Factors Affecting the Metabolic Parameters Measured by ^{18}F FDG PET/CT in Initial Assessment of Lymphoma Patients

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Abstract:

Background: Background activity on fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is frequently used as a reference to evaluate how patients respond to tumor therapy. The purpose of this research was to assess how biological and technical factors alters the uptake of the liver and mediastinal blood pool (MBP) in lymphoma.

Methods: This retrospective study enrolled 62 lymphoma patients underwent initial ^{18}F-FDG PET/CT examinations before receiving any therapy, SUV metrics included SUVmax, SUVmean and SUVpeak for the pathologically proved lesion as well as of the liver and the MBP.

Results: The study included 62 patients, 35 had HL and 27 had NHL (47 males and 15 females, with a mean age of 27.82 ± 23.33 years), we found that the duration of uptake, followed by weight were the most important predictors of SUVmax as well as SUVmean, and SUVpeak of the lesion. Meanwhile, weight was one of the most significant indicators of SUV values of the liver, followed by age. On the other hand, weight was one of the most significant indicators of SUVmax and SUVpeak of the mediastinal blood pool. However, Blood glucose level followed by weight with a slight difference were the most important predictors of SUVmean of the mediastinal blood pool.

Conclusion: biological and procedural factors are essential factors that cause changes in the blood pool and liver SUVs. The so-called reference organs i.e. the MBP and liver, are affected with variation in weight, age, and blood glucose. Our study showed that in all liver and mediastinal blood pool measurements, weight had the upper hand.

Keywords: ^{18}F-FDG-PET/CT, SUV, liver, MBP, lymphoma, HL, NHL.

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Background:

PET imaging has been made successful by ^{18}F-FDG. The molecule's glucose component is more absorbed by cancer cells than by healthy cells, and the ^{18}F element makes the molecule detectable in PET-CT systems [1]. PET, particularly for its use in oncology, has gained widespread clinical acceptance. PET has evolved into a crucial tool for the treatment of individuals suffering from different kinds of cancer, as well as infections and inflammation, when combined with the glucose analogue ^{18}F- FDG [2]. ^{18}F-FDG PET/CT is frequently used in cancer patients for diagnosis, staging, response assessment, and monitoring [3]. Visual evaluation of ^{18}F-FDG uptake and distribution in lesions and throughout the body is frequently the basis for clinical readings [4]. While quantification in ^{18}F-FDG PET assessments have garnered attention due to quantitative uptake measures, such as total lesion glycolysis (TLG), metabolic tumour volume (MTV) as well as standardized uptake values (SUV), which provide diagnostic, prognostic, and predictive significance for various hematological and oncological applications [5].

Many factors influence SUV in ^{18}F-FDG PET/CT; thus, SUV standardization is required. Theoretically, biological variability and technical variability combine to make up the variation in a PET measurement [1]. Nonetheless, inaccuracies in liver and blood pool SUVs can be caused by a range of biological reasons. These variables, which include age as well as gender, body weight, serum glucose level, and hyperthyroidism, can result in incorrectly positive or incorrectly false negative PET/CT findings. Consequently, before physicians can interpret PET/CT scans, normal SUV values of the liver and blood pool must be established. [6] ^{18}F-FDG, a glucose analog that accumulates in cancer cells, is a commonly used radioactive tracer. Its activity is comparable to the reference uptake in the

liver, muscles, mediastinum, and aorta, among other typical organ structures [7].

A hematopoietic cancer, it is common to categorize lymphomas into two groups: non-Hodgkin's disease and Hodgkin's disease. 10% of cases with a recent diagnosis have HL, which is unique in that it has both Reed-Sternberg and Hodgkin cells [8]. Nodular lymphocyte-predominant Hodgkin lymphoma as well as classical Hodgkin lymphoma, which comprises four further sub-categories based on morphology and immunohistochemistry, are two further subtypes of HL [9]. A vital component of managing patients with lymphoma during initial assessment and assessment of response is PET/CT. Efforts to establish standards for PET recording and reporting, including the Deauville scale, have made PET a reliable indicator of treatment effective or unsuccessful in the case of common lymphoma subtyping [10]. Being sensitive and more specific than diagnostic CT for assessing nodal and extra-nodal involvement, PET/CT is becoming more and more common in the assessment of lymphoma patients [11]. The level of utilization of FDG has been reported as a potential tool for identifying various lymphoma subgroups, and it is therapeutically beneficial in a wide range of lymphomas [12].

Patients and Methods:

In our retrospective analysis, 62 lymphoma cases were included who underwent initial FDG PET/CT examinations prior to starting therapy. The study took place in the Nuclear Medicine unit and Oncology department, at Assiut University Hospital.

^{18}F-FDG PET/CT image acquisition and reconstruction:

Approximately 45–90 minutes after the FDG injection, imaging was carried out utilizing a high-spatial-resolution, full-ring PET scanner (Biograph Flow, Siemens Healthcare, Erlangen, Germany) that combined 16-slice CT components with PET crystals based on lutetium oxyorthosilicate (LSO). For attenuation correction and for fusion with emission PET images to allow for anatomical localization of PET findings, a low-dose non-contrast CT scan will be obtained by an integrated multi-slice CT machine, an imaging FOV from the skull vertex to mid-thighs and whenever possible the arms above the head was used. Then after the low-dose CT, an emission PET scan will be done in a 3D mode over the same anatomical regions starting from the mid-thighs to the vertex of the skull. Transverse image reconstruction using an iterative algorithm was performed with reoriented tomograms displayed in the trans-axial, coronal, and sagittal planes. Analysis of the axial, sagittal, coronal, and fused images is done on the manufacturer's workstation (Syngo. via Siemens Healthcare).

Image analysis:

- Qualitative assessment: visual interpretation by nuclear medicine doctors for the presence of hypermetabolic lesions was done.
- Semi-quantitative assessment:
  - FDG PET scans were co-registered and examined on the workstation of manufacturer (Syngo. via Siemens Healthcare).
  - For the regions of interest, attenuation-corrected images based on SUV values were done based on body weight in kilograms (SUVkg).
  - Parameters for SUV calculation included the injected dose of ^{18}F-FDG and the patient's weight.
  - SUV metrics included SUVmax as well as SUVmean and SUVpeak for the pathologically proved lesion in most cases and the most avid lesions in some cases with excisional biopsies as well as SUV values of the liver and SUV values of the MBP.
  - For reference organs, circular ROI was drawn on the liver (3 cm ROI was drawn on the right lobe, without disease involvement), (MBP; 1.2 cm ROI within aortic arch excluding vascular wall and/or atherosclerosis).

Statistical Analysis

Version 25 of the IBM® Statistical Package for Social Sciences (SPSS) ® Statistics (SPSS Inc., Chicago, IL, USA) was used for every calculation of statistics. Chi-square tests were utilized to compare groups when presenting categorical data in the form of frequencies and percentages. The continuous data were presented as means ± standard deviations and medians (interquartile range), and the Shapiro-Wilk test was used to determine if the data were normal. Non-parametric continuous data distributions are compared using independent samples of the Kruskal-Wallis test. In the case of regularly distributed continuous data, two-way repeated measures to compare two groups of repeatedly measured data and repeated measures, the ANOVA test was employed. The not parametric related-samples were used when the data was not regularly distributed. Two sets of regularly measured data were compared using the Wilcoxon Signed Rank test and non-parametric The Dunn-Bonferroni post-hoc test was utilized for pairwise comparisons, and Friedman's Two-Way ANOVA by Ranks test was utilized for comparing data from more than two groups that were tested repeatedly. A p-value of less than 0.05 was deemed statistically significant for every test used for statistical purposes.

Results:

The study patients' demographic information is summarized in table 1. Our study enrolled 62 patients, 35 had HL and 27 had NHL, with a mean age of 27.82 ± 23.33 years. Forty-seven patients (75.8%) were males and fifteen (24.2%) were females with a mean weight of 50.89 ± 26 Kg, mean injected dose of 193.02 ± 88.13 MBq, and mean BGL at the time of injection of 104.42 ± 24.93 mg/dl. Patients with NHL in our study had a higher mean and median age, weight, BGL and injected dose, than HL. There are statistically significant differences between patient groups present for age, sex,

weight, BGL, and FDG injected dosage. No significant changes within the uptake time. The interval of time between the injection of PET tracer and the start of imaging is known as the uptake time, did not differ between groups significantly, Table 2.

Table 1: Demographic and clinical data of all studied patients with lymphomas (including HL and NHL).

Variable	Patients with lymphomas (n = 62)
Age	27.82 ± 23.33 15 (8.75 – 41.5)
Sex	Male: 47 (75.8%) Female: 15 (24.2%)
Weight	50.89 ± 26 51 (24.75 – 75)
Blood glucose levels	104.42 ± 24.93 100 (84.5 – 116.75)
Duration of uptake (minutes)	74.19 ± 24.12 71.5 (59.75 – 89.5)
Injected dose	193.02 ± 88.13 203.5 (111 – 259.93)

IQR: Inter quartile range SD: Standard deviation.

Table 2: General characteristics of different patients' groups in the study, including HL and NHL.

	HL (n = 35)	NHL (n = 27)	P value
Age^{+} (Year)	18.91 ± 17.43 12 (6 – 33)	39.37 ± 25.2 39 (13 – 67)	<0.001*
Sex $^{\$}$	Male: 27 (77.1%) Female: 8 (22.9%)	Male: 20 (74.1%) Female: 7 (25.9%)	<0.001*
Weight^{+} (Kg)	43.49 ± 24.37 45 (23 – 60)	60.48 ± 25.3 65 (31 – 80)	<0.001*
BGL^{+} (Mg/dl)	100.06 ± 18.88 99 (85 – 111)	110.07 ± 30.54 105 (81 – 132)	0.038*
Duration of uptake^{+} (minutes)	77.43 ± 24.6 75 (60 – 92)	70 ± 23.27 66 (56 – 83)	0.46
Injected dose^{+} (MBq)	167.71 ± 79.7 151.7 (111–222)	225.82 ± 89.1 236.8 (148–277.5)	<0.001*

- Continuous data are presented as mean (±SD) and median (IQR).
- Categorical data are presented as count (%).

+ Non-parametric continuous data distributions are compared using independent samples Kruskal-Wallis test.

- $ Categorical data distributions are compared using Pearson's Chi-square test.
- * Statistically significant difference.

NHL had the higher SUVmax, SUVmean, and SUVpeak values of the lesion, liver and MBP than HL, as showed in Table 3.

Table 3: Comparison of PET-CT measurements of the lesion of HL and NHL patients.

	HL (n = 35)	NHL (n = 27)	P value
SUV_{max} $^{+}$	7.55 ± 6.5 5.6 (3 – 10.5)	9.71 ± 11.47 5.55 (3.02 – 12.63)	0.019*
SUV_{mean} $^{+}$	4.29 ± 3.65 3.1 (1.73 – 6)	5.06 ± 4.89 3.4 (1.67 – 7.57)	0.019*
SUV_{peak} $^{+}$	5.69 ± 5.49 3.88 (1.81 – 7.12)	7.3 ± 8.47 4.54 (2.21 – 7.95)	0.004*

- Continuous data are presented as mean (±SD) and median (IQR).
- + Non-parametric continuous data distributions are compared using independent samples Kruskal-Wallis test.
- * Statistically significant difference

Tables 4 to 12 illustrated the results of MANCOVA tests for SUV measurements in patients with lymphomas. On the basis of patient's weight, there was a statistically significant variance in SUVmax values between individuals who had HL and NHL ($F(3, 53) = 4.14$, $p = 0.01$; Wilk's $\Lambda = 0.810$, partial $\eta 2 = 0.190$). In addition, there was a statistically important difference in SUVmean measurements based on a patient's age ($F(3, 53) = 3.60$, $p = 0.019$; Wilk's $\Lambda = 0.831$, partial $\eta 2 = 0.169$). Moreover, there was a statistically important variance in SUVpeak measurements on the basis of patient's weight ($F(3, 53) = 3.24$, $p = 0.029$; Wilk's $\Lambda = 0.845$, partial $\eta 2 = 0.155$) and age ($F(3, 53) = 2.98$, $p = 0.040$; Wilk's $\Lambda = 0.856$, partial $\eta 2 = 0.144$). Weight had a statistically important influence on the SUVmax measurements of the liver ($p = 0.001$) and SUVpeak values of the liver ($p = 0.005$), while age had a statistically significant influence on the SUVpeak values of the liver ($p = 0.011$).

In people with HL, the MANCOVA test findings were proven to be insignificant within this study's settings, probably due to small sample size.

In patients with non-Hodgkin's lymphoma, there was a statistically significant difference in SUVmax measurements based on a patient's weight ($F(3, 18) = 3.306$, $p = 0.044$; Wilk's $\Lambda = 0.645$, partial $\eta 2 = 0.355$). Moreover, weight had a statistically important effect on SUVmax measurements of the liver ($p = 0.005$).

Regression Analysis

Regarding patients with lymphomas (Both Hodgkin and Non-Hodgkin Lymphoma), multiple regression analyses revealed that the duration of uptake could statistically significantly predict SUVmax of the lesion ($F(6, 55) = 3.23$, $p = 0.009$, $R2 = 0.261$), SUVmean of

the lesion ($F(6, 55) = 2.997$, $p = 0.013$, $R2 = 0.246$), and SUVpeak of the lesion ($F(6, 55) = 2.574$, $p = 0.029$, $R2 = 0.219$). Weight added statistically significantly to the prediction, while age, sex, duration of uptake and blood glucose level failed to perform in a similar manner, $p < 0.05$. Meanwhile, weight and age could statistically significantly predict SUVmax of the liver ($F(6, 55) = 37.272$, $p < 0.001$, $R2 = 0.803$) and SUVpeak of the liver ($F(6, 55) = 32.184$, $p < 0.001$, $R2 = 0.778$), while only weight could statistically significantly predict SUVmean of the liver ($F(6, 55) = 25.789$, $p < 0.001$, $R2 = 0.738$). On the other hand, weight could statistically significantly predict SUVmax of the mediastinal blood pool ($F(6, 55) = 8.359$, $p < 0.001$, $R2 = 0.477$).

Regarding patients with Hodgkin's Lymphoma, we found that blood glucose levels and weight could statistically significantly predict SUVmax of the liver ($F(6, 28) = 16.142$, $p < 0.001$, $R2 = 0.776$).

Regarding patients with Non-Hodgkin's Lymphoma, we found that weight could statistically significantly predict SUVmax of the lesion ($F(6, 20) = 2.668$, $p = 0.046$, $R2 = 0.445$). Moreover, weight could statistically significantly predict SUVmax of the liver ($F(6, 20) = 16.108$, $p < 0.001$, $R2 = 0.829$), SUVmean of the liver ($F(6, 20) = 12.619$, $p < 0.001$, $R2 = 0.791$) and SUVpeak of the liver ($F(6, 20) = 12.784$, $p < 0.001$, $R2 = 0.793$).

Of notice, all the SUV measurements of the liver demonstrated larger effect sizes in the regression analysis than those of their counterparts of the mediastinal blood pool, according to their R2 values.

Automatic linear modeling

Automatic linear modeling involving age, sex, weight, blood glucose levels, injected dose and duration of uptake was performed to predict the importance of each predictor on the SUV measurements.

Regarding patients with lymphomas (both Hodgkin and non-Hodgkin), we found that the duration of uptake, followed by weight were the most important predictors of SUVmax, as well as SUVmean, and SUVpeak of the lesion. Meanwhile, weight was one of the most significant predictors of SUV values of the liver, followed by age. On the other hand, weight was the most important predictor of SUVmax and SUVpeak of the mediastinal blood pool.

However, Blood glucose level followed by weight with a slight difference were the most important predictors of SUVmean of the mediastinal blood pool.

In those with HL, we found that the duration of uptake was the most important predictor of SUVmax and SUVmean of the lesion, followed by blood glucose level and sex in SUVmax lesion, while followed by sex and blood glucose level in SUVmean lesion. Meanwhile, blood glucose level, followed by the duration of uptake and sex, were the most important predictors of SUVpeak of the lesion. On the other hand, blood glucose level, followed by weight, were the most important predictors of SUVmax and SUVpeak of the liver, while weight, followed by blood glucose level, were the most important predictors of SUVmean of the liver. Within the mediastinal blood pool, weight was the most important predictor of all SUV measurements, followed by sex in SUVmax and SUVpeak, while followed by blood glucose in SUVmean of the mediastinal blood pool.

We noticed that in all lesion measurements, age had a markedly higher importance than weight. However, in all liver and mediastinal blood pool measurements, weight had the upper hand.

In cases with NHL, we showed that weight was the most important predictor of all SUV measurements of the lesion, followed by blood glucose levels. In addition, we also found that weight was the most important predictor of all SUV measurements of the liver, followed far behind by age. Meanwhile, weight was the most important predictor of SUVmax and SUVpeak of the mediastinal blood pool, while the duration of uptake was the most important predictor of SUVmean of the mediastinal blood pool. Of notice, the linear model for identifying predictors of SUVpeak of the mediastinal blood pool was found to have a very low accuracy, this was most likely because the patient group in this study had a small sample size.

Discussion:

PET-CT using ^{18}F-FDG has a significant improvement in the detection and management of oncological disorders. Elevated metabolism of glucose is highlighted by ^{18}F-FDG absorption in both pathological and physiological processes [13]. The goal of PET imaging in cancer is to distinguish between the injected radiopharmaceutical's normal uptake, as well as abnormal non-malignant uptake, and abnormal malignant uptake [14].

One technique assessed the target lesion's visual uptake with that of the liver parenchyma or MBP. Nevertheless, there was subjectivity involved in this qualitative approach, which may have led to low reproducibility. With FDG PET, semi-quantitative assessment is achievable by producing count statistics that show uptake in malignant target lesions, including the SUV for separating malignant from non-malignant disorders [15]. The most popular way to report uptake is by the SUV, which is calculated by dividing the calculated radioisotope concentration by the patient's weight and the decay-corrected administered dosage [16].

The accepted standard for assessing tumor treatment is the uptake of FDG in normal tissues [17]. SUVs of background healthy tissues, like the MBP and liver, are commonly employed as reference to characterize the disease and evaluate the response of the tumor to treatment [18].

Table 4: Results of MANCOVA tests for SUVmax measurements of the lesion, the liver, and the mediastinal blood pool in patients with Hodgkin's lymphoma or Non-Hodgkin's lymphoma.

Variable	F(3,53)	Wilk's Λ	Partial η^2	P value
Weight	4.14	0.810	0.190	0.01*
Age	2.32	0.884	0.116	0.086
Blood Glucose Level	0.58	0.968	0.032	0.632
Injected Dose	0.65	0.965	0.035	0.587
Duration of Uptake	2.33	0.884	0.116	0.085
Sex	1.96	0.900	0.100	0.131
Between-Subjects Effects				
Independent	Dependent	F(1,55)	Partial η^2	P value
Weight	SUVmax Lesion	3.386	0.058	0.071
	SUVmax Liver	12.309	0.183	0.001*
	SUVmax MBP	4.089	0.069	0.048
Age	SUVmax Lesion	0.091	0.002	0.764
	SUVmax Liver	5.469	0.090	0.023
	SUVmax MBP	0.003	0.000	0.955
Blood Glucose Level	SUVmax Lesion	0.592	0.011	0.445
	SUVmax Liver	0.310	0.006	0.580
	SUVmax MBP	0.702	0.013	0.406
Injected Dose	SUVmax Lesion	1.951	0.034	0.168
	SUVmax Liver	0.238	0.004	0.628
	SUVmax MBP	0.134	0.002	0.716
Duration of Uptake	SUVmax Lesion	5.652	0.093	0.021
	SUVmax Liver	0.028	0.001	0.867
	SUVmax MBP	0.018	0.000	0.894
Sex	SUVmax Lesion	1.657	0.029	0.203
	SUVmax Liver	1.156	0.021	0.287
	SUVmax MBP	0.257	0.005	0.614

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 5: Results of MANCOVA tests for SUVmean measurements of the lesion, the liver, and the mediastinal blood pool in patients with Hodgkin's lymphoma or Non-Hodgkin's lymphoma.

Variable	F(3,53)	Wilk's Λ	Partial η^2	P value
Weight	2.42	0.879	0.121	0.076
Age	3.60	0.831	0.169	0.019*
Blood Glucose Level	1.06	0.943	0.057	0.373
Injected Dose	0.37	0.980	0.020	0.778
Duration of Uptake	2.53	0.875	0.125	0.067
Sex	1.51	0.921	0.079	0.223
Between-Subjects Effects				
Independent	Dependent	F(1,55)	Partial η^2	P value
Weight	SUVmean Lesion	3.346	0.057	0.073
	SUVmean Liver	5.806	0.095	0.019
	SUVmean MBP	3.008	0.052	0.088
Age	SUVmean Lesion	0.908	0.016	0.345
	SUVmean Liver	3.683	0.063	0.060
	SUVmean MBP	0.039	0.001	0.844
Blood Glucose Level	SUVmean Lesion	0.002	0.000	0.961
	SUVmean Liver	1.238	0.022	0.271
	SUVmean MBP	3.058	0.053	0.086
Injected Dose	SUVmean Lesion	1.036	0.018	0.313
	SUVmean Liver	0.005	0.000	0.943
	SUVmean MBP	0.022	0.000	0.882
Duration of Uptake	SUVmean Lesion	4.823	0.081	0.032
	SUVmean Liver	0.588	0.011	0.447
	SUVmean MBP	2.058	0.036	0.157
Sex	SUVmean Lesion	3.259	0.056	0.077
	SUVmean Liver	0.545	0.010	0.464
	SUVmean MBP	0.599	0.011	0.442

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 6: Results of MANCOVA tests for SUVpeak measurements of the lesion, the liver, and the mediastinal blood pool in patients with Hodgkin's lymphoma and Non-Hodgkin's lymphoma.

Variable	F(3,53)	Wilk's Λ	Partial η^2	P value
Weight	3.24	0.845	0.155	0.029*
Age	2.98	0.856	0.144	0.040*
Blood Glucose Level	0.25	0.986	0.014	0.861
Injected Dose	0.72	0.961	0.039	0.543
Duration of Uptake	2.35	0.883	0.117	0.083
Sex	1.11	0.941	0.059	0.353
Between-Subjects Effects				
Independent	Dependent	F(1,55)	Partial η^2	P value
Weight	SUVpeak Lesion	2.503	0.044	0.119
	SUVpeak Liver	8.662	0.136	0.005*
	SUVpeak MBP	1.985	0.035	0.165
Age	SUVpeak Lesion	0.003	0.000	0.959
	SUVpeak Liver	6.932	0.112	0.011*
	SUVpeak MBP	0.000	0.000	0.987
Blood Glucose Level	SUVpeak Lesion	0.162	0.003	0.689
	SUVpeak Liver	0.238	0.004	0.628
	SUVpeak MBP	0.076	0.001	0.784
Injected Dose	SUVpeak Lesion	1.227	0.022	0.273
	SUVpeak Liver	0.076	0.001	0.784
	SUVpeak MBP	0.740	0.013	0.393
Duration of Uptake	SUVpeak Lesion	5.585	0.092	0.022
	SUVpeak Liver	0.002	0.000	0.967
	SUVpeak MBP	0.082	0.001	0.775
Sex	SUVpeak Lesion	1.323	0.023	0.255
	SUVpeak Liver	0.554	0.010	0.460
	SUVpeak MBP	0.077	0.001	0.783

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 7: Results of MANCOVA tests for SUVmax measurements of the lesion, the liver, and the mediastinal blood pool in patients with Hodgkin's lymphoma.

Variable	F(3,26)	Wilk's Λ	Partial η^2	P value
Weight	1.963	0.815	0.185	0.144
Age	1.077	0.889	0.111	0.376
Blood Glucose Level	2.607	0.769	0.231	0.073
Injected Dose	0.360	0.960	0.040	0.782
Duration of Uptake	1.154	0.883	0.117	0.346
Sex	2.172	0.800	0.200	0.115
Between-Subjects Effects				
Independent	Dependent	F(1,28)	Partial η^2	P value
Weight	SUVmax Lesion	0.277	0.010	0.603
	SUVmax Liver	4.628	0.142	0.040
	SUVmax MBP	4.205	0.131	0.050
Age	SUVmax Lesion	1.327	0.045	0.259
	SUVmax Liver	0.190	0.007	0.667
	SUVmax MBP	1.427	0.048	0.242
Blood Glucose Level	SUVmax Lesion	3.362	0.107	0.077
	SUVmax Liver	5.254	0.158	0.030
	SUVmax MBP	0.482	0.017	0.493
Injected Dose	SUVmax Lesion	0.057	0.002	0.812
	SUVmax Liver	0.097	0.003	0.758
	SUVmax MBP	1.134	0.039	0.296
Duration of Uptake	SUVmax Lesion	3.522	0.112	0.071
	SUVmax Liver	0.115	0.004	0.737
	SUVmax MBP	0.027	0.001	0.870
Sex	SUVmax Lesion	3.123	0.100	0.088
	SUVmax Liver	0.172	0.006	0.682
	SUVmax MBP	3.041	0.098	0.092

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 8: Results of MANCOVA tests for SUVmean measurements of the lesion, the liver, and the mediastinal blood pool in patients with Hodgkin's lymphoma.

Variable	F(3,26)	Wilk's Λ	Partial η^2	P value
Weight	0.630	0.932	0.068	0.602
Age	0.861	0.910	0.090	0.474
Blood Glucose Level	1.371	0.863	0.137	0.274
Injected Dose	0.006	0.999	0.001	0.999
Duration of Uptake	1.844	0.825	0.175	0.164
Sex	1.391	0.862	0.138	0.268
Between-Subjects Effects				
Independent	Dependent	F(1,28)	Partial η^2	P value
Weight	SUVmean Lesion	0.038	0.001	0.847
	SUVmean Liver	2.021	0.067	0.166
	SUVmean MBP	1.355	0.046	0.254
Age	SUVmean Lesion	1.230	0.042	0.277
	SUVmean Liver	0.080	0.003	0.780
	SUVmean MBP	0.298	0.011	0.589
Blood Glucose Level	SUVmean Lesion	2.763	0.090	0.108
	SUVmean Liver	1.752	0.059	0.196
	SUVmean MBP	1.048	0.036	0.315
Injected Dose	SUVmean Lesion	0.016	0.001	0.900
	SUVmean Liver	0.003	0.000	0.960
	SUVmean MBP	0.002	0.000	0.963
Duration of Uptake	SUVmean Lesion	4.087	0.127	0.053
	SUVmean Liver	0.019	0.001	0.891
	SUVmean MBP	0.427	0.015	0.519
Sex	SUVmean Lesion	2.972	0.096	0.096
	SUVmean Liver	0.468	0.016	0.500
	SUVmean MBP	0.020	0.001	0.889

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 9: Results of MANCOVA tests for SUVpeak measurements of the lesion, the liver, and the mediastinal blood pool in patients with Hodgkin's lymphoma.

Variable	F(3,26)	Wilk's Λ	Partial η^2	P value
Weight	1.416	0.860	0.140	0.261
Age	1.059	0.891	0.109	0.384
Blood Glucose Level	2.274	0.792	0.208	0.104
Injected Dose	0.496	0.946	0.054	0.688
Duration of Uptake	1.069	0.890	0.110	0.379
Sex	1.750	0.832	0.168	0.181
Between-Subjects Effects				
Independent	Dependent	F(1,28)	Partial η^2	P value
Weight	SUVpeak Lesion	0.031	0.001	0.862
	SUVpeak Liver	2.600	0.085	0.118
	SUVpeak MBP	3.344	0.107	0.078
Age	SUVpeak Lesion	0.844	0.029	0.366
	SUVpeak Liver	0.304	0.011	0.586
	SUVpeak MBP	1.413	0.048	0.245
Blood Glucose Level	SUVpeak Lesion	4.096	0.128	0.053
	SUVpeak Liver	3.803	0.120	0.061
	SUVpeak MBP	0.157	0.006	0.695
Injected Dose	SUVpeak Lesion	0.001	0.000	0.970
	SUVpeak Liver	0.011	0.000	0.918
	SUVpeak MBP	1.365	0.046	0.253
Duration of Uptake	SUVpeak Lesion	3.224	0.103	0.083
	SUVpeak Liver	0.001	0.000	0.978
	SUVpeak MBP	0.132	0.005	0.719
Sex	SUVpeak Lesion	1.706	0.057	0.202
	SUVpeak Liver	0.220	0.008	0.642
	SUVpeak MBP	2.556	0.084	0.121

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 10: Results of MANCOVA tests for SUVmax measurements of the lesion, the liver, and the mediastinal blood pool in patients with non-Hodgkin's lymphoma.

Variable	F(3,18)	Wilk's Λ	Partial η^2	P value
Weight	3.306	0.645	0.355	0.044*
Age	0.834	0.878	0.122	0.493
Blood Glucose Level	1.709	0.778	0.222	0.201
Injected Dose	0.730	0.891	0.109	0.547
Duration of Uptake	1.236	0.829	0.171	0.326
Sex	0.594	0.910	0.090	0.627
Between-Subjects Effects				
Independent	Dependent	F(1,20)	Partial η^2	P value
Weight	SUVmax Lesion	4.520	0.184	0.046
	SUVmax Liver	9.808	0.329	0.005*
	SUVmax MBP	3.052	0.132	0.096
Age	SUVmax Lesion	0.004	0.000	0.950
	SUVmax Liver	1.614	0.075	0.219
	SUVmax MBP	2.679	0.118	0.117
Blood Glucose Level	SUVmax Lesion	2.505	0.111	0.129
	SUVmax Liver	1.259	0.059	0.275
	SUVmax MBP	0.219	0.011	0.645
Injected Dose	SUVmax Lesion	2.135	0.096	0.160
	SUVmax Liver	0.369	0.018	0.550
	SUVmax MBP	0.359	0.018	0.556
Duration of Uptake	SUVmax Lesion	1.556	0.072	0.227
	SUVmax Liver	0.079	0.004	0.782
	SUVmax MBP	1.687	0.078	0.209
Sex	SUVmax Lesion	0.490	0.024	0.492
	SUVmax Liver	0.453	0.022	0.509
	SUVmax MBP	1.072	0.051	0.313

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 11: Results of MANCOVA tests for SUVmean measurements of the lesion, the liver, and the mediastinal blood pool in patients with non-Hodgkin's lymphoma.

Variable	F(3,18)	Wilk's Λ	Partial η^2	P value
Weight	2.481	0.708	0.292	0.094
Age	1.730	0.776	0.224	0.197
Blood Glucose Level	1.992	0.751	0.249	0.151
Injected Dose	0.716	0.893	0.107	0.555
Duration of Uptake	1.733	0.776	0.224	0.196
Sex	1.660	0.783	0.217	0.211
Between-Subjects Effects				
Independent	Dependent	F(1,20)	Partial η^2	P value
Weight	SUVmean Lesion	5.954	0.229	0.024
	SUVmean Liver	4.645	0.188	0.044
	SUVmean MBP	2.350	0.105	0.141
Age	SUVmean Lesion	0.908	0.043	0.352
	SUVmean Liver	2.778	0.122	0.111
	SUVmean MBP	1.476	0.069	0.239
Blood Glucose Level	SUVmean Lesion	1.898	0.087	0.183
	SUVmean Liver	0.023	0.001	0.880
	SUVmean MBP	1.125	0.053	0.301
Injected Dose	SUVmean Lesion	1.713	0.079	0.205
	SUVmean Liver	0.044	0.002	0.836
	SUVmean MBP	0.182	0.009	0.674
Duration of Uptake	SUVmean Lesion	0.705	0.034	0.411
	SUVmean Liver	1.354	0.063	0.258
	SUVmean MBP	3.855	0.162	0.064
Sex	SUVmean Lesion	0.914	0.044	0.350
	SUVmean Liver	0.016	0.001	0.901
	SUVmean MBP	1.057	0.050	0.316

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

Table 12: Results of MANCOVA tests for SUVpeak measurements of the lesion, the liver, and the mediastinal blood pool in patients with non-Hodgkin's lymphoma.

Variable	F(3,18)	Wilk's Λ	Partial η^2	P value
Weight	2.572	0.700	0.300	0.086
Age	1.604	0.789	0.211	0.224
Blood Glucose Level	0.743	0.890	0.110	0.540
Injected Dose	0.717	0.893	0.107	0.555
Duration of Uptake	1.072	0.848	0.152	0.386
Sex	0.428	0.933	0.067	0.736
Between-Subjects Effects				
Independent	Dependent	F(1,20)	Partial η^2	P value
Weight	SUVpeak Lesion	0.031	0.001	0.862
	SUVpeak Liver	2.600	0.085	0.118
	SUVpeak MBP	3.344	0.107	0.078
Age	SUVpeak Lesion	0.844	0.029	0.366
	SUVpeak Liver	0.304	0.011	0.586
	SUVpeak MBP	1.413	0.048	0.245
Blood Glucose Level	SUVpeak Lesion	4.096	0.128	0.053
	SUVpeak Liver	3.803	0.120	0.061
	SUVpeak MBP	0.157	0.006	0.695
Injected Dose	SUVpeak Lesion	0.001	0.000	0.970
	SUVpeak Liver	0.011	0.000	0.918
	SUVpeak MBP	1.365	0.046	0.253
Duration of Uptake	SUVpeak Lesion	3.224	0.103	0.083
	SUVpeak Liver	0.001	0.000	0.978
	SUVpeak MBP	0.132	0.005	0.719
Sex	SUVpeak Lesion	1.706	0.057	0.202
	SUVpeak Liver	0.220	0.008	0.642
	SUVpeak MBP	2.556	0.084	0.121

*Statistical significance is accepted at $p < 0.0167$ for Tests of Between-Subjects Effects after Bonferroni correction.

In the present research, we assessed the impact of biological factors on FDG uptake by liver and MBP in lymphoma and to assess the variation of FDG avidity of HL and NHL. Our study includes 62 patients who underwent initial PET/CT studies, pathologically (by biopsy) proved to have malignant tumors and have not received any treatment yet.

Our result found that there is a statistically important difference between the distributions of SUVmax in the liver and the MBP within age groups ($p < 0.001$) and this came in concordance with Cao, Zhou [6] who found that there were notable differences in physiological FDG absorption between age groups in the MBP and liver. As people aged, MBP and liver background SUVs increased [6].

Our results revealed that age has a significant effect on liver or MBP SUVs while sex has no effect. Contrary to us Malladi, Viner [19] found that sex had statistically significant ($P < 0.05$) effects on the SUVs of the liver and MBP and in concordance with our result they found that age has significant effects on the liver and MBP SUVs.

We found that the duration of uptake, followed by weight were the most important predictors of SUV measurements of the lesion. Meanwhile, weight was the most significant predictor of SUVmax as well as SUVmean and SUVpeak of the liver, followed by age. On the other hand, weight was the most significant SUVmax and SUVpeak predictor of the mediastinal blood pool. However, Blood glucose level followed by weight with a slight difference were the most important predictors of SUVmean of the mediastinal blood pool.

Our results, however, are consistent with research conducted by Kuruva, Mittal [20] that involved eighty-eight patients who had FDG PET/CT for a range of oncological purposes and found that body weight affect the SUVs of the liver, Conversely, none of the variables or approaches had a significant impact on mediastinal SUVs in their study [20].

In contrast to our results a study by Mahmud, Nordin [21] included 51 cancer patients, found that there is no discernible positive correlation between age and liver SUVmax.

Previous studies by Meier, Alavi [22] and Geraghty, Boone [23] noted that the rise of uptake of FDG with age could also be a reflection of changes in liver volume and hepatocyte counts as well as age-related metabolic activity.

In concordance with our result a previous study by April, De Bruycker [24] agreed with us in that the uptake of ^{18}F-FDG in reference organs varies with age, especially for important reference organs like the liver, and the MBP.

Our results are in concordance with Blautzik, Grelich [25] who found that NHL has higher SUVmax and SUVpeak than HL. His study sample size includes only children and adolescent patients despite our study which includes all age groups.

A study by Ngeow, Quek [12] showed that elevated SUV uptake could be a sign of an aggressive NHL and could be utilized to identify low-grade lymphoma histopathological transformation [12].

In conclusion, changes in the blood pool and liver SUVs are mostly influenced by biological and procedural variables. The so-called reference organs, i.e. the MBP and liver, are affected with variation in weight, age, and uptake time. Our study showed that in all liver and mediastinal blood pool measurements, weight had the upper hand.

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