can be attributed to small number of patients with residual disease at interim PET in our study. Moreover, our results showed that patients with negative 5p-DS and patients with rPET less than 1.25 had a similar 2-year PFS (93.4 and 93.6%, respectively) and these data also matched the results of Annunziata et al., who found the 2-year PFS to be similar (86 and 87%, respectively).

Regarding our study, both visual and semiquantitative assessments of interim PET were significantly correlated with prognosis. Also, the 5p-DS and rPET were in agreement with most of the patients (87/89, 97.8%). Only two patients were discordant (positive 5p-DS and rPET < 1.25), and neither of these patients had any adverse events and they were completely free till the last follow-up (34 and 35 months), and therefore, these could be considered as false positives of 5p-DS. Consequently, the rPET cut-point of 1.25 seems to be accurate to identify patients with aggressive disease.

Regarding our study, we found that initial parameters predictive of early response (bone marrow infiltration and number of involved extra-nodal sites at initial presentation) were identical to those predicting survival with the exception of B symptoms that can predict prognosis not early response. This agreed with Mukhtar et al., [12], who found positive bone marrow infiltration to be a significant predictor of survival. Moreover, Vercellino et al. [13] found that extra-nodal involvement in more than 2 sites is a predictor of early

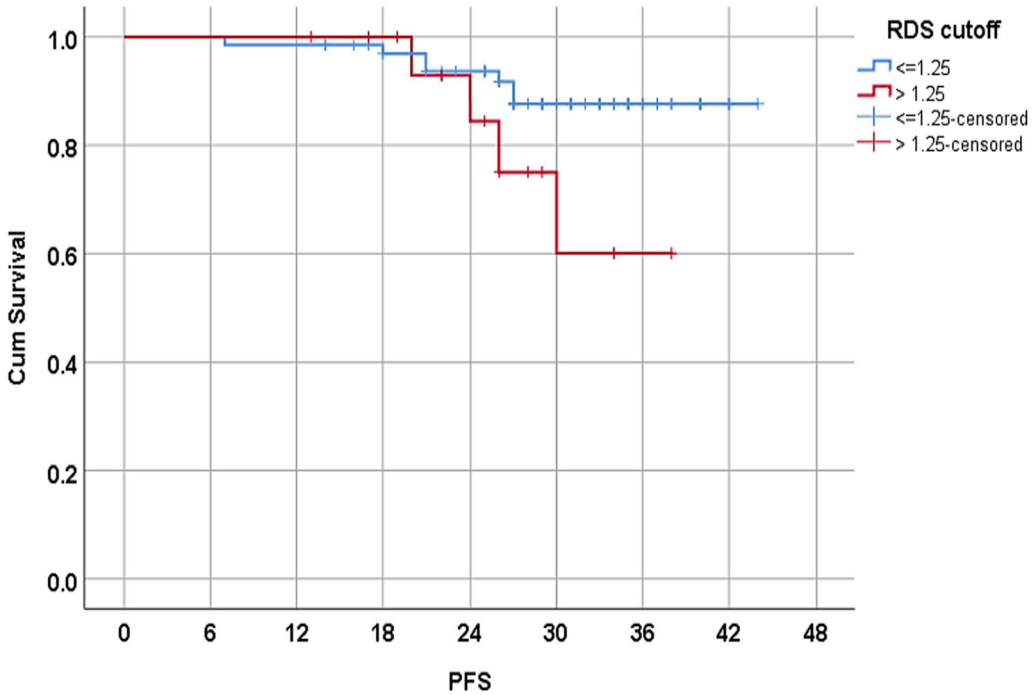

Fig. 4 Progression-free survival curves for rDS above and below the cutoff value

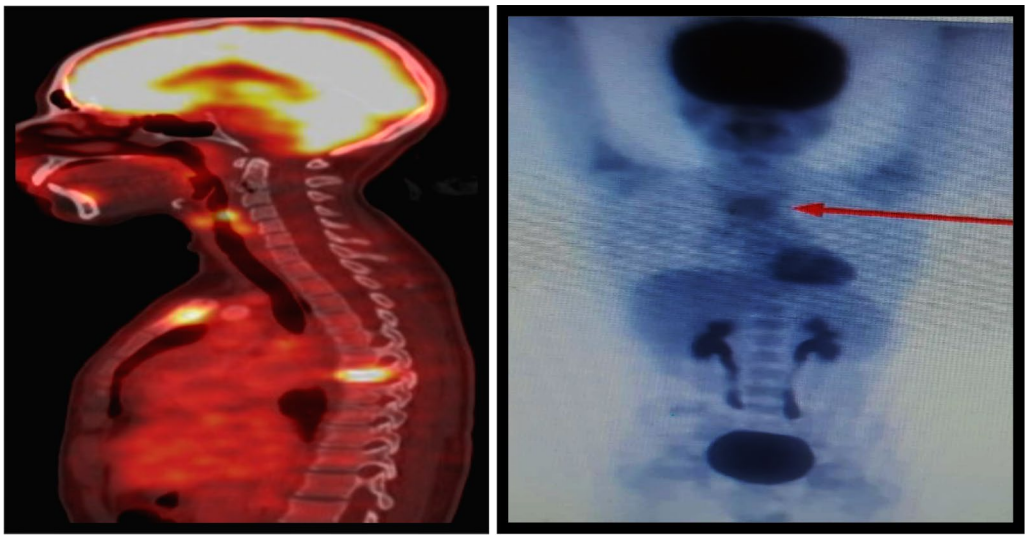

Fig. 5 PET-CT study for a 15-year-old male child complaining rapidly growing anterior chest wall mass that was pathologically proved to be HL, nodular sclerosis type. To the left: Initial study shows metabolically active FDG-avid osseous infiltrates at manubrium sterni and DV7. To the right: Interim PET-CT study shows complete disappearance of DV7 lesion with a still residual lesion at sternum with SUVmax ~ 2.2. The interpretation of this study using DS showing a positive result score 4 as sternal activity is higher than that of liver, while rDS = 1.22 which is less than the cutoff point (liver max 1.8). The patient was free till the last follow-up (36 months)

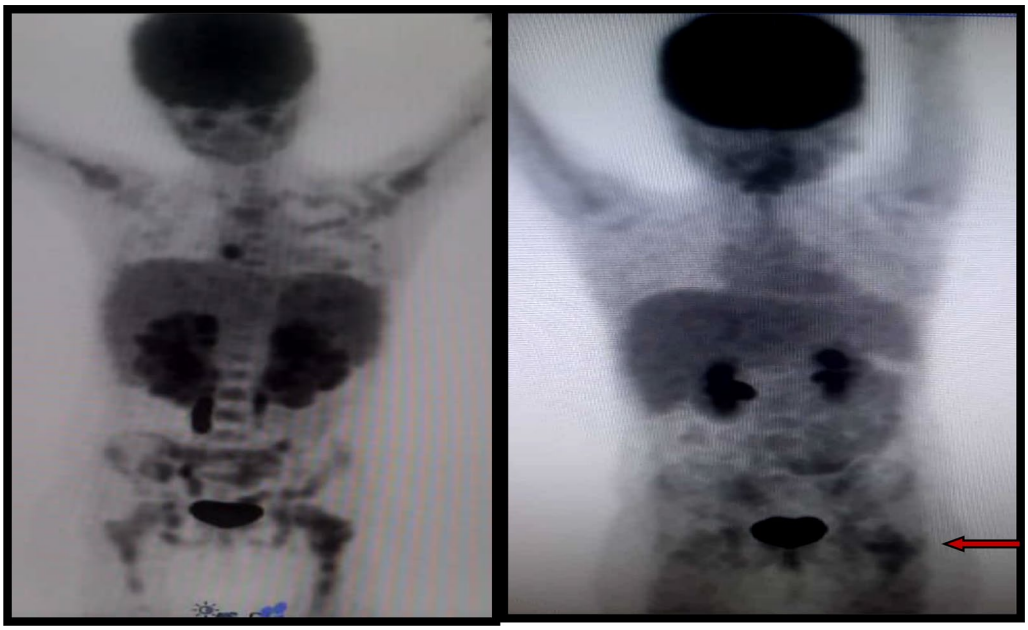

Fig. 6 PET-CT study for an 8-year-old female child presented with fever and abdominal pain. Abdominal US revealed bilateral kidney masses that were pathologically proved to be non-Hodgkin's lymphoblastic lymphoma. To the left: Initial study shows metabolically active FDG-avid infiltrates involving both kidneys, bone marrow, and bone. To the right: Interim PET-CT study shows complete disappearance of all lesions except a residual bone marrow lesion at left femur with SUVmax ~ 2.63. The visual interpretation of this study using 5P-DS was positive (score 4) as left femoral activity was higher than that of liver, while it was negative using rDS (rDS = 1.05) which is less than the cutoff point (liver max ~ 2.5). The follow-up showed complete cure of the patient (35 months)

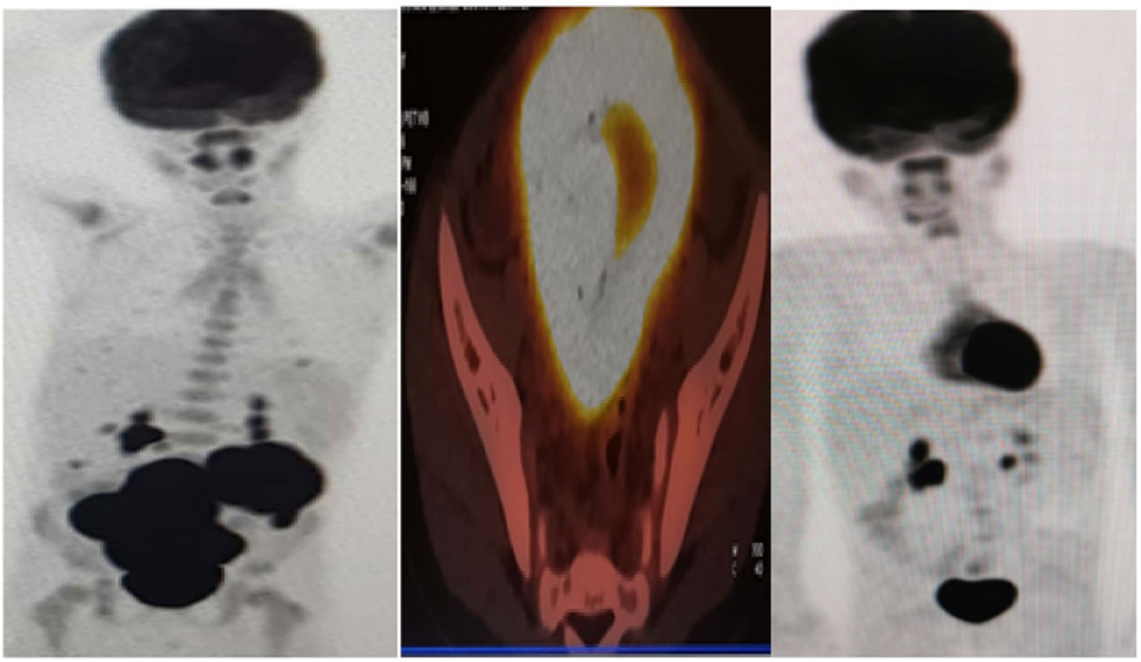

Fig. 7 PET-CT study for a 5-year-old male child presented with an abdominal mass. To the left: Initial study shows metabolically active FDG-avid abdomino-pelvic bowel mass. The mid image: Fused PET-CT image shows FDG-avid abdomino-pelvic bowel mass with marked mucosal thickening. To the right: Interim PET-CT study shows complete disappearance of all lesions. Both visual and semiquantitative interpretation methods were negative, and the patient was free till the last follow-up

and late response to therapy. On the contrary, Yao et al. [14] found that the number of extra-nodal sites was not related to PFS, but was associated with poor OS in a retrospective study of 329 young adults with DLBCL. Also, there was a significant correlation between the number of residual diseased sites at interim PET and survival which could be explained by its reflection of the aggression and widespread of the disease and consequently poorer response to therapy.

Regarding the univariate analysis of our results, semiquantitative parameters of the highest FDG-avid lesions in initial PET study were not correlated with survival. These findings are different from results of most of published papers in this context that can be explained by the non-homogeneity of our sample regarding pathological subtypes and stages. Moreover, this study has some limitations including the small number of patients, heterogeneity of lymphoma subtypes, and first-line treatment modalities used that could affect the outcome. Also, the heterogeneity of liver parenchyma may represent a possible source of mistakes in the measurement of liver SUVmax. We recommend using this easier rPET semiquantitative parameter for interim PET assessment that could be more confirmed by making larger studies with more homogenous sample regarding histopathological subtypes and chemotherapy lines that may help in intra-examination normalization.

Conclusions

Accurate interpretation of early response evaluation PET (interim PET) is crucial for achieving the best management strategy for lymphoma patients; however, it is still a subject of ongoing debate. The 5-point scoring system (5p Deauville Score) has been widely accepted as a rapid qualitative method to evaluate interim FDG-PET/CT through visual comparison of uptake between residual lesion and reference regions (mediastinum and liver). Recently, the ratio between semiquantitative parameters (e.g., target lesion and liver SUV) has been proposed for interim FDG-PET/CT evaluation and few studies compared the prognostic value of both interpretation methods. Our study highlighted the prognostic value of both methods and shows that the rDS could be put in consideration as a more accurate prognostic factor in those children with lymphoma. Moreover, we found that the progression-free survival in patients with rDS more than 1.25 (our selected cutoff) was lower than that of positive DS (score 4 and 5). We recommend making further studies with larger sample size, with more homogenous samples regarding histopathological subtypes and chemotherapy lines to confirm these results.

Abbreviations
HL: Hodgkin's lymphoma; NHL: Non-Hodgkin's lymphoma; FDG: Fluoro-deoxy-glucose; rDS: Ratio Deauville score; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; PET: Positron emission tomography; SUV: Standardized uptake value; DS: Deauville score; DLBCL: Diffuse large B cell lymphoma; PFS: Progression-free survival; OS: Overall survival.

Acknowledgements
Not applicable.

Author contributions
HY and HF collected and interpreted the data. OM performed the statistical analysis of data. HY was the major contributor in writing the manuscript. HM and MH revised the results and discussion. All authors read and approved the final manuscript.

Funding
No funding was obtained for this study.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Our study was approved by the ethical committee of Faculty of medicine, Cairo University, and the radiation safety committee at NCI had given approval for study design. Written informed consents were obtained from all parents.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 18 February 2022 Accepted: 16 September 2022
Published online: 05 October 2022

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